Health Technology Appraisal

Renal cell carcinoma Pathways Pilot [ID6186]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Renal cell carcinoma Pathways Pilot [ID6186]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **NICE process statement on the PATT pathways process**

2. **Company submissions** from Ipsen
   a. Company submission
   b. Median 44-month follow-up data update

3. **Patient group, professional group and NHS organisation submissions on the pathway** from:
   a. Action Kidney Cancer
   b. British Association of Urological Surgeons

4. **Patient group, professional group and NHS organisation submissions on the technology** from:
   a. Action Kidney Cancer
   b. British Association of Urological Surgeons

5. **Final External Assessment Report** prepared by the EAG
   a. Final Assessment Report
   b. Economic Results Addendum

6. **Company, consultee and commentator responses to the EAG report consultation**
   a. Ipsen
   b. Action Kidney Cancer
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   e. Eisai
   f. Merck Sharpe and Dohme

7. **Expert personal perspectives and comments on the Final Assessment Report** from:
   a. Geraldine Fox – patient expert, nominated by Kidney Cancer UK
   b. Steve Pointon – patient expert, nominated by Action Kidney Cancer
   c. Sophie Scott – patient expert, nominated by Kidney Cancer UK
   d. Dr Balaji Venugopal – patient expert, nominated by the UK Kidney Association

8. External Assessment Group (EAG) response to consultation prepared by the EAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pathways approach

Process statement (renal cell carcinoma)

Project summary

1. The overall goal of this work is to use model-based approaches to inform the development of guidance. Time and resource efficiencies for NICE and external stakeholders are expected to be found by assessing multiple technologies in a disease pathway and building an evolving core economic model.

2. The phases of work are as follows:

    - Phase 1 – Scoping and preparatory work
    - Phase 2 – Academic synthesis and modelling work
    - Phase 3 – Evaluation and decision-making

3. The technology appraisal processes are detailed in the NICE health technology evaluations guidance development manual. Pathway appraisals correspond to the steps in the guidance development manual but are re-sequenced and with different timelines in order to allow the exploration of a new approach (in a test and learn environment) that will develop overall process efficiencies and improvements. The overview of each phase outlined below details how the guidance development steps in the manual are followed and timelines are available in tables 1 to 4.

Phase 1 – Scoping and preparatory work

4. The activities in phase 1 broadly correspond to section 2 of the guidance development manual. See section 1.3.10 to section 1.3.19 of the manual for details on the nomination and selection of experts.

5. The scoping process aims to define what question the evaluation will answer and what will and will not be included. The scope provides the framework for the evaluation.

6. A scoping workshop will take place between NICE, External Assessment Groups (EAGs) and relevant stakeholders including company representatives, clinical experts, and patient representatives.

7. The scoping workshop will outline the renal cell carcinoma (RCC) care pathway. This will include any sequence of tests and treatments, any

subgroups of interest, patient characteristics and possible comorbidities for the relevant population.

8. To promote maximum engagement with the process the standard stakeholder list has been expanded to include companies with technologies already recommended for treating renal cell carcinoma, that are not expected to be comparators to the technologies being evaluated.

Phase 2 – Academic synthesis and modelling work

9. The activities in phase 2 broadly correspond to section 5.6 of the guidance development manual.

10. The EAG will develop an analysis plan outlining what the EAG will do during the evaluation and the information it will provide in the external assessment report. This will be based on the draft scope and consultation with clinical experts, and the scope that was updated after the scoping workshop and Phase 1 of the evaluation.

11. The EAG will then carry out an assessment of the publicly available clinical outcomes within the disease area, including accessing data on novel technologies (see section 5.6.15 of the guidance development manual). The assessment will include:

    - Systematic evidence reviews for technologies entering the disease pathway

    - Targeted evidence review of systemic treatments for existing technologies in the treatment pathway, prioritising searches based on volume of results

    - Targeted evidence review for data input parameters and natural history for the economic evaluation.

12. Construction of economic model(s) of the progression and outcomes of the disease.

13. Model validation will be completed during phase 2. Validation will be aligned with the guidance development manual. It is expected that model outputs will be compared to the data used as model inputs (including any real world evidence), to ensure accuracy of model structure and data derivation. The model will then be compared to the projections from other models previously used for NICE technology appraisals in the same decision node.

14. The EAG will develop a preliminary external assessment report, presenting an assessment of the publicly available clinical outcomes and costs throughout the disease pathway. The report will also provide a summary of the expected

model structure and transparently document and justify any expected assumptions.

15. The preliminary external assessment report will be produced and sent to stakeholders to provide comments. Stakeholders will have at least 21 working days to comment on the preliminary external assessment report.

16. NICE will invite stakeholders, including companies with new technologies being evaluated and comparator companies involved in the decision nodes, to submit evidence and comments. Stakeholders will have at least 21 working days to provide evidence.

17. NICE will be seeking evidence from companies that is not included in the preliminary external assessment report, it is expected that this data will primarily comprise clinical trial data.

18. The EAG will incorporate relevant stakeholder evidence into its model and provide responses to consultation comments on the preliminary external assessment report. Responses may include clarifications, rebuttals, or where appropriate summaries of adaptations to the model structure.

19. The EAG will provide a summary of its base case. The EAG will also provide scenarios with alternative assumptions that it did not consider suitable but which were preferred by stakeholder. The EAG will produce a final external assessment report which will present an assessment of the clinical outcomes and cost effectiveness of the technologies. The report should also provide a summary of the model structure, transparently document and justify any assumptions made. Key issues per decision node should also be documented and areas of data paucity should be highlighted. The EAG's assessment should highlight the uncertainties in the evidence.

20. A lay summary of the model for patient and clinical experts will also be developed by the EAG.

21. The final external assessment report will be sent to stakeholders to provide comments. Stakeholders will have at least 21 working days to comment on the final external assessment report.

22. During the consultation on the final external assessment report, NICE and the lead team committee members will also risk assess the external assessment report and model to highlight differences in approaches and additional analyses the EAG should model.

23. Information will be handled as outlined in section 3.2 of the interim proportionate approach methods and process guide, which will be published

shortly. Information marked as confidential should be kept to an absolute minimum.

24. An executable version of the EAG's model will be provided online to stakeholders. It may use dummy data where data from the company whose technology is being appraised is marked as confidential.

25. Previous models submitted to NICE in the pathway will be used (with permission from the original submitting company) for validation purposes. Scenario analyses run by the EAG for validation of the model may encompass values from previous submissions within a range. The EAG will create a confidential appendix to its report where necessary. This will only be shared with NICE and the committee.

Phase 3 – Evaluation and decision-making

26. The committee's consideration of the evidence, draft guidance consultation (where needed) and development of draft final guidance will follow the steps outlined in sections 5 of the guidance development manual.

27. Committee recommendations on the specific technology will be as per section 6 of the guidance development manual.

28. Finalising and publishing the guidance will be as per section 7 of the guidance development manual.

29. Committee recommendations on the pathways assumptions will be summarised in a separate report (Pathways Guidance), and will include conclusions about the model structure, sources to estimates baseline event rates, utilities, resource costs and severity at different decision nodes. The Pathways Guidance will be sent to stakeholders to provide comments, aligning with the principles in section 7 of the guidance development manual.

Table 1: Timelines for Phase 1 for the RCC pilot

	Phase 1
December 2022	External Assessment Group starts work
January 2023	Scoping workshop

Table 2: Timelines for Phase 2 for the RCC pilot

	Phase 2
28 March 2023	Stakeholder information meeting
April 2023	Company evidence submission
April 2023	Preliminary External Assessment Report

April 2023	Consultation on Preliminary External Assessment Report
May 2023	Non-company stakeholder evidence submission
July 2023	Final External Assessment Report
July to August 2023	Consultation on Final External Assessment Report and executable model

Table 3: Timelines for Phase 3 for the RCC pilot

	Phase 3
20 September 2023	**First appraisal committee meeting**
October 2023	Draft final guidance issued for appeal
Dec 2023/Jan 2024	Final guidance published

Table 4: If draft final guidance cannot be produced following the first appraisal committee meeting, the subsequent indicative timelines are currently:

	Phase 3
20 September 2023	**First appraisal committee meeting**
November 2023	Draft guidance consultation
Q1 2024	Second appraisal committee meeting
Q1 2024	Draft final guidance issued for appeal
Q1 2024	Final guidance published

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health technology appraisal

Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6186]

Document A

Company evidence submission

April 2023

File name	Version	Contains confidential information	Date
ID6186_Company evidence submission_AIC_CIC_03Apr2023_FINAL_Updated ACIC_24Aug2023	Version 1	Yes	3rd April 2023

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List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
aRCC	Advanced renal cell carcinoma
AxiAve	Axitinib with avelumab
AxiPembro	Axitinib with pembrolizumab
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
CaboNivo	Cabozantinib with nivolumab
CDF	Cancer Drugs Fund
CNS	Central nervous system
CMH	Cochran-Mantel-Haenszel
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPI	Checkpoint inhibitor
CR	Complete response
CRF	Case report form
CT	Computerised tomography
DHSC	Department of Health and Social Care
DoR	Duration of response
DTC	Differentiated thyroid carcinoma
DMC	Data Monitoring Committee
DRS	Disease-related symptom
DRS-P	Disease-related symptom-Physical
EAG	External assessment group
EMA	European Medicines Agency
EP	Endpoint
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5D
EQ-5D-3L	3 Level version of EuroQol-5D (EQ-5D)
EQ-5D-5L	5 Level version of EuroQol-5D (EQ-5D)
ESMO	European Society for Medical Oncology
FKSI	Functional Assessment of Cancer Therapy Kidney Symptom Index
FWB	Functional well-being
HR	Hazard ratio
HRQoL	Health-related quality of life
IKCC	International Kidney Cancer Coalition
IMAE	Immune-mediated adverse events
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immune-oncology
IpiNivo	Ipilimumab with nivolumab
IRT	Interactive Response Technology
ITC	Indirect treatment comparison

KPS	Karnofsky performance status
LDH	Lactate dehydrogenase
LenPembro	Lenvatinib with pembrolizumab
LLN	Lower limit of normal
MCAR	missing completely at random
MAR	missing at random
MET	mesenchymal-epithelial transition factor
MMRM	Mixed models for repeated measures
mo	Months
mRCC	metastatic renal cell carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
MUGA	Multigated acquisition
N.A.	Not applicable
N.E.	Not estimable
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small-cell lung cancer
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reached
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PR	Partial response
PRO	Patient-reported outcome
PSSRU	Personal Social Services Research Unit
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
QALY	Quality adjusted life year
QD	once daily
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RTK	Receptor tyrosine kinases
SE	Standard error
SD	Standard deviation
SAE	Serious adverse events
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TNM	Tumour, Node, Metastasis
TRAE	Treatment-related adverse events
TTD	Time to treatment discontinuation
TTR	Time to treatment response
UICC	Union of International Cancer Control

UK	United Kingdom
ULN	Upper limit of normal
UTD	Unable to determine
VAS	Visual Analog Scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cells

A.1 Decision problem, description of the technology and clinical care pathway

A.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Table 1 presents the decision problem addressed within this submission.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with untreated advanced or metastatic renal cell carcinoma	Patients with untreated advanced or metastatic renal cell carcinoma	N/A
Intervention	Cabozantinib with nivolumab as a first-line therapy in untreated advanced or metastatic renal cell carcinoma.	Cabozantinib with nivolumab as a first-line therapy in untreated advanced or metastatic renal cell carcinoma.	N/A
Comparator(s)	• Pazopanib • Tivozanib • Sunitinib • Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivolumab with ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Lenvatinib with pembrolizumab	• Pazopanib • Sunitinib • Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivolumab with ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Lenvatinib with pembrolizumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Axitinib with avelumab	Although currently in the CDF, axitinib with avelumab is available to an all-risk aRCC NHS England population. Significantly, axitinib with avelumab has been in the CDF for over four years now, an unusual length of time for the CDF (1). Additionally, as highlighted by a recent ABPI report, the majority of therapies (78%) exit the CDF into routine commissioning suggesting that axitinib with avelumab is also expected to enter routine commissioning (2). Therefore, axitinib with avelumab should be considered as a relevant comparator by NICE and is discussed as such in our submission. Tivozanib is not included as a comparator in this submission as the NMA that was conducted to support Ipsen HTA

	(only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Active surveillance		submissions for other countries determined tivozanib was not widely used in practice. There are data available to link and create a network. However, tivozanib has been assessed as an equivalent treatment to sunitinib and pazopanib in previous NICE submissions (3-7). Active surveillance is not included in this submission; as discussed in the scoping call on 16th January 2023 (1), active surveillance is usually used in first-line favourable risk patients and involves a wait-period before therapy is administered. Therefore, it is not relevant to this submission.
Outcomes	• Overall survival • PFS • Response rates • DoR • Time on treatment/time to next treatment • Adverse effects of treatment • Health-related quality of life	• Overall survival • PFS • Response rates • DoR • Time on treatment • Adverse effects of treatment • HRQoL	Time to next treatment is not presented in this submission as it is not of relevance to the decision problem.
Groups to be considered	Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria	Patients with untreated advanced or metastatic renal cell carcinoma	Cabozantinib with nivolumab is indicated for an all-risk population of 'patients with untreated advanced or metastatic renal cell carcinoma' and should be appraised in line with this indication (8, 9). The phase 3 CheckMate 9ER trial of cabozantinib with nivolumab compared to sunitinib demonstrated consistent clinical benefits across all patients, irrespective of

			prognostic risk profile.

Key: ABPI, The Association of the British Pharmaceutical Industry; aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; DoR, duration of response; HRQoL, Health Related Quality of Life; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; RCC, renal cell carcinoma; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFS, Progression Free Survival.

A.1.2 Description of the technology being evaluated

Table 2 presents a description of cabozantinib with nivolumab. The summary of product characteristics (SmPC) (8, 9) and the European Public Assessment Report (EPAR) (10) is presented in Appendix B.

Table 2: Technology being appraised

UK approved name **Brand name** **Manufacturers**	Cabozantinib with nivolumab Cabometyx® / Opdivo® (8, 9) Ipsen / BMS
Mechanism of action	Receptor tyrosine kinases (RTKs) are receptors for many growth factors and proteins implicated in the development and progression of cancer, including (11-13): • Vascular endothelial growth factor (VEGF) which promotes the growth of new blood vessels • Hepatocyte growth factor that regulates several physiological processes including proliferation, scattering, morphogenesis, and survival of cells, and • Growth factor growth arrest specific 6 (GAS6) which is involved in several cellular functions including growth, migration, aggregation, and differentiation Cabozantinib is a tyrosine kinase inhibitor (TKI) that inhibits multiple RTKs involved in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer (8). Cabozantinib is a potent inhibitor of multiple RTKs, such as c-MET and VEGF, known to play important roles in tumour cell proliferation and/or tumour neovascularisation in RCC (14, 15). There is an interaction between angiogenesis and immunosuppression in tumour development. VEGF primarily inhibits the innate immune system by upregulating PD-L1 and CTLA-4 expression, thereby maintaining an immunosuppressive environment. In addition, antiangiogenic activity leads to normalisation of the tumour vasculature and exhibits a positive effect on immune-cell infiltration into tumours (16). Nivolumab is a fully human, monoclonal immunoglobulin antibody (IgG4) that acts as a checkpoint inhibitor of PD-1 and blocks its interaction with its ligands. Tumours use PD-L1 expression as defence or escape mechanisms against the host's anti-tumour T cell response; inhibiting PD-L1 restores the function of these anti-tumour T cells which have become ineffective or suppressed (16). Therefore, the efficacy of PD-L1 inhibition relies on a pre-existing immune response (16). The combination of cabozantinib with nivolumab therefore potentiates immune-mediated tumour destruction in parallel to targeted inhibition of tumour growth and progression.
Marketing authorisation	Cabozantinib (Cabometyx®) with nivolumab received MHRA approval on 13/05/2021 (8).

Indications and any restriction(s) as described in the summary of product characteristics	In accordance with the current marketing authorisation, cabozantinib with nivolumab is indicated for the treatment of previously untreated adult patients with advanced or metastatic RCC. Cabometyx® monotherapy is licensed for the following indications (8): • Treating aRCC in treatment-naïve adults with intermediate or poor-risk • Treating aRCC in adults following prior VEGF-targeted therapy • Treating hepatocellular carcinoma in adults who have previously been treated with sorafenib • Treating adults with locally advanced or metastatic DTC, refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy. Opdivo® monotherapy is licensed for the following indications (9): • Treating aRCC after prior therapy in adults • Treating advanced (unresectable or metastatic) melanoma in adults • Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease after complete resection • Treating locally advanced or metastatic NSCLC after prior chemotherapy in adults • Treating adult patients with relapsed or refractory classical Hodgkin's lymphoma after autologous stem cell transplantation and treatment with brentuximab vedotin • Treating recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy • Treating locally advanced, unresectable, or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy
Method of administration and dosage	Cabozantinib is available as 20 mg, 40 mg, and 60 mg film-coated tablets. The recommended dose for cabozantinib is 40 mg once daily in combination with nivolumab 240 mg every two weeks or 480 mg every 4 weeks. The treatment should continue until disease progression or unacceptable toxicity. Nivolumab treatment should continue until disease progression or unacceptable toxicity or up to a maximum duration of 2 years in patients without disease progression (8, 9). For cabozantinib, temporary treatment interruption and/or dose reduction is recommended for management of adverse drug reactions. In monotherapy, dose is reduced to 40 mg daily, and further to 20 mg daily. Whereas, in combination with nivolumab, it is recommended to reduce the dose to 20 mg of cabozantinib once daily, and then to 20 mg every other day. For nivolumab, dose reduction is not recommended, and in case of AEs or liver enzymes elevation, either withhold dose or discontinue treatment (8, 9).
Additional tests or investigations	No additional tests or investigations are needed to identify patients eligible for cabozantinib with nivolumab over those needed to identify advanced or metastatic RCC.
List price and average cost of a course of treatment	List price: £5,143.00 per 30 x 40 mg tablet pack of cabozantinib (17) £1,097.00 per 100 mg vial; £439.00 per 40 mg vial of nivolumab (18)

Patient access scheme (if applicable)	A confidential simple patient access scheme is available for cabozantinib. The pack price under this scheme is [redacted] (a [redacted]% discount to the list price). There is a confidential patient access scheme in place for nivolumab, approved by the DHSC.

Key: aRCC, advanced renal cell carcinoma; AEs, adverse events; BMS**,** Bristol Myers Squibb; CHMP, Committee for Medicinal Products for Human Use; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DHSC, Department of Health and Social Care; DTC, differentiated thyroid carcinoma, EMA, European Medicines Agency; GAS6, growth arrest specific 6; IgG, immunoglobulin; IV, intravenous; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death protein-1; RCC, renal cell carcinoma; RET, rearranged during transfection; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor

A.1.3 Health condition and position of the technology in the treatment pathway

A.1.3.1 Overview of the disease

Kidney cancer is the eighth most common cancer in the United Kingdom (UK) (19). It accounts for 4% of all new cancer cases in the UK, with average 13,392 new cases of kidney cancer each year (2016-2018) (20). Renal cell carcinoma (RCC), where cancerous cells develop within the epithelia of the renal tubules, is the most common type of kidney cancer, responsible for more than 80% of all cases diagnosed in the UK (21, 22). Several histological subtypes of RCC are recognised, of which the most common are clear cell (~75%), papillary (~10–15%), and chromophobe (~5%) (21).

In England, around 30% of all cancer patients are diagnosed at advanced or metastatic disease (stage 3 and 4, respectively) thereby, emphasising the need for continuous monitoring (23, 24). RCC spread occurs most commonly to the lung, bone, lymph node, and liver, leading to significant morbidity and poor prognosis (25). Metastatic RCC progresses rapidly, the five-year age-standardised survival from diagnosis for patients with distant metastatic disease is around 10% (23). Incidence rates for kidney cancer are projected to rise by 26% in the UK between 2014 and 2035 (23).

While the causes of RCC are unknown, several risk factors are associated with its development (26, 27). Age is a strong risk factor, with approximately 34% of all new kidney cancer cases in the UK diagnosed in people aged 75 or above. It is also more common in males and people of white ethnicity (20). Furthermore, links to certain lifestyle factors such as obesity, hypertension and smoking are well-established (28).

A.1.3.1.1 Disease staging, scoring and prognosis

The European Society for Medical Oncology (ESMO) guidelines recommend RCC classification and staging according to the Union of International Cancer Control (UICC) Tumour, Node, Metastasis (TNM) Classification of Malignant Tumours system (29). T is used to describe the size and location of the tumour, N indicates spread to regional lymph nodes and M describes the spread of cancer to other parts

of the body, called metastasis (30). Stages are assigned by clinicians by combination of T, N and M classifications (30). Stage I includes patients where the tumour is 7 cm or smaller and is only located in the kidney and has not spread to the lymph nodes or distant organs (30). In Stage II patients, the tumour is larger than 7 cm and is only located in the kidney (30). It has not spread to the lymph nodes or distant organs (30). Stage III patients have either of these conditions (30):

- A tumour of any size located only in the kidney that has spread to the regional lymph nodes but not to other parts of the body.
- The tumour has grown into major veins or perinephric tissue and may or may not have spread to regional lymph nodes, however the tumour has not spread to other parts of the body.

Stage IV patients have either of these conditions (30):

- The tumour has spread to areas beyond Gerota's fascia, extending into the adrenal gland on the same side of the body as the tumour, possibly to lymph nodes, but not to other parts of the body.
- The tumour has spread to any other organ, such as the lungs, bones, or the brain.

The most common scoring systems used to characterise prognosis in advanced RCC are the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC), summarised in Table 3. Each scoring system categorises patients as favourable- (0 factors), intermediate- (1–2 factors) or poor-risk (≥ 3 factors) according to multiple prognostic factors, including Karnofsky performance status (KPS), time from diagnosis to treatment, haemoglobin value and corrected calcium concentration (31, 32). Both scoring systems are used in clinical practice, and both demonstrate good concordance with one another (33).

Table 3: Summary of International Metastatic Renal Cell Carcinoma Database Consortium and Memorial Sloan Kettering Cancer Center scoring systems

Prognostic factor	MSKCC	IMDC
Time from diagnosis to systemic treatment < 1 year	Yes	Yes
Haemoglobin < LLN[a]	Yes	Yes
Calcium >10 mg/dL (> 2.5 mmol/L)	Yes	Yes
LDH > 1.5x ULN[b]	Yes	No
Karnofsky performance status < 80%	Yes	Yes
Absolute neutrophil count > ULN	No	Yes
Platelet count > ULN	No	Yes
Number of adverse factors for:		
Favourable-risk	0	0
Intermediate-risk	1–2	1–2
Poor-risk	≥ 3	≥ 3

Key: LDH, lactate dehydrogenase; LLN, lower limit of normal; ULN, upper limit of normal.

Notes: [a], normal range defined as 13.5–17.5 g/dL for men and 12.0–15.5 g/dL for women; [b], normal value defined as 140 U/L

Source: Heng et al. 2009 (32); Motzer et al. 1999 (31).

A.1.3.1.2 Burden of disease

Symptomatic burden and impact on health-related quality of life

The diagnosis of RCC in the UK is often incidental (in over half of cases) as the common symptoms are mostly observed when the disease is in the advanced stage (34). Patients who experience symptoms usually present with pain or discomfort in the upper abdomen or back (flank pain), gross haematuria and a palpable lump or mass in the kidney area; these make up the classic triad of kidney cancer symptoms (35, 36). The altered immune response caused by the tumour also gives rise to paraneoplastic syndromes such as hypercalcaemia, unexplained fever, erythrocytosis and Stauffer's syndrome, which occur relatively frequently (37). Other vaguer symptoms include weight loss, high temperature, hyperhidrosis, fatigue and a loss of appetite (35). In addition, patients with metastatic disease may experience further physical symptoms based on the size and location of their metastatic tumours – for example, lung metastases may cause airway obstruction, bleeding, and dyspnoea; bone metastases may

cause headache, seizures, or dizziness; and liver metastases may cause jaundice or swelling in the belly (38, 39).

The symptoms of advanced or metastatic RCC coupled with the psychological impact of suffering from a life-threatening disease can significantly impact an individual patients' everyday life and overall wellbeing (38, 40-42). The International Kidney Cancer Coalition (IKCC) global patient survey reported that patients with RCC observed impact of the disease on both their physical conditions (e.g., fatigue, bowel changes, muscle weakness and sleeplessness) and psychosocial issues (e.g., general and disease-related anxiety and fear of recurrence and dying) (43). The symptom burden of RCC has a negative impact on patient's health-related quality of life (HRQoL) (44). Data showing the impact on HRQoL is lacking, specifically in the UK. However, data from the national Dutch PERCEPTION registry demonstrated that disease progression led to a worsening of HRQoL in patients with advanced RCC, with patients reporting significantly lower scores on the EORTC QLQ-C30 global health status compared to stable disease (change in mean score from 0.69 to 0.61 after progression) (40). Similarly, health status worsening after disease progression showed a notable decline in EuroQol-5D (EQ-5D) utility scores, highlighting the negative impact of progression on patient's HRQoL (40). Disease progression is an important HRQoL factor in RCC as patients with advanced RCC experiencing greater reductions in HRQoL compared to those with stable disease (45, 46).

Progression to metastatic disease leads to significant HRQoL impairment due to symptom worsening (40, 44). In particular, symptoms of fatigue, pain and shortness of breath are associated with significant impairment of HRQoL. It was shown that patients who experience fatigue and pain report significantly lower scores across multiple EQ-5D dimensions including "self-care", "usual activities", and "pain/discomfort" (40).

Advanced RCC is associated with treatment-related adverse events (TRAE) which impact all domains of patient HRQoL, including physical and psychosocial function (42, 46, 47). TRAEs from systemic therapies (e.g., fatigue and gastrointestinal side

effects) can reduce HRQoL and affect patient's daily living, thereby contributing to the increased disease burden (44).

Survival and mortality

Disease stage at diagnosis is strongly associated with survival, and metastatic or advanced disease is particularly life threatening. The 1-year relative survival rate for patients diagnosed with Stage IV disease in the UK is 39%, compared with 96% for patients diagnosed with Stage I disease (23, 48). The burden of disease becomes more apparent with late diagnosis, with a historical 5-year relative survival rate of just 12% for Stage IV, compared with 87% for Stage I disease (23, 48). However, anecdotal evidence from clinicians suggests that the 1-year and 5-year relative survival rates are an under-estimate as they do not account for the improvements in life expectancy resulting from recently approved therapies such as ipilimumab with nivolumab (IpiNivo) and lenvatinib with pembrolizumab (LenPembro) (1).

Life expectancy has also been shown to decrease with increasing adverse prognostic factors (33). Kidney cancer is the thirteenth most common cause of cancer death in the UK, accounting for approximately 3% of all cancer deaths between 2017-2019 (23). In the UK, there were 4,700 deaths per year due to kidney cancer between 2017 and 2019, equating to approximately 13 deaths per day (23). Kidney cancer mortality rates increased by 73% in the UK between 1971-1973 and 2017-2019, for females and males combined (23).

Caregivers and societal burden

In addition to patient burden, advanced or metastatic RCC can present a significant burden to informal caregivers and wider society, primarily as a result of direct care requirements and reduced life expectancy, both of which are worsened with disease progression and treatment-related toxicity (42, 49).

Although there are limited data on the economic burden of all-risk advanced RCC (aRCC), it has been suggested that disease progression to metastatic stages leads to more frequent hospitalisations with higher admissions to palliative care (50-52). Few studies report on indirect costs to aRCC patients and their caregivers in general (e.g., non-medical costs such as disability costs, social services, lost productivity due

to morbidity and mortality, caregiver time, etc.). Indirect costs attributed to sick leave and medical transportation accounted for 6.7% of the total costs associated with advanced RCC (data by prognostic risk-group were not reported) in France (51). There are no published studies addressing indirect costs incurred by aRCC patients in the UK or studies estimating the effect of disease progression on indirect costs.

A.1.3.2 Clinical care pathway and proposed positioning of cabozantinib with nivolumab

Currently, there are no UK-specific clinical guidelines for the treatment of RCC. The National Institute for Health and Care Excellence (NICE) has issued guidance on the first- and second-line treatment of advanced or metastatic RCC, which encompasses information from relevant technology appraisals (53).

For the first-line treatment of advanced or metastatic RCC, NICE recommends the following tyrosine kinase inhibitors (TKI) monotherapies:

• Sunitinib for the first-line treatment of advanced and/or metastatic RCC (54)

• Pazopanib for the first-line treatment of aRCC (3)

• Tivozanib for treatment of aRCC in adults who have had no previous treatment (5)

or

• Cabozantinib, for treatment of untreated aRCC in patients with IMDC intermediate- or poor-risk disease (55)

Sunitinib, pazopanib and tivozanib are considered equivalents and have been assessed as such in previous NICE submissions (3-7).

NICE also recommends the dual immune-oncology (IO) regimen of IpiNivo and the IO and TKI combination of LenPembro as an option for intermediate- or poor-risk patients (56). Axitinib with avelumab (AxiAve) currently in the Cancer Drugs Fund (CDF), is expected to be appraised at the start of 2024 (57). However, AxiAve is widely used by clinicians in an aRCC patient group and has been in the CDF for over 4 years, an unusual length of time (1). Further, as described in a recent report by the Association of the British Pharmaceutical Industry (ABPI), most oncology treatments

enter routine commissioning following the CDF, specifically, 78% (2). Based on previous established trends, it is expected that AxiAve will enter routine commissioning following exit from the CDF. As such, AxiAve should have been considered as a relevant comparator to cabozantinib with nivolumab in aRCC in this appraisal.

For the second-line treatment of advanced or metastatic RCC, NICE recommends:

• Axitinib (a further TKI) for patients who have previously received sunitinib (4)

• Cabozantinib for patients who have previously received vascular endothelial growth factor (VEGF)-targeting therapy (55)

• Everolimus, a mammalian target of rapamycin (mTOR) inhibitor (58)

• Lenvatinib plus everolimus, a TKI+mTOR combination (59), or

• Nivolumab monotherapy (60)

The clinical pathway of care for advanced or metastatic RCC based on NICE recommendations is depicted in Figure 1.

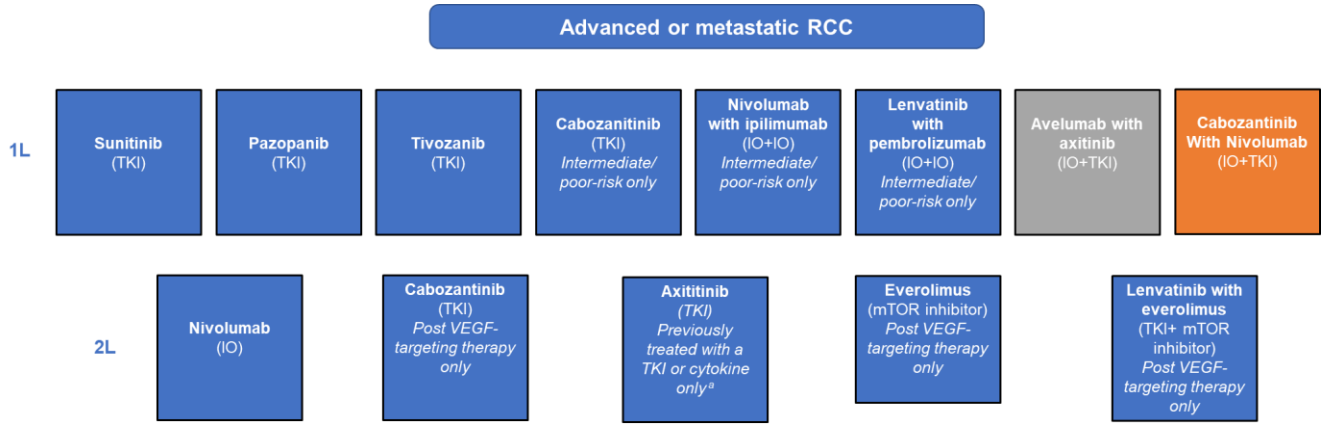
The scoping meeting held on the 16th January 2023 discussed the clinical pathway (1). It was noted that sunitinib, pazopanib and tivozanib are given in first line and that an IO would not be rechallenged with a different IO although a TKI may be re-challenged with a different TKI. It was also discussed during the NICE scoping meeting that there is a reluctance among clinicians to provide immunotherapy in first line aRCC if a patient had received adjuvant therapy, and a 6-12 month gap would be recommended in this instance (1). It was stated that active surveillance, a proposed re-classification for best supportive care involving a wait period before treatment is initiated, is usually used in favourable risk first-line patients (1); this is beyond the scope of the decision problem. It should be noted that nivolumab would not be given after first-line IO as patients are only eligible for a single treatment line for a specific IO, as per National Health Service England (NHSE) guidance (57, 61).

Combining IO and TKI treatments represents a new therapeutic approach to build upon previous step-changes in the management of advanced or metastatic RCC

(53). Figure 1 presents the potential positioning of cabozantinib with nivolumab within the current pathway based on NICE recommendations. Based on data from countries where cabozantinib with nivolumab is already launched, including France and Germany, it is anticipated that cabozantinib with nivolumab would primarily shift the current use of TKI monotherapy at first-line to second-line and indirectly displace the use of cabozantinib monotherapy and nivolumab monotherapy at second-line (1, 56).

There is consensus across the clinical community that the most effective treatment options should be made available as early as possible (62). Nearly one-third of advanced RCC patients receive only one line of treatment, therefore it is important to provide patients with efficacious treatments early on in the pathway to ensure that they benefit from the best possible outcomes (62).

Figure 1: Clinical pathway of care for advanced or metastatic RCC based on NICE recommendations, and proposed positioning of cabozantinib with nivolumab



Key: IO, immune-oncology; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

Notes: [a], axitinib has a UK marketing authorisation only for use after failure with first-line sunitinib or a cytokine. If it is considered for use after any other first-line treatments, the prescriber should obtain and document informed consent and follow the relevant guidance.
Blue boxes established first- and second-line therapies recommended by NICE; orange box, proposed positioning of cabozantinib with nivolumab; grey box, Cancer Drugs Fund.
Source: Adapted from the National Institute for Health and Care Excellence, 2022 (53).

A.1.3.2.1 Remaining unmet need

The treatment landscape for advanced or metastatic RCC has evolved significantly over the past few decades. aRCC requires a variety of therapeutic options to allow for treatment approaches that take into account at the same time the patient's and the tumour's characteristics (63, 64). The introduction of targeted treatments to the clinical pathway of care represented the first step-change in the management of advanced or metastatic RCC with TKI monotherapies, demonstrating significant improvements in response rates and progression-free survival (PFS) compared to historical standard of care, as summarised in Table 4.

However, none of the TKI monotherapies have demonstrated a significant overall survival (OS) benefit versus control arms in a first-line clinical trial setting, and while TKI monotherapy is often effective at inducing local remissions, treatment responses are rarely sustained as RCC tumours often develop resistance to conventional TKIs that primarily target VEGF (65).

Sunitinib has been the standard of care in aRCC for over a decade and is the most widely used approved first-line therapy (66-69). Prior to the approval of the immune checkpoint inhibitor (CPI) combinations, first-line monotherapy agents had not demonstrated significant OS improvement over sunitinib (70-74).

In 2019, IpiNivo, a combination of two CPIs, was approved for the management of intermediate and poor-risk aRCC patients, based on the demonstration of significant OS improvement (hazard ratio [HR]=0.63, p value<0.001) (9). Axitinib with pembrolizumab (AxiPembro, a combination of a CPI and a TKI) were granted regulatory approval in all-risk categories of aRCC patients on the basis of significant OS improvement (HR=0.59, p value=0.001) (75), but not given to patients as it is not recommended by NICE. Recently, LenPembro was recommended in intermediate- or poor-risk disease when IpiNivo would otherwise be offered, on the basis of improved PFS (HR=0.42, 95% CI 0.34 - 0.52) and improved OS (median not reached) (76).

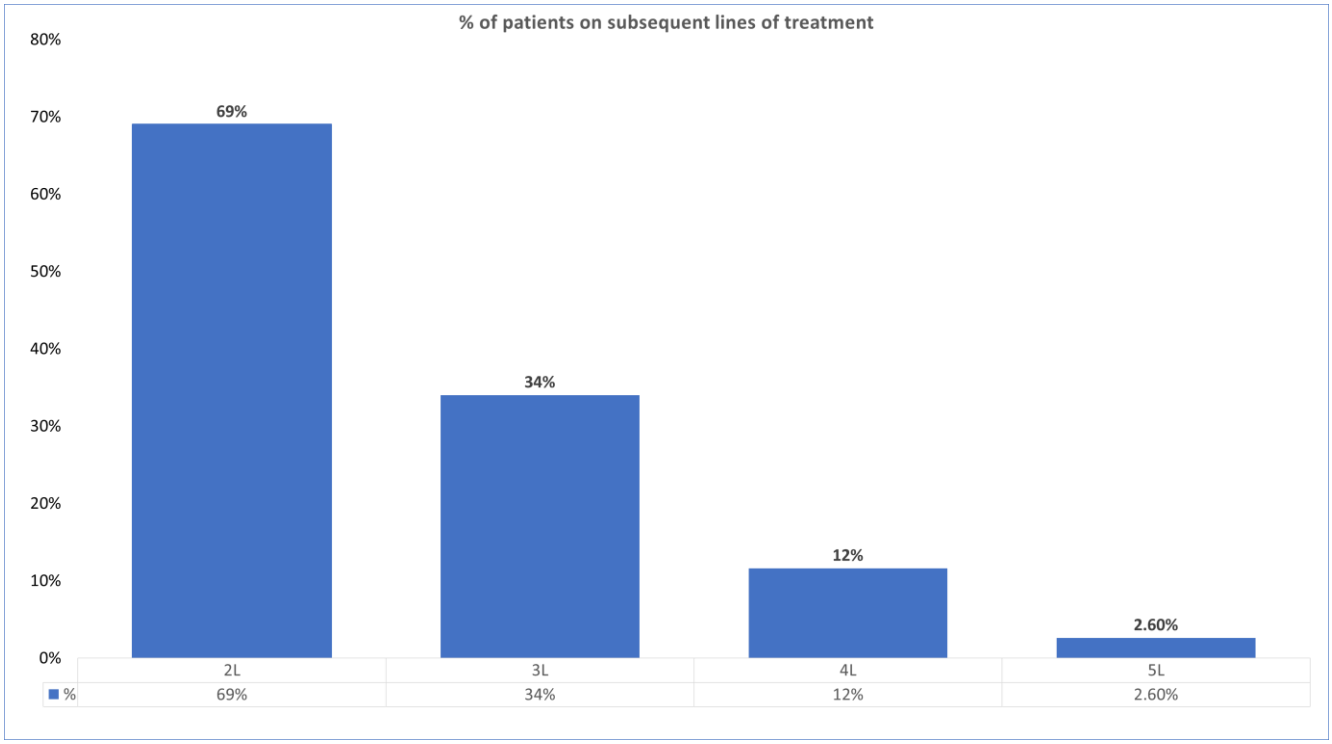
Another combination of a CPI and TKI, AxiAve, currently available via the CDF, was also approved in all aRCC patients after demonstrating significant PFS benefit

(HR=0.69, p value<0.001). For AxiAve, the NICE committee identified the immaturity of the OS data and the companies' approach to modelling OS over the long term as areas of concern (57). Further, AxiAve is not included in the ESMO guidelines because it has not shown an overall survival benefit while all other combinations approved by the regulator are included: lenvatinib with everolimus, IpiNivo, AxiPembro and cabozantinib with nivolumab (6, 37, 57, 77, 78).

Of note, different CPI and CPI+TKI combinations have demonstrated limited improvement in HRQoL scores (79, 80). IpiNivo is the only combination that has shown improvement in HRQoL over sunitinib during the first 6 months of therapy of intermediate-/poor-risk aRCC patients (as observed on the Functional Assessment for Cancer Therapy (FACT) - G [p<0.0005] and FACT- Kidney Symptom Scale (FKSI)-19 [p value<0.001] instruments) and a trend towards improvement on the 5 Level version of EuroQol-5D (EQ-5D-5L) scale (79, 80). AxiPembro has been shown to lead to slightly worse HRQoL compared to sunitinib during the treatment period (observed as lower mean total scores on QLQ-C30 Global Health Scale, FKSI-Disease Related Symptoms [DRS] scale and 3 Level version of EuroQol-5D (EQ-5D-3L) at week 30) (75, 79, 81). For LenPembro no significant difference compared to sunitinib has been demonstrated for the FKSI-DRS, EORTC QLQ-C30 or EQ-5D-3L QoL instruments (82). To date, no evidence has been published on the impact of AxiAve on HRQoL.

A recent UK real-world evidence study indicated that 69.0% of patients receive a second line treatment with 34.0%, 12.0% and 2.6% receiving third, fourth and fifth, respectively. These high drop-off rates highlight the need for "efficacious treatment first" for better outcomes (Figure 2) (62).

Figure 2: Percentage of patients on subsequent lines of treatment



Source: McGrane et al. 2022 (62)

Thus, there is a remaining unmet need in the advanced or metastatic RCC treatment pathway for additional first-line treatment options that can offer immediate and sustained treatment effect to a broad spectrum of patients, extend life expectancy, delay progression, and improve disease control while maintaining quality of life in all aRCC patients.

Table 4: Summary of outcomes from key trials of treatment-naïve patients with advanced or metastatic RCC treated with the currently available first-line TKI monotherapies

Intervention	Study	Study design and follow-up	Control	ORR, % (95% CI) p value		Median PFS, months (95% CI) HR [95% CI]		OS, months (95% CI) HR [95% CI]	
				Intervention	Control	Intervention	Control	Intervention	Control
Cabozantinib	CABOSUN (83)	Phase II RCT Intermediate-/poor-risk mRCC 1° EP = PFS N = 157 Median FU: 25.0 mo PFS; 35.4 mo OS	Sunitinib	20 (12.0, 30.8)	9 (3.7, 17.6)	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)	26.6 (14.6, NE)	21.2 (16.3, 27.4)
				NR		0.48 [0.31, 0.74]		0.80 [0.53, 1.21][a]	
Tivozanib	TIVO-1 (84)	Phase III RCT mRCC 1° EP = PFS N = 517 Minimum FU: 2 yrs	Sorafenib	33.1 (27.4, 39.2)	23.3 (18.3, 29.0)	12.7 (9.1, 15.0)	9.1 (7.3, 10.8)	29.3 (NR)	28.8 (NR)
				NR		0.76 [0.58, 0.99]		1.25 [0.95, 1.62]	
Pazopanib	COMPARZ (85, 86)	Phase III RCT[b] mRCC 1° EP = PFS N = 1,110 Median FU: NR	Sunitinib	31	25	8.4 (8.3, 10.9)	9.5 (8.3, 11.1)	28.3 (26.0, 35.5)	29.1 (25.4, 33.1)
				p=0.03		1.05 [0.90, 1.22]		0.92 [0.79, 1.06]	
	VEG105192 (87, 88)	Phase III RCT aRCC 1° EP = PFS N = 435	Placebo	32 (24.3, 38.9)	4 (0.0, 8.1)	11.1 (NR)	2.8 (NR)	22.9 (17.6, 25.4)	23.5 (12.0, 34.3)
				NR		0.40 [0.27, 0.60]		1.01 [0.72, 1.42]	
Sunitinib	A6181034 (NCT00083889) (89)	Phase III RCT mRCC 1° EP = PFS N = 750 Median FU: NR	IFN-α	47 (42, 59)	12 (9, 16)	11 (11, 13)	5 (4, 6)	26.4 (23.0, 32.9)	21.8 (17.9, 26.9)
				p< 0.001		0.54 [0.45, 0.64]		0.82 [0.67, 1.0]	

Key: 1° EP, primary endpoint; aRCC, advanced renal cell carcinoma; CI, confidence interval; DC, discontinuation; EP, endpoint; FU, follow-up; HR, hazard ratio; IFN-α, interferon-alpha; mo, months; mRCC, metastatic renal cell carcinoma; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor; yrs, years.
Notes: [a], stratified hazard ratio. *Italic text presents data for a mixed population of treatment-naïve and treatment-exposed patients*; [b], COMPARZ was a noninferiority study.

A.1.4 Equality considerations

No equality considerations have been identified or are anticipated.

A.2 Clinical effectiveness

A.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical trial evidence for this submission from the current treatment landscape for previously untreated adults with advanced or metastatic RCC. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix C.

A.2.2 List of relevant clinical effectiveness evidence

The pivotal randomised controlled trial (RCT) providing evidence of the clinical benefits of cabozantinib with nivolumab for the treatment of advanced or metastatic RCC is the Phase III CheckMate 9ER trial, as summarised in

Table 5**.**

Table 5: Clinical effectiveness evidence

Study	CheckMate 9ER				
Trial number	NCT03141177				
Study design	Phase III, open-label, randomised trial				
Population	Adult patients with previously untreated, advanced or metastatic renal cell carcinoma.				
Intervention(s)	Cabozantinib with nivolumab				
Comparator(s)	Sunitinib				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	Not applicable as not requested by NICE in this pilot pathway appraisal
	No			No	
Rationale if trial not used in model	Pivotal trial supporting this indication				
Reported outcomes specified in the decision problem	• OS • PFS • Response rates (ORR, BOR, DoR, TTR) • Time on treatment • Adverse effects of treatment • HRQoL				

Study	CheckMate 9ER
Trial number	NCT03141177
All other reported outcomes	• Treatment exposure • Immunogenicity of nivolumab (Appendix G) • PFS after next line of treatment (PFS-2; Appendix G)
Key: BOR, best objective response; DoR, duration of response; HRQoL, health-related quality of life; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; TTR, time to treatment response.	

A.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A.2.3.1 Study design

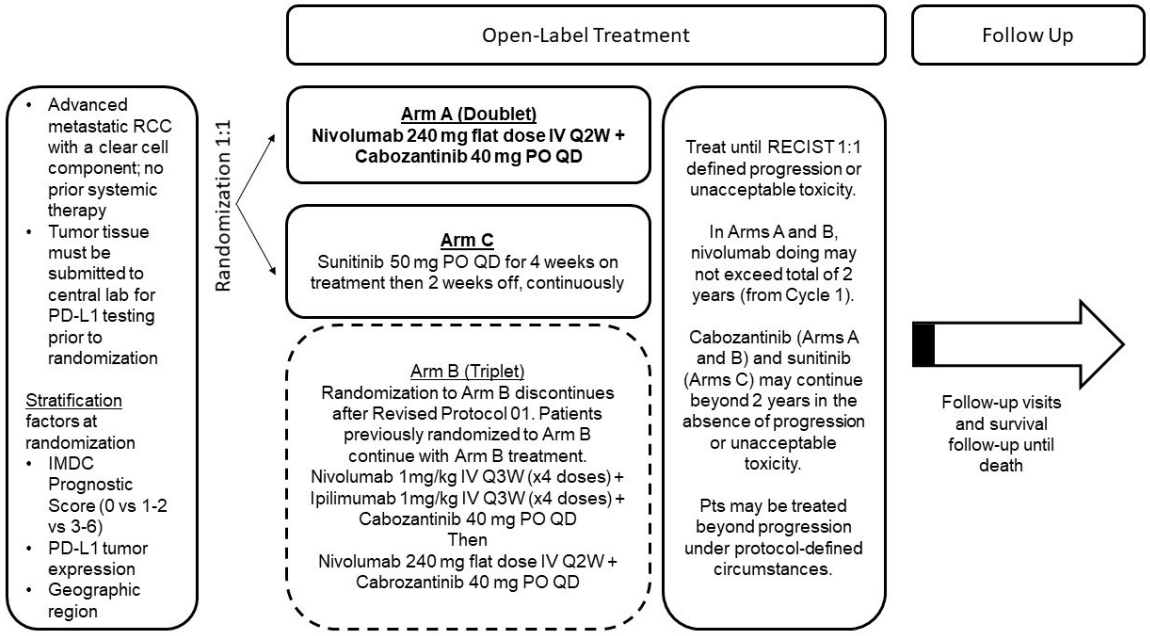
CheckMate 9ER is an ongoing Phase III, randomised, open-label study that provides evidence of the clinical benefit of cabozantinib with nivolumab compared with sunitinib monotherapy in adult patients with previously untreated, advanced, or metastatic RCC (90, 91). CheckMate 9ER is the pivotal trial supporting this indication and was the key trial used in regulatory submissions. The trial was conducted at 125 sites in 18 countries including three sites in the UK (90, 91). The study consisted of three phases: screening (> 3 to ≤ 12 months), treatment (approximately 2 years) and follow-up (at least 100 days for each patient) (90, 91).

Figure 3 presents a study design schematic for CheckMate 9ER. Note that a triplet regimen was also under investigation at study design, but randomisation to this arm was discontinued in an early protocol revision; only arms A and C were explored fully and are relevant to this appraisal (91). Patients were randomised in a 1:1 ratio to receive either cabozantinib with nivolumab (Arm A) or sunitinib (Arm C) (91). Patients are permitted to continue cabozantinib or sunitinib treatment until disease progression or unacceptable toxicity, whereas nivolumab is restricted to a maximum treatment period of 2 years (91). Select patients (regardless of treatment arm) that meet specific criteria (provided in Appendix C) may continue study treatment beyond Response Evaluation Criteria in Solid Tumours (RECIST)-defined disease progression (90). One of the key eligibility criteria is no prior systemic therapy for RCC, except one prior adjuvant or neoadjuvant therapy for completely resectable RCC (excluding agents that target VEGF or VEGF (R) and if recurrence occurred ≥ 6 months after the last dose of adjuvant or neoadjuvant therapy (90). Patients who

discontinue study treatment will be followed until death or study conclusion to obtain survival data; treatment cross-over was not permitted (90).

Regarding dose, reductions were permitted with cabozantinib and sunitinib but not with nivolumab. Furthermore, dose delays were permitted for managing AEs experienced during nivolumab, cabozantinib, or sunitinib treatment, and dosing of nivolumab could be delayed without delaying cabozantinib dosing if toxicity was felt to be related to only nivolumab, and vice versa (91).

Figure 3: CheckMate 9ER study design schematic



Key: DMC, data monitoring committee; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenous; PD-L1, programmed death-ligand 1; PO, orally by mouth; Pts, patients; Q2W, every 2 weeks; Q3W, every 3 weeks; QD, once daily; RCC, renal cell carcinoma.
Source: CheckMate 9ER clinical study report, 2020, Choueiri et al., 2021 (90, 91)

The primary endpoint of the CheckMate 9ER study was PFS, assessed per blinded independent central review (BICR) and defined as the time between the date of randomisation and the date of documented progression per RECIST 1.1, or death due to any cause (91).

A.2.3.2 Comparative summary of the methodology of the CheckMate 9ER trial

Table 6 presents a summary of the CheckMate 9ER methodology. Key eligibility criteria for patients are included in this table; the full criteria are presented in Appendix C.

Table 6: Summary of CheckMate 9ER methodology

Trial number	NCT03141177
Location	125 sites in 18 countries: Argentina, Australia, Brazil, Chile, Czechia, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, Turkey, the UK, and the US.
Trial design	Phase III, open-label, randomised trial
Key eligibility criteria for patients	**Inclusion criteria** • Histological confirmation of RCC with a clear cell component, including patients who may also have sarcomatoid features • Advanced (i.e., not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC • No prior systemic therapy for RCC except one prior adjuvant or neoadjuvant therapy for completely resectable RCC (excluding agents that target VEGF or VEGF receptors) and if recurrence occurred ≥ 6 months after the last dose of adjuvant or neoadjuvant therapy • Karnofsky performance status ≥ 70% • Measurable disease as per RECIST v1.1 per investigator • Either a formalin-fixed, paraffin-embedded tissue block or unstained tumour tissue sections • Patients with favourable, intermediate- or poor-risk categories. To be eligible for the intermediate-risk cohort, at least one of the following prognostic factors as per IMDC must be present; to be eligible for the poor-risk cohort, at least three of the following need to be present: − Karnofsky performance status equal to 70% o Less than 1 year from initial diagnosis (including original localised disease if applicable) to randomisation o Haemoglobin < LLN o Corrected calcium concentration > 10 mg/dL o Absolute neutrophil count > ULN o Platelet count > ULN Note: if none of the above factors are present, patients are only eligible for the favourable-risk cohort • Males and females aged ≥ 18 years or alternative age of majority (see list of included countries) **Exclusion criteria** • Any active CNS metastases. Patients with treated, stable CNS metastases for at least 1 month are eligible if they meet the following criteria: o Treated CNS metastases are defined as having no ongoing requirement for corticosteroids for at least 2 weeks prior to randomisation and no evidence of progression or haemorrhage after treatment completed at least 1 month prior to randomisation, as ascertained by clinical examination and brain imaging (MRI or CT) • Any active, known, or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic

	treatment, or conditions not expected to recur in the absence of an external trigger (e.g., coeliac disease) are permitted to enrol • Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomisation. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease • Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured • Any tumour invading the superior vena cava or other major blood vessels • Any tumour invading the gastrointestinal tract or any evidence of endotracheal or endobronchial tumour within 30 days prior to randomisation • Known history of positive test for HIV or known AIDS • Known medical condition (e.g., a condition associated with diarrhoea or acute diverticulitis, aortic aneurysm, aortic dissection) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results • History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, bowel obstruction, or gastric outlet obstruction within the past 6 months prior to randomisation • Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of cabozantinib or sunitinib • Evidence of active bleeding or bleeding susceptibility; or medically significant haemorrhage within prior 3 months prior to randomisation • Uncontrolled adrenal insufficiency • History of cerebrovascular accident including transient ischaemic attack within the past 6 months prior to randomisation • History of deep vein thrombosis or pulmonary embolism within past 6 months prior to randomisation unless stable, asymptomatic, and treated with low-molecular-weight heparin for at least 3 weeks prior to randomisation • Any unstable cardiac arrhythmia within 6 months prior to randomisation • Poorly controlled hypertension (systolic blood pressure > 150 mmHg, or diastolic blood pressure > 90 mmHg), despite antihypertensive therapy • History of any of the following cardiovascular conditions within 6 months of randomisation: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, Class III or IV congestive heart failure, as defined by the New York Heart Association • Any radiological or clinical evidence of pancreatitis within 30 days prior to randomisation • Inability to swallow oral medications

	• Prior treatment with therapy targeting VEGF, MET, AXL, KIT, or RET (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, sorafenib, lenvatinib, bevacizumab and cabozantinib) • Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways • Concomitant strong CYP3A4 inducers or inhibitors within 14 days prior to randomisation • Concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, thrombin or factor Xa inhibitors. Aspirin (up to 325 mg/day) and prophylactic and therapeutic low-molecular-weight heparin are permitted • Major surgery less than 6 weeks – and nephrectomy less than 4 weeks – prior to randomisation, with complete wound healing and no ongoing post-operative complications • Any of the following prior radiotherapy procedures: − Radiotherapy to the thoracic cavity or abdomen within 4 weeks prior to randomisation o Radiotherapy to bone lesions within 2 weeks prior to randomisation o Radiotherapy to any other site within 4 weeks prior to randomisation **Note:** In all cases, there must be complete recovery and no ongoing complications from prior radiotherapy • Ejection fraction ≤ 50% on screening echocardiogram or MUGA • WBC < 2000/μL • Neutrophils < 1500/μL • Platelets < 100 x 103/μL • Haemoglobin < 9.0 g/dL (support with transfusion is acceptable) • Serum creatinine > 1.5 x ULN unless calculated creatinine clearance ≥ 40 mL/min (using the Cockcroft–Gault formula) • AST/ALT > 3.0 x ULN • Total bilirubin > 1.5 x ULN (except patients with Gilbert Syndrome, who must have a total bilirubin level of < 3.0 x ULN) • Urine protein/creatinine ratio > 1.5, unless 24-hour urine protein is ≤ 1.5 g • International normalised ratio > 1.5 • Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., hepatitis B surface antigen (HBsAg) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative)
Settings and locations where the data were collected	An independent DMC was set up to provide oversight of patient safety. The DMC reviewed all data at the planned interim analyses and also provided recommendations to the Sponsor regarding continuation of the study. Data were collected locally by fully trained investigators. Site monitoring and pre-specified data validation checks were regularly conducted to ensure data quality.

Trial drugs	**Arm A** Nivolumab 240 mg IV Q2W combined with cabozantinib 40 mg orally once daily • Nivolumab is administered until disease progression or unacceptable toxicity with maximum treatment of 2 years • Cabozantinib was administered until disease progression or unacceptable toxicity (no limit on treatment duration) **Arm C** Sunitinib 50 mg orally once daily for 4 weeks, followed by 2 weeks off-treatment (6-week cycle). • Sunitinib cycles were continued until disease progression or unacceptable toxicity (no limit on treatment duration)
Dose modifications	Dose reductions were permitted with cabozantinib and sunitinib but not with nivolumab. Dose holds/delays were permitted for managing AEs experienced during nivolumab, cabozantinib, or sunitinib treatment, and dosing of nivolumab can be delayed without delaying cabozantinib dosing if toxicity is felt to be related to only nivolumab, and vice versa: • For nivolumab, a dose was considered as delayed if the delay exceeded 3 days • For cabozantinib, daily dose of 0 mg entered with CRF reason 'AE' was considered a delay if cabozantinib was given daily ○ If cabozantinib was given every other day, then more than one 0 mg daily dose entered with CRF reason 'AE' consecutively was considered as delay • For sunitinib, a dose was considered delayed if patients had 0 mg with a CRF reason 'AE'
Permitted and disallowed concomitant medication	The following medications are prohibited during the study: • Immunosuppressive agents • Immunosuppressive doses of systemic corticosteroids (except those stated below) • Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents) • Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalised locally • Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted, in the absence of active auto immune disease.
Primary outcomes (including scoring methods and	PFS per BICR, defined as the time between the date of randomisation and the first date of the documented progression per RECIST 1.1, or death due to any cause, whichever occurs first.

timings of assessments)	The first post-baseline tumour assessment was performed at Week 12 (± 7 days). Subsequent tumour assessments were performed every 6 weeks until Week 60, then every 12 weeks until radiographic progression.

Other outcomes used in the economic model/specified in the scope	**Secondary outcomes**
	• OS, defined as the time between the date of randomisation and the date of death due to any cause. Death status was reviewed after 30 days (FU1), 100 days (FU2) and then every 3 months for patients discontinuing from the study for reasons other than death.
	• Response rates − ORR per BICR, defined as the proportion of randomised patients who achieve a best response of CR or PR per RECIST 1.1
	  ○ BOR, defined as the best response designation recorded between the date of randomisation and the date of objectively documented progression per RECIST 1.1 or the date of subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first
	  ○ DoR, defined as the time between the date of first confirmed documented response (CR or PR) to the date of first documented progression per RECIST 1.1 or death due to any cause, whichever occurs first
	  ○ TTR per BICR, defined as the time from randomisation to the date of the first confirmed documented response (CR or PR) per RECIST 1.1
	• Safety
	  ○ Incidence of AEs
	  ○ Incidence of SAEs
	  ○ AEs leading to discontinuation
	  ○ AEs leading to deaths
	  ○ Laboratory abnormalities and changes from baseline
	Safety assessments were performed at each visit, and AEs were recorded at each visit. AEs were documented for a minimum of 100 days after last dose.
	Exploratory outcomes
	• PFS-2, defined as the time from randomisation to objectively documented progression after the next line of treatment, per investigator assessment, or to death from any cause, whichever occurred first
	• HRQoL, assessed by the NCCN FKSI-19 and the EQ-5D-3L. HRQoL assessment was performed on Day 1 of each treatment cycle, prior to any study-related procedures

Pre-planned subgroups	Pre-planned subgroup analyses were conducted based on several demographic and clinical characteristics at baseline, including: • Baseline IMDC prognostic score (favourable-risk vs intermediate-risk vs poor-risk) • PD-L1 expression status (≥ 1% vs < 1%) • Region (US/Canada/Europe vs rest of world)

	• Site of metastasis

Key: AE, adverse event; AIDS, acquired immunodeficiency syndrome; AJCC, American Joint Committee on Cancer; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AXL, anexelekto; BICR, blinded independent central review; BOR, best overall response; CNS, central nervous system; CR, complete response; CRF, case report form; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DMC, data monitoring committee; DoR, duration of response; EQ-5D-3L, 3-level EQ-5D; FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index; FU1, follow-up visit 1; FU2, follow-up visit 2; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; HBsAg; hepatitis B surface antigen; HCV, hepatitis C virus; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; KIT, LLN, lower limit of normal; MET, mesenchymal-epithelial transition factor; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NCCN, National Comprehensive Cancer Network; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS-2, progression-free survival on next line of treatment; PR, partial response; Q2W, every 2 weeks; RCC, renal cell carcinoma; RET, rearranged during transfection; RECIST, Response Evaluation Criteria In Solid Tumours; RNA, ribonucleic acid; SAE, serious adverse event; TTR, time to response; ULN, upper limit of normal; UK, United Kingdom; US, United States; VEGF, vascular endothelial growth factor; WBC, white blood cell.
Source: Choueiri et al., 2021; CheckMate 9ER clinical study report, 2020 (90, 91).

A.2.3.3 Baseline characteristics

Table 7 presents the baseline characteristics for all patients randomised to the cabozantinib with nivolumab and sunitinib arms of the study.

Overall, baseline characteristics were well balanced between each treatment arm. The median age of all randomised patients was similar between treatment arms (cabozantinib with nivolumab: 62.0 years; sunitinib: 61.0 years), and most patients were white (cabozantinib with nivolumab, 82.7%; sunitinib, 81.1%) and male (cabozantinib with nivolumab, 77.1%; sunitinib, 70.7%) (90, 91). The proportion of patients with two or more sites of metastasis was similar between treatment arms (cabozantinib with nivolumab, 80.2%; sunitinib, 78.0%), with the most common sites being the lung, lymph node and bone (91). Of patients who had a baseline tumour tissue quantifiable for testing for programmed death-ligand 1 (PD-L1), the proportion of patients positive for PD-L1 expression (≥ 1%) at baseline was consistent between treatment arms: 25.7% in cabozantinib with nivolumab arm and 25.3% in the sunitinib arm (91). In addition, the majority of patients in the study had disease that was classified as being intermediate- or poor-risk per IMDC score (cabozantinib with nivolumab, 77.1%; sunitinib, 78.0%) (91).

The majority of patients received no prior systemic therapy, with only 3 (0.9%) patients in the cabozantinib with nivolumab arm, and 2 (0.6%) patients in the sunitinib arm receiving prior systemic anticancer therapy, all of which were adjuvant systemic therapies as per the study protocol (90, 91).

Table 7: Baseline characteristics of all randomised patients, CheckMate 9ER

Randomised population (n = 651)		
	Cabozantinib with Nivolumab (n = 323)	**Sunitinib (n = 328)**
Median age, years (min, max)	62.0 (29, 90)	61.0 (28, 86)
Male, n (%)	249 (77.1)	232 (70.7)
Race, n (%)		
White	267 (82.7)	266 (81.1)
Black or African American	1 (0.3)	4 (1.2)
Asian	26 (8.0)	25 (7.6)
American Indian or Alaska Native	3 (0.9)	2 (0.6)
Others*	26 (8.0)	30 (9.1)

KPS, n (%)		
100	147 (45.5)	129 (39.3)
90	110 (34.1)	112 (34.1)
80	52 (16.1)	67 (20.4)
70	14 (4.3)	18 (5.5)
IMDC prognostic score, n (%)		
Favourable (0)	74 (22.9)	72 (22.0)
Intermediate (1–2)	188 (58.2)	188 (57.3)
Poor (3–6)	61 (18.9)	68 (20.7)
PD-L1 expression, n (%)		
≥ 1%	83 (25.7)	83 (25.3)
<1%	240 (74.3)	245 (74.7)
Common sites of metastasis, n (%)		
Lung	238 (73.7)	249 (75.9)
Lymph node	130 (40.2)	131 (39.9)
Bone	78 (24.1)	72 (22.0)
Liver	73 (22.6)	53 (16.2)
Number of sites with ≥ 1 target/non-target lesion, n (%)		
1	63 (19.5)	69 (21.0)
≥ 2	259 (80.2)	256 (78.0)
Sarcomatoid features, n (%)		
Yes	34/313 (10.9)	41/319 (12.9)
No	279/313 (89.1)	278/319 (87.1)
Prior nephrectomy, n (%)		
Yes	222 (68.7)	233 (71.0)
No	101 (31.3)	95 (29.0)
Prior systemic therapy, n (%)		
Adjuvant/Neo-adjuvant	3 (0.9)	2 (0.6)
Metastatic	0	0
Prior surgery, n (%)		
Yes	262 (81.1)	266 (81.1)
No	61 (18.9)	62 (18.9)
Prior radiotherapy, n (%)		
Yes	46 (14.2)	45 (13.7)
No	277 (85.8)	283 (86.3)

Key: IMDC, international metastatic renal cell carcinoma database consortium; KPS, Karnofsky performance status; PD-L1, programmed death-ligand 1.
Notes: *, including Hispanic, Latino, unknown, and not specific.
Source: Choueiri et al., 2021; CheckMate 9ER clinical study report, 2020 (90, 91).

A.2.3.4 Methods used for expert elicitation or expert opinion

The company is aware that the external assessment group (EAG) are conducting a structured expert elicitation as part of this appraisal; as such, no expert elicitation has been undertaken by the company.

A.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The patient disposition data for CheckMate 9ER are fully detailed in Appendix C, alongside a Consolidated Standards of Reporting Trials diagram of patient flow. In total, 651 patients were enrolled to the cabozantinib with nivolumab and sunitinib treatment arms, and 640 were treated (90). Three patient analysis populations relevant to this submission were evaluated during the study (90, 92):

- The randomised (intention-to-treat) population (n = 651 [cabozantinib with nivolumab: 323; sunitinib: 328]), defined as all patients randomised to any treatment arm
- The treated population (n = 640 [cabozantinib with nivolumab: 320; sunitinib: 320]), defined as all randomised patients who received at least one dose of study treatment
- The immunogenicity population (n = 263), defined as all patients with available data treated with nivolumab

These populations and their relevant sections are described in Table 8.

Table 8: Populations used in this study

Population type		N for cabozantinib with nivolumab	N for sunitinib	Sections
Randomised (intention-to-treat) population, (all-treated) (N = 651)	All patients randomised to any treatment arm	323	328	A.2.6.1.- A.2.6.4., A.2.7; A.2.8.1.1 – A.2.8.1.3; A.2.8.2.1 – A.2.8.2.4
Treated population (as-treated) (N = 640)	All the patients who underwent randomisation and received at least one dose of study treatment	320	320	A.2.8.1.4
Immunogenicity population (*subset of as-treated population*) (N = 263)	All patients with available data treated with nivolumab	263 (only nivolumab)	-	Appendix G
Key: N, number of patients.				

Table 9 presents the hypothesis and associated statistical analysis methods adopted in the CheckMate 9ER trial.

Statistical analysis plans were developed and approved prior to study initiation. The primary endpoint (PFS) analysis occurred after 9 months of follow-up on all randomised patients (90). Three (two interim and one final) analyses of OS are planned: the first interim analysis was conducted at the time of final PFS analysis; the second interim and final analyses are expected once 211 deaths among randomised patients have been observed (83% targeted OS events) (90). Objective response rate (ORR) was also analysed at the time of the PFS analysis (91).

Data presented for the CheckMate 9ER study in this submission are based on a database lock 3 date: 24 June 2021, with the median study follow-up of 32.9 (30.4-35.9) months (92, 93).

- **NOTE: The latest update, database lock 4 date: 27 May 2022 will be provided to NICE and the EAG by 12th April 2023 after this document has been submitted. This will contain data with a median follow-up of 44.0 months.**

All efficacy analyses were conducted in the randomised population; safety analyses were conducted in the treated and immunogenicity populations (90, 93). The overall alpha for the CheckMate 9ER study is 0.05 (two-sided). PFS was evaluated for treatment effect at an alpha of 0.05 (two-sided), with at least 95% power. OS was evaluated for treatment effect at an alpha level of 0.05 (two-sided) with 80% power, accounting for the two interim analyses (92).

Table 9: Summary of statistical analyses, CheckMate 9ER

Hypothesis objective	Treatment with cabozantinib with nivolumab will demonstrate an improvement in PFS per BICR compared with sunitinib monotherapy in participants with previously untreated, advanced or metastatic RCC.
Statistical analysis	The overall alpha for this study is 0.05 (two-sided). This is split with 0.049 (two-sided) to evaluate PFS after penalising 0.001 (two-sided) to evaluate ORR since it is planned to have an early assessment of ORR. PFS will be evaluated for treatment effect at an alpha of 0.049 (two-sided), with at least 90% power. No interim analysis of PFS is planned. OS will be evaluated for treatment effect at an alpha level of 0.049 (two-sided) with 75% power, accounting for two formal interim analyses to assess efficacy. ORR will be analysed on a descriptive basis and will occupy an administrative adjustment of alpha of 0.001. The primary formal comparisons of PFS (Arm A vs Arm C) and interim and final comparisons of OS (Arm A vs Arm C) will be conducted using a two-sided 0.049 stratified log-rank test, with IMDC scores, PD-L1 tumour expression, and region at screening per IRT as stratification factors among all randomised participants. Median PFS/OS will be estimated via the Kaplan–Meier product limit method. Two-sided 95% CI for the median PFS/OS will be computed for each randomised arm using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors, corresponding to the comparison of PFS/OS. ORRs and corresponding 95% exact CIs will be calculated using the Clopper–Pearson method within each treatment arm. A two-sided 95% CI for difference of response rate between Arm A and Arm C will also be computed.
Sample size, power calculation	The sample size of this study accounts for the primary endpoint of PFS per BICR in Arm A versus Arm C. Assuming a 25% screen failure rate, it is expected that approximately 774 participants will need to be enrolled in order to randomise 580 participants (290 per arm) in a 1:1 ratio. To represent the normal frequency of having favourable-risk disease in metastatic RCC, the number of enrolled participants with favourable-risk disease was capped at approximately 25%; thus, at most 194 participants with favourable-risk disease (97 per arm) were enrolled to randomise 146 participants with favourable-risk disease in a 1:1 ratio. The rest

	of the enrolled participants will provide approximately 434 randomised participants with intermediate-/poor-risk disease (217 per each arm). The primary endpoint analysis will be triggered by approximately 285 events. The 285 PFS events provide at least 90% power to detect an HR of 0.68 for PFS of Arm A versus Arm C with a type I error of 0.049 (two-sided). The HR of 0.68 corresponds to a 47% increase in the median PFS, assuming a median PFS of 18.2 months for Arm A and 12.4 months for Arm C. It is projected that an observed HR of 0.792 or less, which corresponds to a 3.3 month or greater improvement in median PFS (12.4 versus 15.7 months), would result in a statistically significant improvement in PFS for the Arm A versus Arm C comparison. If the formal analysis of PFS among all randomised participants is statistically significant, the formal interim analysis of OS among all randomised participants will be tested, as per hierarchical testing procedure. Among all randomised participants, approximately 337 events (i.e., deaths) in Arm A and Arm C provides at least 75% power to detect an HR of 0.76 for OS of Arm A and Arm C, with an overall type 1 error of 0.049 (two-sided) for each test. The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 43.4 months for Arm A and 33 months for Arm C.
Data management, patient withdrawals	**PFS** • Patients who die without a reported progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumour assessment • Patients who did not have any on-study tumour assessments and did not die will be censored on their date of randomisation. Patients who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumour assessment prior to the initiation of first subsequent anti-cancer therapy **OS** • A patient who has not died will be censored at the last known alive date **ORR** • Patients who neither progress nor die will be censored on the date of their last tumour assessment • Responders who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumour assessment prior to the initiation of first subsequent anti-cancer therapy
Key: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; IRT, Interactive Response Technology; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCC, renal cell carcinoma. **Source**: CheckMate 9ER clinical study report, 2020 (90)	

A.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 10 presents a summary of quality assessment for CheckMate 9ER. Further details for complete quality assessment can be found in Appendix C.

CheckMate 9ER was conducted in accordance with Good Clinical Practice as defined by the International Council on Harmonisation, and in accordance with the ethical principles underlying the European Union Directive (2001/20/EC) and the Declaration of Helsinki (90, 92). All protocol amendments and patient-informed consent forms received approval by the Institutional Review Board/Independent Ethics Committee at each site, prior to the initiation of study; it was determined that there was no impact from protocol deviations on the interpretability of study results (90, 92). The study was conducted by qualified investigators, in accordance with a single protocol to promote consistency across sites and measures taken to minimise bias (90). In addition, CheckMate 9ER was monitored by an independent data monitoring committee (DMC) to provide independent oversight of safety, efficacy, and study conduct.

Although CheckMate 9ER was designed as an open-label trial (due to the distinct differences in administration methods between treatment arms), the efficacy endpoints are not subjectively assessed; therefore, a lack of blinding was not thought to have a considerable effect on the outcome of the study (90). Six patients did withdraw their consent to participate in the study upon randomisation to sunitinib, compared with one patient randomised to cabozantinib with nivolumab, suggesting the open-label design had a small impact on attrition. However, the withdrawal of consent represented < 2% of patients enrolled to the sunitinib arm, which would not have an impact on the statistical plan and thus the overarching conclusions of the study (90).

Baseline demographics and disease characteristics for patients in CheckMate 9ER were generally well-balanced between treatment arms (see A.2.3.2 Comparative summary of the methodology of the CheckMate 9ER trial), and the overall population was representative of the general patient population with aRCC (90). Disease evaluation and safety evaluation methods are consistent with other studies of RCC therapy, and outcome assessments were all conducted in accordance with trial-validated methodology (90). However, in recognition of the limitations of validated RECIST criteria for assessing immunotherapy drugs, patients were allowed to receive treatment beyond RECIST-defined progression to better reflect clinical practice (90). Indeed, the trial is thought to reflect routine clinical practice in England

with respect to population, comparator choice, treatment administration and outcomes being assessed (see section A.2.10 Interpretation of clinical effectiveness and safety evidence for further details). It is also important to note that alongside clinical efficacy and safety outcomes, HRQoL outcome was also measured, as requested by reimbursement agencies, which was included in the trial as an exploratory endpoint.

Table 10: Quality assessment for CheckMate 9ER

Was randomisation carried out appropriately?	Yes
	Randomisation was carried out centrally using an interactive response technology system.
Risk of bias	**Low**
Was the concealment of treatment allocation adequate?	Yes
	Randomisation was carried out centrally using an interactive response technology system.
Risk of bias	**Low**
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
	Baseline demographics and clinical characteristics were well balanced between treatment arms.
Risk of bias	**Low**
Were the care providers, patients and outcome assessors blind to treatment allocation?	CheckMate 9ER is an open-label study, so care providers and patients are not blinded to treatment allocation. However, efficacy endpoints are objectively assessed by a blinded independent review committee in the case of tumour assessment-based endpoints.
Risk of bias	**Low**
Were there any unexpected imbalances in drop-outs between groups?	Small
	There was a slightly higher rate of consent withdrawal in patients randomised to sunitinib compared with that of patients randomised to cabozantinib with nivolumab (1.8% vs 0.3%), but the number of withdrawals was still very low across both treatment arms.
Risk of bias	**Low**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Risk of bias	**Low**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
	All randomised patients were included in the efficacy analysis set with standard censoring methods applied to handle missing data.
Risk of bias	**Low**
Source: CheckMate 9ER clinical study report, 2020 (90)	

A.2.6 Clinical effectiveness results of the relevant studies

All results in this section are presented for the randomised population (n = 651). At the time of primary analysis (data cut-off: 26 April 2021; database lock 3 date: 24 June 2021), the median study follow-up was 32.9 (30.4-35.9) months, the data for which is presented in this document (92, 93).

- **NOTE: The latest update, database lock 4 date: 27 May 2022 will be provided to NICE and the EAG by 12th April 2023 after this document has been submitted. This will contain data with a median follow-up of 44.0 months.**

A.2.6.1 Primary efficacy outcome: Progression-free survival

Table 11 presents a summary of PFS per BICR assessment. A total of 430 BICR-assessed PFS events were observed at data cut-off: 207 (64.1%) in the cabozantinib with nivolumab arm and 223 (68.0%) in the sunitinib arm (93). A total of 221 patients were censored, mostly due to patients still being progression-free and on treatment (93).

PFS was significantly improved with cabozantinib with nivolumab versus sunitinib with a doubling of PFS (median: 16.6 versus 8.3 months), resulting in a HR of 0.56 (95% confidence interval [CI]: 0.46, 0.68; p<0.0001) (92). Throughout the study, PFS rates were consistently higher with cabozantinib with nivolumab compared with sunitinib; at 6 months, the PFS rates were 79.6% versus 60.0%, at 9 months, PFS rates were 68.3% versus 47.8%, at 12 months were 58.1% versus 36.9% (93), and at 24 months were 39.5% versus 20.9%, respectively (92). Separation of the Kaplan–Meier (KM) curves occurred early (in favour of cabozantinib with nivolumab), with no crossing of the curves (Figure 4). Overall, the PFS results show an extension in progression-free living with cabozantinib with nivolumab among treatment-naïve patients with advanced or metastatic RCC compared with currently available first-line TKI monotherapy. Further, the analysis of PFS on next line of treatment (PFS-2), showed cabozantinib with nivolumab continued to provide clinically meaningful improvements as compared to sunitinib (93) (refer to Appendix G for details of PFS-2).

Table 11: Summary of progression-free survival per blinded independent central review assessment– All Randomised Subjects

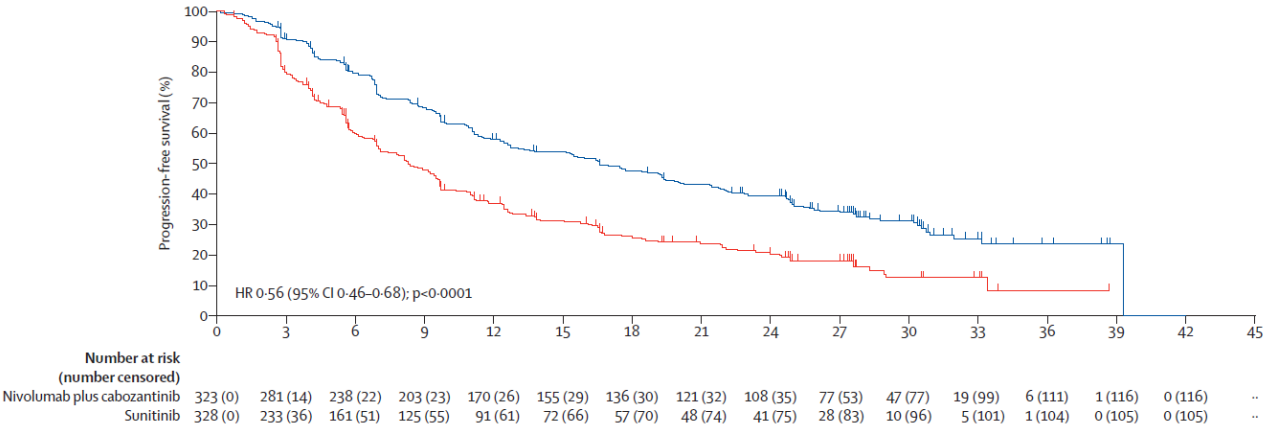
	Cabozantinib with Nivolumab (n = 323)	Sunitinib (n = 328)
PFS events, n (%)	207 (64.1)	223 (68.0)
Censored, n (%)	116 (35.9)	105 (32.0)
Median PFS, months (95% CI) [a]	16.6 (12.8, 19.8)	8.3 (7.0, 9.7)
HR (95% CI) [b]	0.56 (0.46, 0.68)	
p-value [c, d]	<0.0001	
PFS rate at 6 months, % (95% CI) [a]	79.6 (74.7, 83.7)	60.0 (54.0, 65.4)
PFS rate at 9 months, % (95% CI) [a]	68.3 (62.7, 73.2)	47.8 (41.8, 53.6)
PFS rate at 12 months, % (95% CI) [a]	58.1 (52.3, 63.4)	36.9 (31.2, 42.7)
PFS rate at 24 months, % (95% CI) [a]	39.5 (33.9, 45.1)	20.9 (16.0, 26.3)

Key: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Notes: [a], based on Kaplan–Meier estimates; [b], stratified Cox proportional hazards model. Hazard ratio is cabozantinib with nivolumab over sunitinib; [c], 2-sided p-values from stratified regular log-rank test; [d], log-rank test stratified by IMDC prognostic risk score (0, 1–2, 3–6), PD-L1 tumour expression (≥ 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, rest of world) as entered in the IRT system

Source: Motzer 2022 (92); CheckMate 9ER clinical study report addendum 2021 (93)

Figure 4: Kaplan–Meier curve of progression-free survival per blinded independent central review



Source: Motzer 2022 (92)

A.2.6.2 Secondary efficacy outcome: Overall survival

Table 12 presents a summary of OS. At the time of primary analysis, the minimum and median follow-up for OS across both treatment arms was 25.4 and 32.9 months, respectively, and there were a total of 271 OS events (deaths): 121 (37.5%) in the cabozantinib with nivolumab arm and 150 (45.7%) in the sunitinib arm (92). A total of 380 patients were therefore censored, mostly due to patients still being alive and on treatment (93).

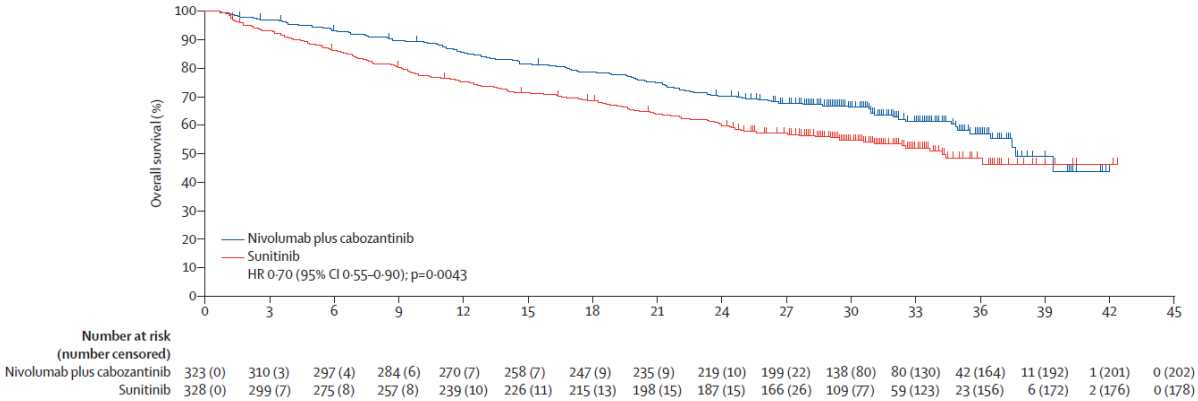
OS was significantly improved with cabozantinib with nivolumab versus sunitinib, with a HR of 0.70 (95% CI: 0.55, 0.90; p value =0.0043) (92). Median OS was 37.7 (95% CI: 35.5, not estimable [N.E]) months with cabozantinib with nivolumab and 34.3 (95% CI: 29.0, N.E.) months with sunitinib (92), as shown in Figure 5. Throughout the study, OS rates were consistently higher with cabozantinib with nivolumab compared with sunitinib; at 6 months, the OS rates were 93.1% versus 86.0%, at 9 months the OS rates were 89.7% versus 80.4%, at 12 months were 85.5% versus 75.3% (93), at 24 months were 70.0% versus 60.0% (92), respectively.

Table 12: Summary of overall survival– All randomised subjects

	Cabozantinib with Nivolumab (n = 323)	Sunitinib (n = 328)
Events, n (%)	121 (37.5)	150 (45.7)
Censored, n (%)	202 (62.5)	178 (54.3)
Median OS, months (95% CI) [a]	37.7 (35.5, N.E.)	34.3 (29.0, N.E.)
HR (95% CI) [b]	0.70 (0.55, 0.90)	
p-value [c, d]	0.0043	
OS rate at 6 months, % (95% CI) [a]	93.1 (89.8, 95.4)	86.0 (81.7, 89.4)
OS rate at 9 months, % (95% CI) [a]	89.7 (85.8, 92.5)	80.4 (75.6, 84.3)
OS rate at 12 months, % (95% CI) [a]	85.5 (81.2, 89.0)	75.3 (70.2, 79.7)
OS rate at 24 months, % (95% CI) [a]	70.0 (65.0, 75.0)	60.0 (55.0, 66.0)

Key: CI, confidence interval; HR, hazard ratio; N.E., not estimable; OS, overall survival.
Notes: [a], based on Kaplan–Meier estimates; [b], stratified Cox proportional hazards model. Hazard ratio is cabozantinib with nivolumab over sunitinib; [c], log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% vs <1% or indeterminate) and region (US/Canada/W Europe/N Europe, rest of world) as entered in the IRT system. 2-sided p-values from stratified regular log-rank test; [d], log-rank test stratified by IMDC prognostic risk score (0, 1–2, 3–6), PD-L1 tumour expression (≥ 1% versus < 1% or indeterminate) and region (US/Canada/W Europe/N Europe, rest of world) as entered in the IRT system.
Source: Motzer 2022 (92); CheckMate 9ER clinical study report addendum 2021 (93)

Figure 5: Kaplan–Meier curve of overall survival in all randomised subjects



Source: Motzer 2022 (92)

A.2.6.3 Secondary efficacy outcome: Objective response rate

Table 13 presents a summary of response rates. The ORR was higher with cabozantinib with nivolumab versus sunitinib: 56.0% (95% CI: 50.0, 61.0) versus 28.0% (95% CI: 24.0, 34.0) (92). A higher proportion of patients in the cabozantinib with nivolumab arm achieved complete response (CR) and a partial response (PR) compared with patients in the sunitinib arm (CR: 12.0% versus 5.0%; PR: 43.0% vs 23.0%%), and a lower proportion of patients had progressive disease (PD: 6.0% vs 14.0%) (92). Furthermore, a higher proportion of patients achieved a CR or PR with cabozantinib with nivolumab versus sunitinib within the first 6 (49.8% versus 19.2%) and 12 (54.8% versus 26.5%) months of treatment (93).

Table 13: Summary of confirmed objective response by blinded independent central review – All randomised subjects

	Cabozantinib with Nivolumab (n = 323)	**Sunitinib (n = 328)**
ORR, n (% [95% CI] [a])	180 (56.0 [50.0, 61.0])	93 (28.0 [24.0, 34.0)
Confirmed BOR		
CR, n (%)	40 (12.0)	17 (5.0)
PR, n (%)	140 (43.0)	76 (23.0)
SD, n (%)	105 (33.0)	134 (41.0)
PD, n (%)	20 (6.0)	45 (14.0)
UTD, n (%)	18 (6.0)	55 (17.0)
Not reported	0	1 (<1.0)
Median TTR, months (IQR)	2.8 (2.8–4.2)	4.2 (2.8– 7.1)
Median DoR, months (95% CI) [b]	23.1 (20.2, 27.9)	15.1 (9.9, 20.5)

Key: BOR, best overall response; CI, confidence interval; CR, confirmed response; DoR, duration of response; IQR, interquartile range; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response; UTD, unable to determine
Notes: [a], CR+PR, confidence interval based on the Clopper and Pearson method; [b], based on Kaplan–Meier estimates. Data are n(%), unless otherwise specified. Response was assessed according to Response Evaluation Criteria in Solid Tumours version 1.1 by blinded independent central review.
Source: Motzer 2022 (92)

A.2.6.3.1. Best overall response

Best overall response (BOR) was defined as the best response recorded between randomisation and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy.

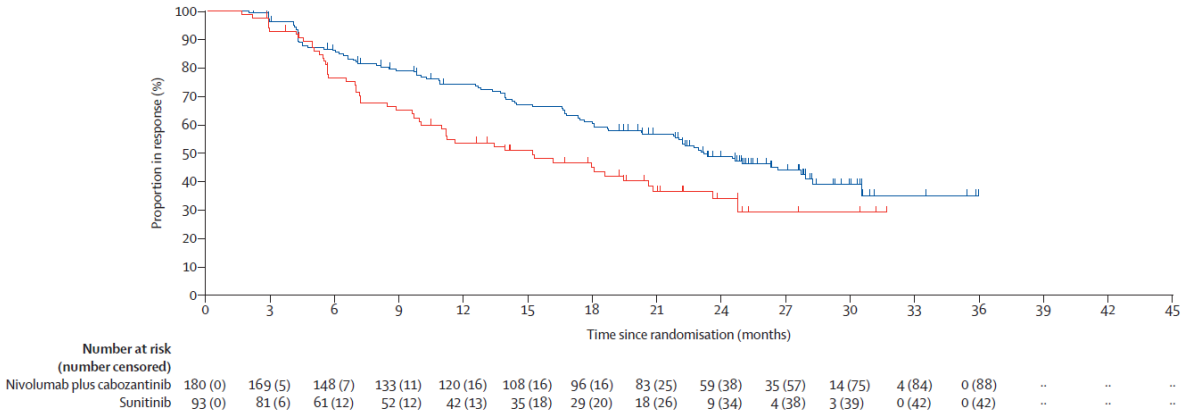
Per BICR assessment, in the cabozantinib with nivolumab arm compared with the sunitinib arm, a numerically higher proportion of subjects had a BOR of CR (12.0% versus 5.0%) or PR (43.0% versus 23.0%), and a numerically lower proportion of subjects had a BOR of PD (6.0% versus 14.0%) or UTD (6.0% versus 17.0%), due to various reasons including deaths prior to disease assessment (Table 13) (92).

Concordance between BICR and investigator-assessed BOR was high, with a concordance rate of 80.8% and 80.4% for cabozantinib with nivolumab and sunitinib arms, respectively (90).

A.2.6.4 Secondary efficacy outcome: Time to response and duration of response

More patients had a CR in the cabozantinib with nivolumab arm than in the sunitinib arm (40 [12%] vs 17 [5%]), and median time to response (TTR) was 2.8 months (interquartile range [IQR] 2·8–4·2) versus 4·2 months (IQR 2·8–7·1). Median duration of response (DoR) was 23·1 months (95% CI 20·2, 27·9) in the cabozantinib with nivolumab arm versus 15·1 months (95% CI 9·9, 20·5) with sunitinib arm, and 88 (49.0%) of 180 versus 42 (45.0%) of 93 responses were ongoing at database lock. Median time to CR (post-hoc analysis) was 11·5 months (IQR 5·6–19·2) in cabozantinib with nivolumab arm versus 7·1 months (IQR 4·2–19·2) with sunitinib arm; 26 (65.0%) of 40 versus 10 (59.0%) of 17 CR were ongoing at database lock (92). Figure 6 presents a KM plot of DoR.

Figure 6: Kaplan–Meier plot of duration of response with a Best Overall Response of Complete or Partial Response per Blinded Independent Central Review



Source: Motzer 2022 (92)

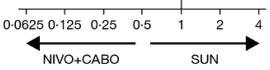
A.2.7 Subgroup analysis

The treatment effect of cabozantinib with nivolumab on PFS, OS and ORR per BICR was assessed in patient subgroups at baseline, using either prespecified (age, sex, geographical region, race, KPS, IMDC prognostic score, previous nephrectomy, previous radiotherapy, tumour PD-L1 expression, sarcomatoid features, disease stage at initial diagnosis, and bone metastasis) or post-hoc (liver metastasis and lung metastasis) analysis (92).

The HR point estimates in the pre-defined subgroups favoured cabozantinib with nivolumab in all clinically relevant subsets. Superior PFS was observed with cabozantinib with nivolumab over sunitinib among patients with sarcomatoid features, with previous nephrectomy, with liver metastasis, with bone metastasis, or with lung metastasis at baseline (Figure 7) (92). OS (Figure 8) and ORR (Figure 9) benefits were also generally observed with cabozantinib with nivolumab over sunitinib among patient subgroups of clinical interest at baseline including sarcomatoid features, with previous nephrectomy and organ sites of metastasis (92).

Figure 7: Forest Plot of Treatment on Progression-free survival according to predefined or post-hoc patient subgroup at baseline

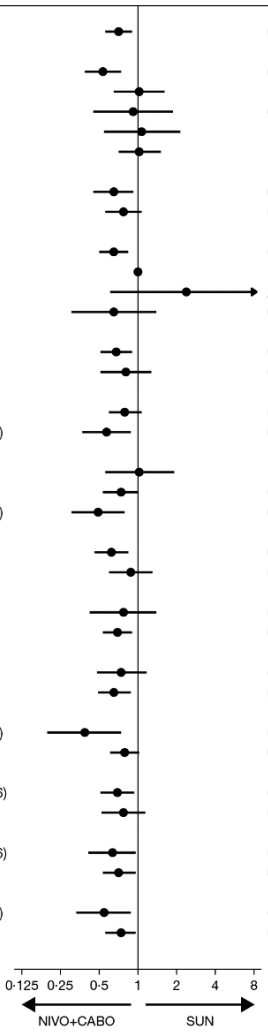
	N	Nivolumab plus cabozantinib group Events/patients	Median PFS (95% CI), months	Sunitinib group Events/patients	Median PFS (95% CI), months	Unstratified hazard ratio (95% CI)
Overall	651	207/323	16·59 (12·78–19·84)	223/328	8·31 (6·97–9·69)	0·56 (0·46–0·68)
Age group, years						
<65	401	119/191	16·59 (12·75–20·04)	151/210	7·85 (5·65–9·23)	0·50 (0·39–0·63)
≥65 and <75	188	65/103	17·51 (11·17–24·77)	55/85	9·53 (6·90–13·37)	0·67 (0·47–0·96)
≥75 and <85	56	19/27	15·38 (6·14–22·93)	16/29	11·20 (5·82–24·41)	0·75 (0·38–1·51)
≥85	6	2/2	9·00 (2·04–15·97)	1/4	9·69 (NE–NE)	1·22 (0·08–19·86)
≥75	62	21/29	15·38 (6·14–22·93)	17/33	11·20 (5·82–24·41)	0·82 (0·42–1·60)
≥65	250	88/132	15·97 (11·17–21·88)	72/118	9·69 (7·10–13·37)	0·70 (0·51–0·96)
Region						
USA/Canada/ W Europe/N Europe	319	97/158	19·15 (15·38–23·03)	103/161	9·56 (8·11–11·76)	0·54 (0·41–0·72)
Rest of the world	332	110/165	12·58 (9·72–19·32)	120/167	7·03 (5·65–9·43)	0·58 (0·44–0·75)
Race						
White	533	171/267	16·95 (13·08–21·78)	187/266	8·15 (6·80–9·40)	0·52 (0·42–0·64)
Asian	51	16/26	16·39 (6·97–NE)	9/25	24·48 (6·93–NE)	1·25 (0·55–2·84)
Other	61	20/29	9·99 (6·90–19·35)	23/32	8·31 (4·21–12·62)	0·73 (0·40–1·34)
Sex						
Male	481	160/249	17·48 (13·08–21·39)	161/232	8·38 (6·97–9·69)	0·52 (0·42–0·65)
Female	170	47/74	13·34 (9·07–21·78)	62/96	7·13 (5·88–11·17)	0·67 (0·46–0·99)
Karnofsky performance status						
100–90	499	157/257	19·15 (15·44–22·14)	159/242	9·69 (8·11–11·20)	0·57 (0·45–0·71)
<90	150	50/66	9·76 (6·93–15·97)	64/84	5·68 (4·11–8·15)	0·58 (0·40–0·85)
Baseline IMDC prognostic score (IRT)						
0	146	45/74	21·42 (13·08–24·77)	44/72	13·86 (9·56–18·46)	0·73 (0·48–1·11)
1–2	376	120/188	17·48 (12·29–20·27)	126/188	8·51 (7·00–9·76)	0·59 (0·46–0·76)
3–6	129	42/61	9·92 (5·91–17·68)	53/68	4·21 (2·92–5·62)	0·35 (0·23–0·55)
Previous nephrectomy						
Yes	455	139/222	19·38 (16·39–24·77)	161/233	8·90 (7·00–10·38)	0·52 (0·41–0·65)
No	196	68/101	11·30 (8·80–15·97)	62/95	7·06 (5·49–9·40)	0·66 (0·47–0·94)
Previous radiotherapy						
Yes	91	30/46	18·43 (12·75–24·87)	26/45	7·89 (3·98–9·76)	0·50 (0·29–0·86)
No	560	177/277	16·56 (12·29–19·84)	197/283	8·51 (6·97–9·69)	0·57 (0·46–0·70)
Baseline PD-L1 status per 1% cutoff						
≥1%	162	48/81	15·61 (8·71–25·72)	59/81	4·67 (3·15–9·69)	0·40 (0·27–0·60)
<1%	472	150/232	17·51 (15·18–21·39)	160/240	9·23 (7·85–9·76)	0·60 (0·48–0·75)
Sarcomatoid features*						
Yes	75	22/34	13·80 (5·62–NE)	33/41	4·21 (2·79–8·31)	0·34 (0·19–0·61)
No	557	178/279	17·48 (13·08–20·27)	184/278	9·23 (7·39–9·76)	0·60 (0·49–0·74)
Stage at initial diagnosis						
Stage IV	341	108/168	11·30 (9·36–17·68)	127/173	6·80 (5·32–8·38)	0·53 (0·41–0·69)
Non–stage IV	297	96/149	20·27 (16·49–24·77)	93/148	9·69 (8·31–12·39)	0·59 (0·44–0·79)
Bone metastasis						
Yes	152	53/79	16·59 (8·71–24·71)	49/73	5·32 (3·78–8·15)	0·41 (0·27–0·62)
No	499	154/244	16·59 (12·58–21·39)	174/255	9·46 (7·89–11·04)	0·60 (0·48–0·74)
Liver metastasis						
Yes	127	51/73	10·91 (7·00–15·18)	44/54	5·59 (2·83–8·15)	0·48 (0·32–0·73)
No	524	156/250	19·25 (15·97–22·11)	179/274	9·40 (7·10–11·04)	0·56 (0·45–0·70)



Key: CI, confidence interval; IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium; no, Number; %, Percentage; PD-L1, programmed death ligand; yr, year
Notes: HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Source: Motzer 2022 (92)

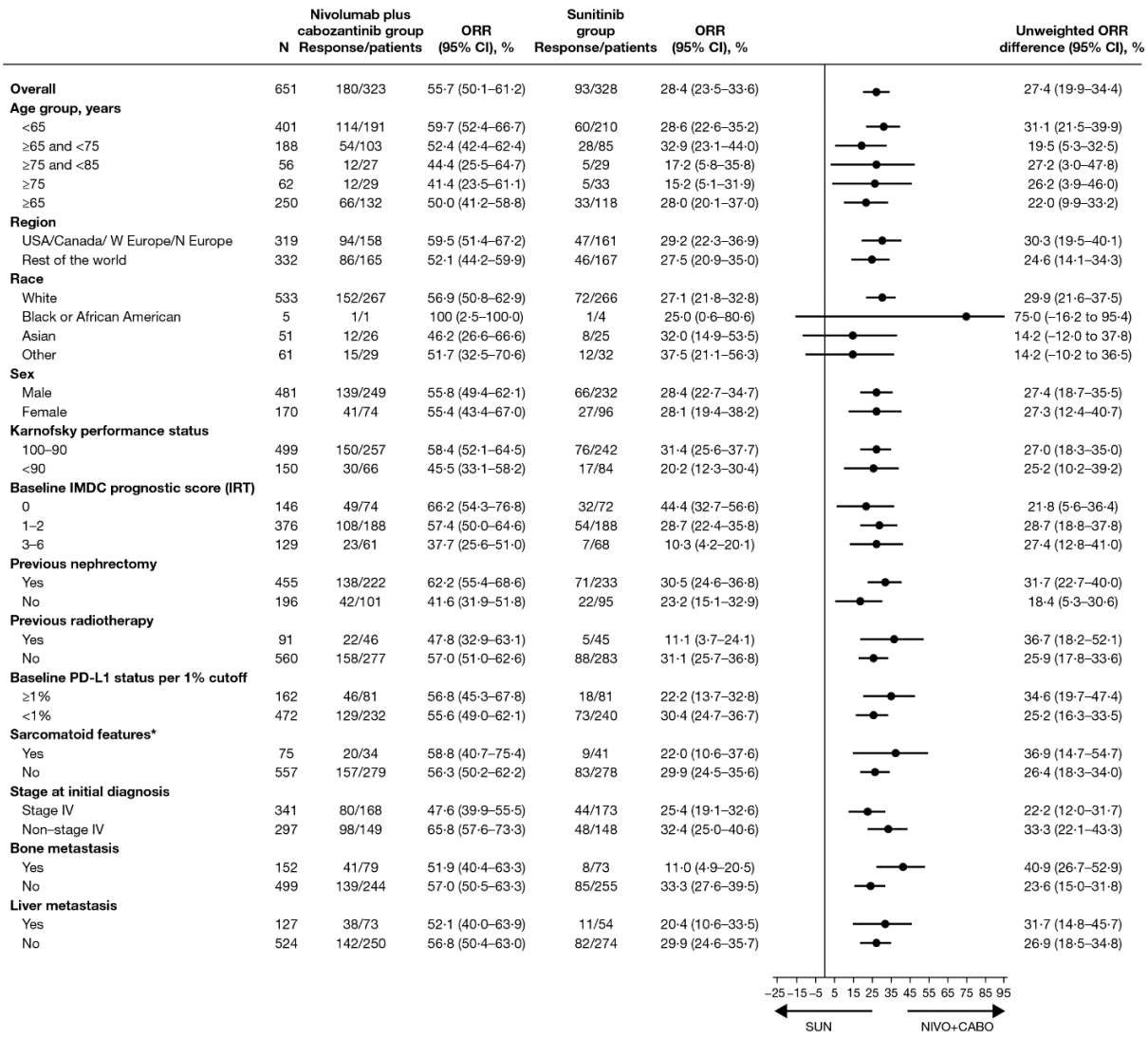
Figure 8: Forest Plot of Treatment on Overall survival according to predefined or post-hoc patient subgroup at baseline

	N	Nivolumab plus cabozantinib group Events/patients	Median OS (95% CI), months	Sunitinib group Events/patients	Median OS (95% CI), months	Unstratified hazard ratio (95% CI)
Overall	651	121/323	37·68 (35·52–NE)	150/328	34·27 (29·04–NE)	0·71 (0·56–0·90)
Age group, years						
<65	401	61/191	NR (36·53–NE)	101/210	32·36 (24·57–NE)	0·54 (0·39–0·74)
≥65 and <75	188	42/103	39·36 (34·86–NE)	33/85	NR (29·47–NE)	1·02 (0·65–1·62)
≥75 and <85	56	16/27	25·72 (18·83–37·68)	15/29	24·90 (12·32–NE)	0·91 (0·44–1·86)
≥75	62	18/29	24·67 (15·97–37·68)	16/33	28·35 (17·51–NE)	1·08 (0·54–2·14)
≥65	250	60/132	37·55 (26·35–NE)	49/118	36·17 (28·35–NE)	1·03 (0·71–1·51)
Region						
USA/Canada/ W Europe/N Europe	319	54/158	37·68 (37·55–NE)	71/161	36·17 (25·66–NE)	0·64 (0·45–0·92)
Rest of the world	332	67/165	34·92 (32·23–NE)	79/167	33·64 (24·41–NE)	0·78 (0·56–1·07)
Race						
White	533	101/267	37·68 (36·53–NE)	131/266	32·36 (24·57–NE)	0·66 (0·51–0·85)
Black or African American	5	0/1	NA	0/4	NA	1·00 (1·00–1·00)
Asian	51	8/26	35·52 (35·52–NE)	3/25	NA	2·37 (0·61–9·15)
Other	61	12/29	NR (18·83–NE)	16/32	25·07 (9·46–NE)	0·65 (0·31–1·38)
Sex						
Male	481	88/249	37·68 (36·53–NE)	104/232	34·46 (29·47–NE)	0·68 (0·51–0·90)
Female	170	33/74	NR (22·77–NE)	46/96	30·62 (18·66–NE)	0·81 (0·52–1·26)
Karnofsky performance status						
100–90	499	87/257	NR (37·68–NE)	95/242	NR (33·34–NE)	0·79 (0·59–1·06)
<90	150	34/66	32·00 (20·07–NE)	55/84	17·81 (9·23–21·32)	0·57 (0·37–0·88)
Baseline IMDC prognostic score (IRT)						
0	146	21/74	NR (37·68–NE)	19/72	NA	1·03 (0·55–1·92)
1–2	376	71/188	37·55 (34·86–NE)	85/188	34·27 (25·66–NE)	0·74 (0·54–1·01)
3–6	129	29/61	32·53 (20·93–39·36)	46/68	10·51 (6·83–20·67)	0·49 (0·31–0·79)
Previous nephrectomy						
Yes	455	71/222	39·36 (37·55–NE)	101/233	36·17 (31·08–NE)	0·62 (0·45–0·83)
No	196	50/101	31·11 (22·28–NE)	49/95	27·07 (19·38–NE)	0·87 (0·59–1·30)
Previous radiotherapy						
Yes	91	21/46	34·92 (23·52–NE)	22/45	25·66 (14·09–NE)	0·77 (0·42–1·40)
No	560	100/277	39·36 (37·55–NE)	128/283	34·27 (29·47–NE)	0·69 (0·53–0·90)
Baseline PD-L1 status per 1% cutoff						
≥1%	162	36/81	NR (21·42–NE)	42/81	29·47 (19·68–NE)	0·74 (0·48–1·16)
<1%	472	79/232	37·68 (36·53–NE)	106/240	34·46 (28·35–NE)	0·65 (0·49–0·87)
Sarcomatoid features*						
Yes	75	13/34	37·55 (26·64–NE)	28/41	22·14 (8·94–25·66)	0·38 (0·20–0·74)
No	557	105/279	39·36 (34·92–NE)	118/278	36·17 (32·59–NE)	0·80 (0·61–1·03)
Stage at initial diagnosis						
Stage IV	341	75/168	36·53 (30·92–NE)	94/173	24·05 (19·38–32·36)	0·70 (0·51–0·94)
Non–Stage IV	297	46/149	NR (37·68–NE)	53/148	NR (34·27–NE)	0·77 (0·52–1·15)
Bone metastasis						
Yes	152	41/79	30·98 (21·42–39·36)	46/73	19·91 (12·48–25·66)	0·63 (0·42–0·97)
No	499	80/244	NR (37·55–NE)	104/255	NR (33·64–NE)	0·71 (0·53–0·95)
Liver metastasis						
Yes	127	33/73	37·55 (23·52–NE)	35/54	18·50 (9·43–30·62)	0·54 (0·34–0·87)
No	524	88/250	39·36 (35·52–NE)	115/274	36·17 (32·59–NE)	0·73 (0·56–0·97)



Key: CI, confidence interval; IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium; no, Number; %, Percentage; PD-L1, programmed death ligand; yr, year
Notes: HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Source: Motzer 2022 (92)

Figure 9: Forest Plot of Treatment on Objective Response according to predefined or post-hoc patient subgroup at baseline



Key: CI, confidence interval; IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium; no, Number; %, Percentage; PD-L1, programmed death ligand; yr, year
Notes: HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Source: Motzer 2022 (92)

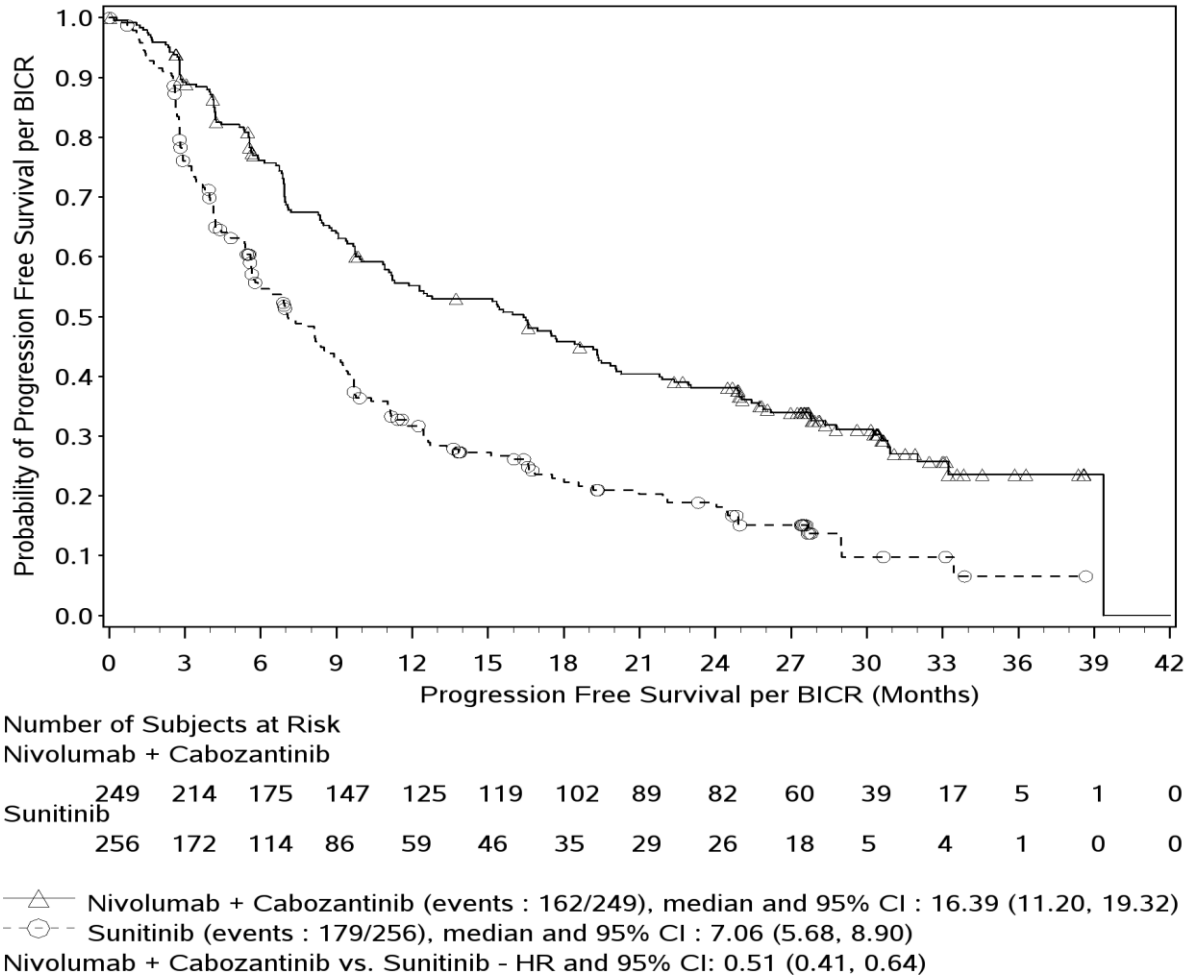
However, the primary focus of the decision problem is the intermediate/poor subgroup which is presented in the below section.

Intermediate/Poor Risk results for PFS, OS and ORR

KM plots, per BICR, for intermediate/poor-risk subjects reported favourable results for cabozantinib with nivolumab compared to the sunitinib group for PFS (HR= 0.51)

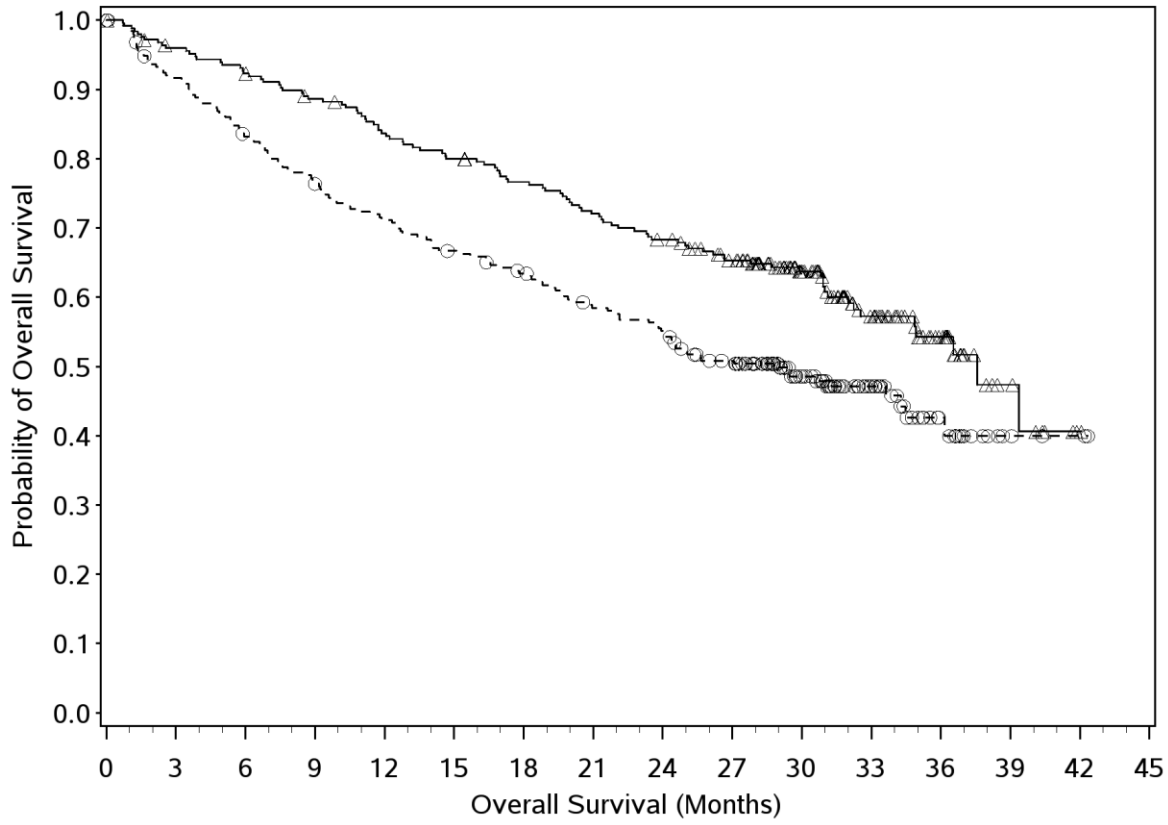
Figure 10) and OS (HR=0.66) (Figure 11). Further, the ORR was substantially higher with cabozantinib with nivolumab versus sunitinib with an absolute increase of 52.6% versus 23.8% (Table 14) (93). A higher proportion of patients in the cabozantinib with nivolumab arm achieved CR and PR compared with patients in the sunitinib arm (CR: 12.0% versus 3.5%; PR: 40.6% vs 20.3%), and a lower proportion of patients had PD: 7.2% vs 16.8% (93).

Figure 10: Kaplan–Meier curve of progression-free survival per blinded independent central review, for all intermediate/ poor-risk randomised subjects



Key: BICR, Blinded Independent Central Review; CI, confidence interval.
Source: CheckMate 9ER clinical study report addendum 2021 (93)

Figure 11: Kaplan–Meier curve of overall survival per blinded independent central review, for all intermediate/ poor-risk randomised subjects



Number of Subjects at Risk

Nivolumab + Cabozantinib	249	236	227	216	203	194	184	173	163	148	99	57	28	8	1	0
Sunitinib	256	229	207	190	176	164	154	140	132	115	73	41	16	4	2	0

Nivolumab + Cabozantinib (events : 100/249), median and 95% CI : 37.55 (32.53, N.A.)
Sunitinib (events : 131/256), median and 95% CI : 29.04 (23.39, 36.17)
Nivolumab + Cabozantinib vs. Sunitinib - HR and 95% CI: 0.66 (0.50, 0.85)

Key: BICR, Blinded Independent Central Review; CI, confidence interval.
Source: CheckMate 9ER clinical study report addendum 2021 (93)

Table 14: Summary of response rates per blinded independent central review, for all intermediate/ poor-risk randomised subjects

	Cabozantinib with Nivolumab (n = 249)	Sunitinib (n = 256)
ORR, n (% [95% CI] [a])	**131 (52.6 [46.2, 58.9])**	**61 (23.8 [18.7, 29.5])**
Confirmed BOR		
CR, n (%)	**30 (12.0)**	**9 (3.5)**
PR, n (%)	**101 (40.6)**	**52 (20.3)**
SD, n (%)	**82 (32.9)**	**105 (41.0)**
PD, n (%)	**18 (7.2)**	**43 (16.8)**
UTD, n (%)	**18 (7.2)**	**46 (18.0)**
Not reported	**0**	**1 (0.4)**

Key: BOR, best overall response; CI, confidence interval; CR, confirmed response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; UTD, unable to determine
Notes: [a], CR+PR, confidence interval based on the Clopper and Pearson method. **Source:** CheckMate 9ER clinical study report addendum 2021 (93)

Overall, cabozantinib with nivolumab showed higher improvements compared to sunitinib in patients with sarcomatoid features and previous nephrectomy versus those without (92). Therefore, a consistently favourable treatment effect was observed for cabozantinib with nivolumab irrespective of baseline IMDC risk group, PD-L1 tumour expression status and presence of bone metastases (92, 93).

A.2.8 Adverse reactions

Unless otherwise specified, all results in this section are presented for the treated population (n = 640), for the CheckMate 9ER study. There were no other relevant studies which stated additional AEs, except the ones covered in this section below.

A.2.8.1 Treatment exposure

Table 15 presents a summary of the treatment exposure during the CheckMate 9ER study. At the time of primary analysis (median study follow-up: 32.9 months), 28.8% and 14.4% of patients were still receiving study treatment in the cabozantinib with nivolumab and sunitinib arms, respectively; the median duration of treatment (defined as last dose date – start dose date + 1 day) was 21.8 months for cabozantinib with nivolumab (nivolumab: 16.6 months; cabozantinib:18.8 months) and 8.9 months for sunitinib (92, 93).

The median average daily dose of cabozantinib and sunitinib (27.8 and 27.5 mg/day, respectively) were lower than their planned daily doses (40.0 and 33.3 mg/day, respectively) as a result of permitted dose reductions, dose holds and dose delays due to AEs for cabozantinib and sunitinib (92, 93).

Table 15: Summary of treatment exposure in CheckMate 9ER, mFU 32.9 months

	Cabozantinib with Nivolumab (n = 320)		Sunitinib (n = 320)
	Nivolumab	Cabozantinib	
Duration of treatment (months)			
Median (IQR)	16.6 (6.9 – 23.7)	18.8 (7.2 – 29.5)	8.9 (2.9 – 20.7)
	Overall 21·8 (8·8–29·5)		
Number of doses received			
Median (IQR)	35.0 (14.0 – 50.0)	451.5 (195.5 – 812.0)	165.5 (56.5 – 394.5)
Relative dose intensity n (%)‡			
≥ 110	0	0	6 (2.0)
90 – < 110	237 (74.0)	103 (32.0)	118 (37.0)
70 – < 90	69 (22.0)	54 (17.0)	102 (32.0)
50 – < 70	14 (4.0)	96 (30.0)	82 (26.0)
< 50	0	67 (21.0)	11 (3.0)
Not reported	0	0	1 (<1)
Average daily dose (mg/day)			
Median (IQR)	N/A	27.8 (20.7 – 38.6)	27.5 (22.5 – 32.1)
Patients with at least one dose reduction, n (%)†	N/A	196 (61.0)	172 (54.0)
Median time to first dose level reduction due to adverse events (IQR), days	N/A	108.5 (64.5–206.0)	61.0 (42.0–168.0)
Patients with at least one dose delay, n (%)*	238 (74)	270 (84)	239 (75)
	Both 289 (90)		

Key: IQR, interquartile range; max, maximum; min, minimum; mg, milligram; N/A, not applicable; SD, standard deviation.

*Reasons for dose delay of nivolumab only (based on total number of dose delays): adverse event, 345 (52%); dosing error, two (<1%); other, 278 (42%); not reported 33 (5%). Reasons for dose delay of cabozantinib only (based on total number of dose delays): adverse event, 1135 (67%); dosing error, 246 (14%); no change, 55 (3%); other, 269 (16%). Reasons for dose delay of both nivolumab plus cabozantinib (based on total number of dose delays): adverse event, 1480 (63%); dosing error, 248 (10%); no change, 55 (2%); other, 547 (23%); not reported, 33 (1%). Reasons for dose delay of sunitinib (based on total number of dose delays): adverse event, 569 (52%); dosing error, 95 (9%); no change, 173 (16%); other, 266 (24%); not reported, one (<1%).

†No dose reductions were allowed for nivolumab but were permitted for cabozantinib and sunitinib per protocol. Reasons for dose reduction of cabozantinib (based on total number of dose reductions): adverse event, 207 (65%); no change, 104 (33%); other, nine (3%). Reasons for dose reduction of sunitinib (based on total number of dose reductions): adverse event, 225 (87%); no change, 26 (10%); other, eight (3%).

‡Defined as the actual dose received relative to the planned dose.

Source: Motzer 2022 (92), CheckMate 9ER clinical study report addendum 2021 (93)

A.2.8.1.1 Time to treatment discontinuation

The median (95% CI) time to treatment discontinuation (TTD) based on KM analysis was [redacted] and [redacted] months for the cabozantinib with nivolumab and sunitinib arms, respectively, as depicted in Figure 12 (93). In this analysis, patients in the cabozantinib with nivolumab arm were considered as off-treatment if both nivolumab and cabozantinib were discontinued.

Figure 12: Kaplan–Meier plot of time to treatment discontinuation (cabozantinib with nivolumab considered dependently), mFU 32.9 months

Key: CI, confidence interval.
Source: CheckMate 9ER clinical study report addendum 2021 (93)

The differences in TTD based on KM analysis (Figure 12) compared to duration of treatment at the time of primary analysis (Table 15) were due to a large number of patients still receiving treatment at data cut-off and thus censored at their last available dose date (90).

A.2.8.1.2 Infusion interruptions and infusion rate reductions of nivolumab

In the cabozantinib with nivolumab arm, most patients received all doses of nivolumab without infusion interruptions or rate reductions: only 2.5% had a dose interruption, and 1.3% had an infusion rate reduction (90).

A.2.8.1.3 Dose delays and dose reductions

In the cabozantinib with nivolumab arm, 90.0% of patients experienced a delay of either nivolumab or cabozantinib (63.0% were due to AEs): 74.0% of patients experienced delays in nivolumab treatment only (i.e., a delay exceeding 3 days; 52.0% were due to AEs), and 84.0% of patients experienced delays in cabozantinib only (i.e., missed single or consecutive days; 67.0% were due to AEs) (92). A total of 61.0% of patients had dose reductions for cabozantinib (Table 15), primarily due to AEs (65.0%); per protocol, dose reductions were not permitted with nivolumab treatment (92).

In the sunitinib arm, 75.0% of patients experienced dose delays; as with cabozantinib. In addition to the planned 2 weeks off treatment, 52.0% dose delays were due to AEs by definition (92). A total of 54.0% of patients had dose reductions with sunitinib (Table 15), 87.0% resulted from AEs (92).

A.2.8.1.4 Subsequent therapy

In the randomised population, subsequent anti-cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 104 patients (32.0%) in the cabozantinib with nivolumab arm and 139 patients (42.0%) in the sunitinib arm, as summarised in Table 16 (92). Subsequent systemic therapy was received by 70 subjects (22.0%) in the cabozantinib with nivolumab arm and 122 subjects (37.0%) in the sunitinib arm (92). Subsequent anti-PD1/anti-PD-L1 therapy was received by 5.0% of subjects in the cabozantinib with nivolumab arm compared with 28.0% for the sunitinib arm. A similar percentage of subjects in the cabozantinib with nivolumab arm and sunitinib arm received VEGF(R) targeted therapy (19.0% vs 18.0%) (92).

Table 16: Summary of subsequent therapy in all randomised patients, mFU 32.9 months

Therapy*	Randomised (Intention-to-treat) population		Patients who discontinued study treatment	
	Nivolumab plus cabozantinib (n=323)	Sunitinib (n=328)	Nivolumab plus cabozantinib (n=228)	Sunitinib (n=274)
Any subsequent therapy†	104 (32)	139 (42)	104 (46)	139 (51)
Any subsequent systemic therapy	70 (22)	122 (37)	70 (31)	122 (45)
Any PD-(L)1 inhibitor	16 (5)	92 (28)	16 (7)	92 (34)
Nivolumab	14 (4)	84 (26)	14 (6)	84 (31)
Pembrolizumab	4 (1)	6 (2)	4 (2)	6 (2)
Atezolizumab	0	1 (<1)	0	1 (<1)
Durvalumab	0	4 (1)	0	4 (1)
Any Anti-CTLA-4 inhibitor	7 (2)	20 (6)	7 (3)	20 (7)
Ipilimumab	7 (2)	19 (6)	7 (3)	19 (7)
Tremelimumab	0	1 (<1)	0	1 (<1)
Any VEGF(R) inhibitor	61 (19)	58 (18)	61 (27)	58 (21)
Axitinib	25 (8)	18 (5)	25 (11)	18 (7)
Sunitinib	21 (7)	7 (2)	21 (9)	7 (3)
Pazopanib	10 (3)	7 (2)	10 (4)	7 (3)
Lenvatinib	8 (2)	3 (<1)	8 (4)	3 (1)
Cabozantinib	5 (2)	28 (9)	5 (2)	28 (10)
Sorafenib	2 (<1)	6 (2)	2 (<1)	6 (2)
Sorafenib tosylate	1 (<1)	0	1 (<1)	0
Tivozanib	1 (<1)	0	1 (<1)	0
Other	14 (4)	14 (4)	14 (6)	14 (5)
Everolimus	8 (2)	6 (2)	8 (4)	6 (2)
Investigational antineoplastic drugs	3 (<1)	3 (<1)	3 (<1)	3 (1)
BMS 986179	1 (<1)	0	1 (<1)	0
Gimeracil/oteracil potassium/tegafur	1 (<1)	0	1 (<1)	0
Talazoparib	1 (<1)	0	1 (<1)	0
Investigational drug	0	1 (<1)	0	1 (<1)
Monoclonal antibodies	0	1 (<1)	0	1 (<1)
Savolitinib	0	2 (<1)	0	2 (<1)
Trolimus	0	1 (<1)	0	1 (<1)

Notes: Data are n (%)
BMS**,** Bristol Myers Squibb; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-(L), programmed death- 1, programmed death ligand 1; VEGF(R)= vascular endothelial growth factor (receptor).
*Patients may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after the date of first study dose (date of randomization if patient was never treated)
†Includes patients who received subsequent radiotherapy, surgery, or systemic therapy.
Source: Motzer et al, 2022 (92)

A.2.8.2 Adverse events

A.2.8.2.1 Summary of treatment-emergent adverse events

Table 17 presents a summary of all-cause and drug-related AEs. Almost all patients in both treatment arms experienced an AE, but most were non-serious and were medically manageable, with < 40% of patients discontinuing treatment due to AEs (93). As of the 24-Jun-2021, median follow-up 32.9 months, 37.2% subjects in the cabozantinib with nivolumab arm and 45.9% of subjects in the sunitinib arm had died. The frequency of deaths attributed to study drug toxicity was low and similar between the cabozantinib with nivolumab and sunitinib arms. Disease progression was the most common cause of death in both arms (93).

Table 17:Summary of adverse events in CheckMate 9ER, mFU 32.9 months

	Cabozantinib with Nivolumab (n = 320)	**Sunitinib (n = 320)**
Any AE, n (%)	319 (100.0)	317 (99.0)
Drug-related	311 (97.0)	298 (93.0)
Grade 3–4 AEs, n (%)	264 (83.0)	241 (75.0)
Drug-related	208 (65.0)	172 (54.0)
Any SAEs, n (%)	170 (53.1)	135 (42.2)
Drug-related	83 (26.0)	42 (13.0)
Grade 3–4 SAEs, n (%)	121 (37.8)	100 (31.3)
Drug-related	70 (22.0)	31 (10.0)
AEs leading to DC, n (%)	119 (37.2)	67 (20.9)
AEs leading to DC of nivolumab only	37 (11.6)	N/A
AEs leading to DC of cabozantinib only	41 (12.8)	N/A
AEs leading to DC of nivolumab and cabozantinib (due to the same AE at the same time, or sequentially)	41 (12.8)	N/A
Drug-related AEs leading to DC‖	87 (27.0)¶	33 (10.0)
Drug-related AEs leading to DC of nivolumab only	34 (11.0)**	N/A
Drug-related AEs leading to DC of cabozantinib only	29 (9.0)††	N/A
Drug-related AEs leading to DC of nivolumab and cabozantinib‡‡ due to the same AE at the same time, or sequentially)	24 (7.0)	N/A
Grade 3–4 AEs leading to DC, n (%)	66 (20.6)	46 (14.4)
Drug-related	53 (16.6)	25 (7.8)

Drug-related AEs leading to deaths[a], n (%)	1 (0.3)	3 (0.9)

Key: AE, adverse event; DC, discontinuation; mFU, median follow up; N/A, not applicable; SAE, serious adverse event.
Notes: [a], causes of death per investigator were as follows: four patients had treatment-related adverse events leading to death: one in the cabozantinib with nivolumab arm (small-intestine perforation), and three in the sunitinib group (pneumonia, respiratory distress, sudden death [one patient each]). Of these deaths, only sudden death has occurred since the primary analysis (database lock March 30, 2020).
‖Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients.
¶ Includes events leading to discontinuation of either nivolumab or cabozantinib at any time; the assessments for discontinuation of nivolumab and cabozantinib were made separately for each drug, and it was acceptable to continue treatment with only the study drug that was not considered related to the observed toxicity.
#The most common (>1% of patients) treatment-related adverse event leading to discontinuation of sunitinib was proteinuria in seven patients (2%).
**The most common (>1% of patients) treatment-related adverse event leading to discontinuation of nivolumab only was pneumonitis in five patients (2%).
††The most common (>1% of patients) treatment-related adverse event leading to discontinuation of cabozantinib only was proteinuria in five patients (2%).
‡‡The most common (>1% of patients) treatment-related adverse event leading to discontinuation of both nivolumab and cabozantinib (either simultaneously or sequentially) was diarrhoea in four patients (1%).
Source: Motzer 2022 (92), CheckMate 9ER clinical study report addendum 2021 (93)

A.2.8.2.2 Most common adverse events

Table 18 provides a summary of the most commonly observed drug-related AEs reported in ≥ 10% of patients in either treatment arm during the CheckMate 9ER study (92).

The most commonly observed drug-related AEs were consistent between treatment arms (cabozantinib with nivolumab versus sunitinib): diarrhoea (60.0% versus 46.0%), palmar-plantar erythrodysaesthesia syndrome (39.0% versus 42.0%), hypothyroidism (37.0% versus 31.0%), hypertension (33.0% versus 33.0%), and fatigue (28.0% versus 32.0%). In the cabozantinib with nivolumab arm, the most frequently reported Grade 3–4 drug-related AEs were hypertension (13.0%), palmar-plantar erythrodysaesthesia syndrome (8.0%), diarrhoea (7.0%), lipase increased (7.0%), and alanine aminotransferase increased (6.0%). In the sunitinib arm, the most common Grade 3–4 drug-related AEs were hypertension (12.0%), palmar-plantar erythrodysaesthesia syndrome (8.0%), diarrhoea (5.0%) and neutrophil count decreased (5.0%) (92).

A summary of all-cause adverse events occurring in ≥10% of all treated patients in either treatment group and serious adverse events (SAEs) is provided in Appendix D (92). The most common drug-related SAEs in the cabozantinib with nivolumab arm were diarrhoea (3.0%), pneumonitis (3.0%), pulmonary embolism (2.0%), hyponatraemia (2.0%), and adrenal insufficiency (2.0%); in the sunitinib arm, the most common drug-related SAEs were anaemia (1.0%) and hyponatraemia (<1%) (92).

Table 18: Summary of drug-related adverse events by grade in ≥ 10% of patients in either treatment arm, mFU 32.9 months

	Cabozantinib with Nivolumab group (n=320)			**Sunitinib group (n=320)**		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any	103 (32%)	186 (58%)	22 (7%)	125 (39%)	152 (48%)	20 (6%)
Diarrhoea	168 (53%)	20 (6%)	2 (<1%)	132 (41%)	15 (5%)	0
Hypothyroidism	115 (36%)	1 (<1%)	0	95 (30%)	1 (<1%)	0
Palmar-plantar erythrodysaesthesia	98 (31%)	25 (8%)	0	108 (34%)	26 (8%)	0
Fatigue	79 (25%)	8 (3%)	0	86 (27%)	15 (5%)	0
Nausea	73 (23%)	1 (<1%)	0	87 (27%)	0	0
Alanine aminotransferase increased	71 (22%)	18 (6%)	0	19 (6%)	3 (<1%)	0
Aspartate aminotransferase increased	71 (22%)	12 (4%)	0	33 (10%)	2 (<1%)	0
Dysgeusia	69 (22%)	0	0	67 (21%)	0	0
Hypertension	65 (20%)	39 (12%)	1 (<1%)	68 (21%)	39 (12%)	0
Decreased appetite	65 (20%)	4 (1%)	0	53 (17%)	2 (<1%)	0
Mucosal inflammation	62 (19%)	3 (<1%)	0	75 (23%)	7 (2%)	1 (<1%)
Rash	60 (19%)	6 (2%)	0	21 (7%)	0	0
Pruritus	57 (18%)	2 (<1%)	0	14 (4%)	0	0
Asthenia	48 (15%)	11 (3%)	0	41 (13%)	8 (3%)	0
Stomatitis	47 (15%)	7 (2%)	0	69 (22%)	8 (3%)	0
Vomiting	37 (12%)	4 (1%)	0	50 (16%)	2 (<1%)	0
Dysphonia	37 (12%)	1 (<1%)	0	8 (3%)	0	0
Hypomagnesaemia	35 (11%)	0	1 (<1%)	10 (3%)	0	0

Lipase increased	34 (11%)	15 (5%)	5 (2%)	24 (8%)	11 (3%)	5 (2%)
Anaemia	33 (10%)	2 (<1%)	0	55 (17%)	11 (3%)	1 (<1%)
Amylase increased	32 (10%)	14 (4%)	0	23 (7%)	7 (2%)	0
Arthralgia	31 (10%)	0	0	16 (5%)	0	0
Dyspepsia	21 (7%)	0	0	32 (10%)	1 (<1%)	0
Thrombocytopenia	20 (6%)	1 (<1%)	0	49 (15%)	11 (3%)	4 (1%)
Platelet count decreased	18 (6%)	0	0	45 (14%)	12 (4%)	2 (<1%)
Gastro-oesophageal reflux disease	16 (5%)	0	0	33 (10%)	0	0
Neutropenia	13 (4%)	2 (<1%)	1 (<1%)	39 (12%)	13 (4%)	1 (<1%)

Notes: Data are n (%). Shown are grade 1-2 treatment- related adverse events that occurred in at least 10 % of patients in either group while patients were receiving the assigned treatment or within 30 days after the end of the trail treatment period. Events are listed in descending order of frequency in the nivolumab plus cabozantinib group. Four patients had treatment- related adverse events leading to death: one in the nivolumab plus cabozantinib group (small-intestine perforation), and three in sunitinib group (pneumonia, respiratory distress, sudden death (one patient each)). Of these deaths, only sudden has occurred since the primary analysis (database lock March 30,2022).

Source: Motzer et al: 2022 (92)

A.2.8.2.3 Adverse events leading to discontinuation of study treatment

The number of any-grade, all-causality, Grade 3–4 and drug-related AEs leading to discontinuation of study treatment is summarised in Table 17 (92, 93).

In the cabozantinib with nivolumab arm, 34 patients (11.0%) discontinued nivolumab only and 29 patients (9.0%) discontinued cabozantinib only due to drug-related AEs; 24 patients (7.0%) discontinued both nivolumab and cabozantinib due to the same drug-related AE occurring at the same time (92, 93). The most common any-grade, drug-related AEs leading to discontinuation of either nivolumab or cabozantinib were diarrhoea (2.8%), pneumonitis (2.5%), proteinuria (1.9%), alanine aminotransferase increased (1.6%) and aspartate aminotransferase increased (1.6%) (93).

In the sunitinib arm, 33 patients (10.0%) discontinued treatment due to drug-related AEs (92, 93). The most common any-grade, drug-related AEs leading to discontinuation of treatment was proteinuria (2.2%) (93).

A.2.8.2.4 Summary of immune-mediated adverse events

Table 19 presents a summary of the immune-mediated adverse events (IMAEs) assessed during CheckMate 9ER. IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (i.e., with extended follow-up) (93). These analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate aetiology and an immune mediated component (93).

Overall, the majority of IMAEs were Grade 1–2 in severity. The most common in both treatment arms was hypothyroidism/thyroiditis (cabozantinib with nivolumab: 28.0%; sunitinib: 9.0%) (92). Across IMAE categories, most events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (typically systemic corticosteroids) were administered (92, 93). For non-endocrine IMAEs, 57.1% to 100.0% of events resolved with a median time to resolution ranged from 3.07 to 10.14 weeks (93). Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy (93). The results of the immunogenicity of nivolumab is provided in Appendix G (90).

Grade 3 or worse IMAEs were uncommon in all patients treated in the cabozantinib with nivolumab arm (Table 19); the most common were increased alanine aminotransferase (9 [3.0%]), diarrhoea (8 [3.0%]), and hepatotoxicity (7 [2.0%]). In the sunitinib group, grade 3 or worse IMAEs were reported for hypothyroidism, hepatotoxicity, and hyperbilirubinaemia (each, 1 [<1.0%] of 320) (92). Seventy (22.0%) of 320 patients treated with cabozantinib with nivolumab arm received corticosteroids (≥40 mg of prednisone daily or equivalent) for any duration of time to manage IMAEs (occurring on therapy or ≤100 days after the end of the trial treatment period); 40 (13.0%) patients received corticosteroids (≥40 mg of prednisone daily or equivalent) continuously for at least 14 days and 16 (5.0%) patients continuously for at least 30 days. Since the primary analysis (database lock

on March 30, 2020), no new deaths that investigators considered to be related to treatment occurred with nivolumab plus cabozantinib; one additional death that was considered to be related to treatment occurred with sunitinib (sudden death) (92).

Table 19: Immune-mediated adverse events in CheckMate 9ER, as treated patients, mFU 32.9 months

Event *	Nivolumab plus cabozantinib (n=320)		Sunitinib (n=320)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypothyroidism	88 (28)	1 (<1)	30 (9)	1 (<1)
Hyperthyroidism	31 (10)	2 (<1)	1 (<1)	0
Rash	25 (8)	5 (2)	1 (<1)	0
Diarrhoea	18 (6)	8 (3)	0	0
Hepatoxicity	12 (4)	7 (2)	6 (2)	1 (<1)
Pneumonitis	13 (4)	5 (2)	1 (<1)	0
Increased alanine aminotransferase	13 (4)	9 (3)	1 (<1)	0
Adrenal insufficiency	13 (4)	6 (2)	0	0
Increased aspartate aminotransferase	9 (3)	5 (2)	1 (<1)	0
Maculo-papular rash	9 (3)	0	1 (<1)	0
Hepatitis	5 (2)	3 (<1)	0	0
Increased blood bilirubin	5 (2)	0	1 (<1)	0
Autoimmune hepatitis	3 (<1)	3 (<1)	0	0
Renal failure	3 (<1)	1 (<1)	1 (<1)	0
Increased transaminases	2 (<1)	1 (<1)	0	0
Dermatitis	2 (<1)	1 (<1)	0	0
Pemphigold	2 (<1)	1 (<1)	0	0
Increased blood creatinine	2 (<1)	0	2 (<1)	0
Hypophysitis	2 (<1)	0	0	0
Colitis	2 (<1)	0	0	0
Hepatic failure	1 (<1)	1 (<1)	0	0
Acute thyroiditis	1 (<1)	1 (<1)	0	0
Immune-mediated dermatitis	1 (<1)	1 (<1)	0	0
Hyperbilirubinaemia	1 (<1)	0	2 (<1)	1 (<1)
Dermatitis acneiform	1 (<1)	0	1 (<1)	0
Secondary adrenocortical insufficiency	1 (<1)	0	0	0
Thyroiditis	1 (<1)	0	0	0
Acute kidney injury	1 (<1)	0	0	0
Nephritis	1 (<1)	0	0	0
Rash pruritic	1 (<1)	0	0	0
Hypersensitivity	1 (<1)	0	0	0
Infusion related hypersensitivity reaction	1 (<1)	0	0	0
Diabetes mellitus	1 (<1)	0	0	0
Scrotal dermatitis	1 (<1)	0	0	0
Infusion related reaction	1 (<1)	0	0	0

Colitis ulcerative	0	0	1 (<1)	0

Notes: Data are n (%)
*Specific events (or groups of preferred terms describing specific events) including diarrhoea/colitis, hepatitis, pneumonia, nephritis/ renal dysfunction, rash, endocrine, and others, considered by investigators to be potentially immune-mediated, that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication, had no clear alternate aetiology, or had an immune-mediated component. Adrenal insufficiency, hypophysitis, hypothyroidism/ thyroiditis, hyperthyroidism, and diabetes mellitus were considered immune-mediated adverse events regardless of immune-modulating medication use, as these endocrine events were often managed without immune-modulating medication
Source: Motzer et al, 2022 (92)

A.2.8.3 Safety overview

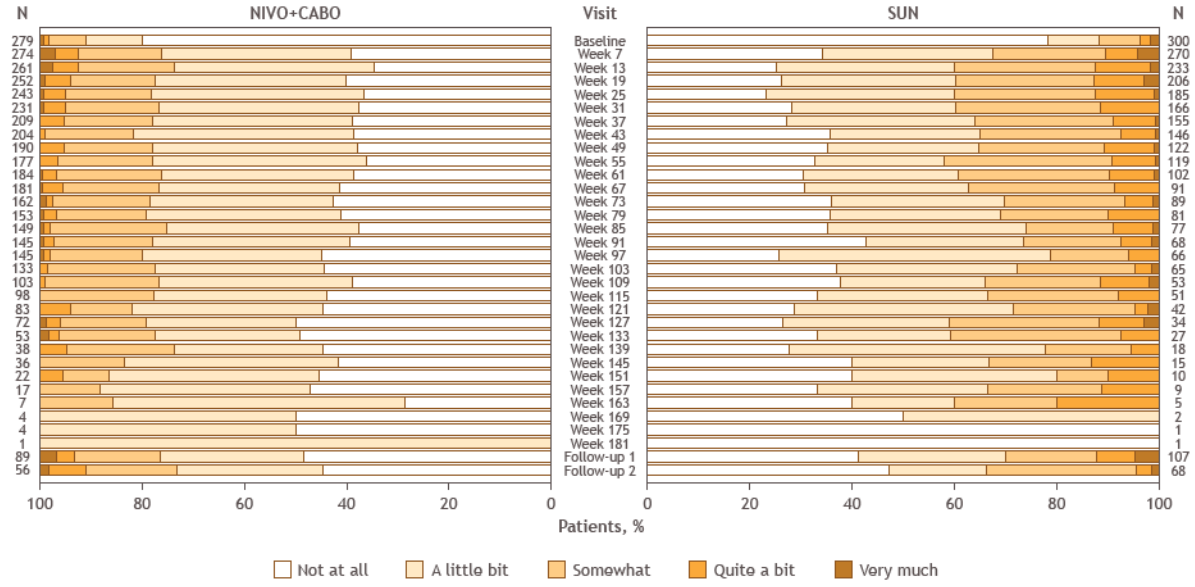
Overall, cabozantinib with nivolumab demonstrated a favourable benefit–risk profile during the CheckMate 9ER study. Cabozantinib with nivolumab was generally well tolerated with a low rate of treatment-related discontinuations (27.0%) and treatment-related deaths (n = 1) (Table 17) (92, 93). There was one additional death, compared with previous analysis (90) due to study drug toxicity in the sunitinib arm (sudden death) and no new deaths due to study drug toxicity in the cabozantinib with nivolumab arm (93). The overall frequencies of all-causality and drug-related AEs leading to discontinuation were greater in the cabozantinib with nivolumab arm and sunitinib arm than those reported in the previous analysis (90, 93). The safety profile of the cabozantinib with nivolumab combination was reflective of the known safety profiles of nivolumab and cabozantinib, and no new safety concerns were identified (93).

The safety profile of cabozantinib with nivolumab was acceptable compared with that of sunitinib; the overall frequencies of all-causality and drug-related AEs were similar between the two treatment arms (Table 17) (92, 93). As expected, given the immune-modulating mechanism of action of nivolumab, IMAEs and other events of special interest relating to IO treatment occurred more frequently with cabozantinib with nivolumab than with sunitinib; however, these AEs were manageable using the well-established safety algorithms for IO treatments (93).

Of note, fewer patients in the cabozantinib with nivolumab arm reported to be bothered by side effects compared with the sunitinib arm as shown in the Figure 13 below as measured by item GP5, “I am bothered by side effects of treatment” in NCCN FKSI-19 instrument. Based on the weighted generalised estimating

equations, patients in the cabozantinib with nivolumab arm were 48.0% less likely to be notably bothered by side effects than patients in sunitinib arm (odds ratio, 0.52; 95% CI, 0.35–0.77) (94).

Figure 13: Distribution of responses to FKSI-19 GP5 item, "I am bothered by side effects of treatment", mFU 32.9 months



Key: FKSI-19, Functional Assessment of Cancer Therapy Kidney Symptom Index-19; mFU, median follow-up; NIVO+CABO, cabozantinib with nivolumab; SUN, sunitinib;
Notes: Follow-up visit 1 had to occur 30 days (±7 days) from the last dose of study drug or could be performed on the date of discontinuation if that date was greater than 42 days from last dose. Follow-up visit 2 had to occur -100 days (±7 days) from last dose of study drug. Both follow-up visits were conducted in person.
Source: Cella etal.2022 (94).

A.2.9 Ongoing studies

No other trials are investigating this regimen in the advanced or metastatic RCC setting.

A.2.10 Interpretation of clinical effectiveness and safety evidence

A.2.10.1 Principal findings from the clinical evidence

Although there have been several advancements in treatment landscape for advanced or metastatic RCC over the last two decades, there remains an unmet need for further first-line treatment options that will extend life expectancy, delay progression and improve disease control while improving and maintaining quality of life in aRCC patients.

Cabozantinib with nivolumab has shown considerable benefit over current first-line standard of care sunitinib in the pivotal CheckMate 9ER trial with a doubling of median PFS along with 56% reduction in the risk of progression or death, improvement in OS with 70% reduction in risk of death, as well as an improved ORR, disease control, and durable response versus sunitinib (92, 93). Importantly, this was achieved while maintaining patient wellbeing, as cabozantinib with nivolumab was generally well tolerated and exploratory analyses showed patients had significantly better HRQoL compared with patients treated with sunitinib.

A.2.10.2 Strengths and limitations of the evidence base

The source of clinical trial data for this appraisal is the Phase III, randomised, open-label CheckMate 9ER study, a high-quality trial providing evidence of the clinical benefit of cabozantinib with nivolumab compared with sunitinib monotherapy in adult patients with previously untreated, advanced, or metastatic RCC (91-93). The trial's design is reflective of the decision problem addressed in this submission (section A.2.3.1 Study design).

A strength of the study is that the data from CheckMate 9ER are generalisable to the NHS in England and Wales as the trial population includes patients who are broadly representative of the treated aRCC population in England and Wales, as in a UK audit 22.1%, 50.6% and 27.2% of patients were favourable, intermediate and poor risk respectively (62). If this is compared to other combination trials, then it can be seen that the CheckMate 9ER trial is more generalisable to the UK than most other TKI-IO combination studies. The AxiAve study is also similar and is currently recommended by NICE in the all-risk population within the CDF, as shown in the Table 20 below.

Table 20: Generalisability of TKI-IO combination trials to the UK population

	CaboNivo (CM-9ER) n=323 (91)	LenPembro (CLEAR) N=355 (95)	AxiPem (KN-426) N=432 (96)	AxiAve (JAVELIN 101) N=886 (97)	Real world population studies (33, 98, 99)	UK audit (2022) (62)

IMDC Risk Group, %						
Favourable	22.9	31.0	32.0	21.4	16-23	22.1
Intermediate	58.2	59.2	55.0	65.0	51-63	50.6
Poor	18.9	9.3	13.0	10.8	21-31	27.2
Intermediate/ Poor	77.1	68.5	68.0	75.8	72-84	77.8

Key: AxiPembro, axitinib with pembrolizumab; AxiAve, Axitinib with avelumab; CaboNivo, cabozantinib with nivolumab; CDF, Cancer Drugs Fund; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LenPembro, lenvatinib with pembrolizumab; NICE, National Institute for Health and Care Excellence; TKI-IO, tyrosine kinase inhibitor- immune-oncology; UK, United Kingdom
Source: Choueiri 2021 (91), Motzer 2021 (95), Powles 2020 (96), Motzer 2019 (97), Heng 2013 (33), Hall 2020 (98), Noize 2017 (99), McGrane 2022 (62).

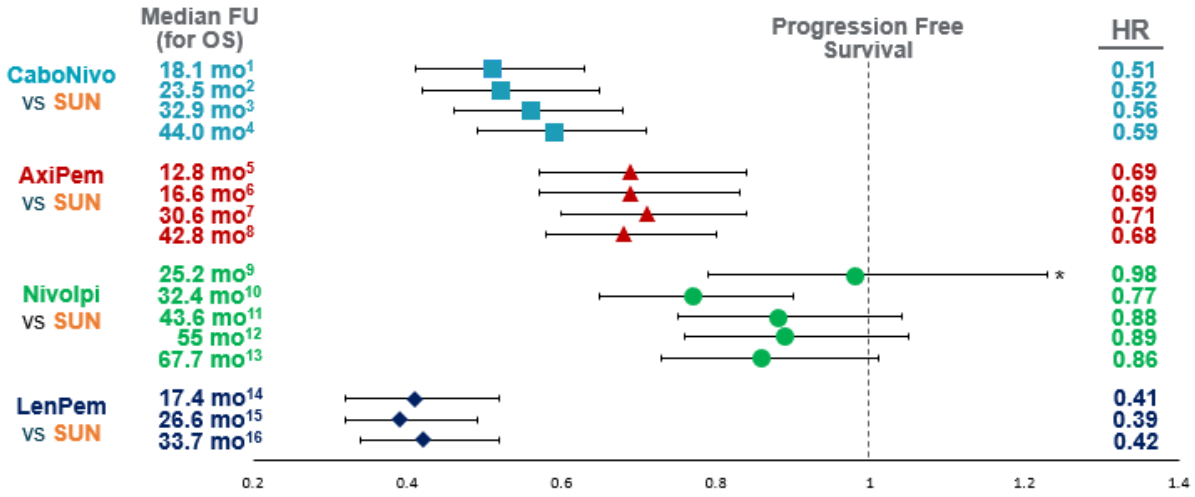
Further, the intervention arm of CheckMate 9ER reflects the anticipated posology and administration recommendations for cabozantinib with nivolumab, while the control arm of CheckMate 9ER reflects conventional TKI monotherapies most commonly used when TKI treatment is administered first-line in current clinical practice, as reported by UK clinical experts in the NICE scoping meeting of 16th January 2023 (1).

A key strength of the trial is that it provides relatively mature data with a median follow-up of 44 months. This is compared to other combinations such as LenPembro with 33.7-month median follow-up (100) and AxiAve where the NICE committee identified the immaturity of the OS data as an area of concern (57) (TA645 for AxiAve relied on 12-month median follow-up data) (6). The 44-month follow-up data available from CheckMate 9ER provides evidence for a sustained response with improved clinical benefits in terms of PFS and OS (section A.2.6 Clinical effectiveness results of the relevant studies) as well as HRQoL (section A.3.1 Health-related quality of life data from clinical trials); the latter a key differentiator of treatment with cabozantinib with nivolumab (section A.1.3.2 Clinical care pathway and proposed positioning of cabozantinib with nivolumab).

The maturity of the results of cabozantinib with nivolumab compared to other combinations used to treat RCC is shown below for PFS (Figure 14) and OS (

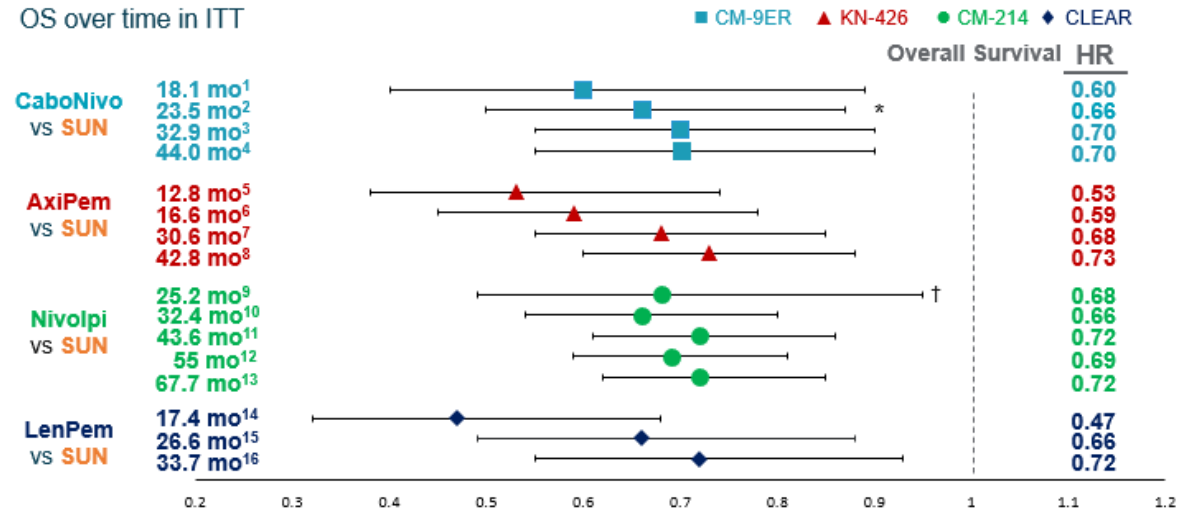
Figure 15).

Figure 14: PFS over time in ITT population in pivotal first-line combination trials in RCC



Key: AxiPembro, axitinib with pembrolizumab; CaboNivo, cabozantinib with nivolumab; FU, follow-up; HR, hazard ratio; ITT, intention-to-treat; LenPembro, lenvatinib with pembrolizumab; IpiNivo, ipilimumab with nivolumab; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.
Notes: *99.1% CI; All other range bars are 95% CI.
Source: 1. Choueiri 2021 (91); 2. Motzer 2021 (101); 3. Motzer 2022 (92);4. Ipsen, DOF 2023 (102); 5. Rini 2019 (81); 6. EMA 2019 (103); 7. Powles 2020 (96); 8. Rini 2021 (104); 9. Motzer 2018 (80); 10. Motzer 2019 (79); 11. Motzer 2020 (105); 12. Albiges 2020 (106); 13. Motzer 2021(107); 14. Motzer 2021 (95); 16. Choueiri 2023 (100).

Figure 15: OS over time in ITT population in pivotal first-line combination trials in RCC



Key: AxiPembro, axitinib with pembrolizumab; CaboNivo, cabozantinib with nivolumab; FU, follow-up; HR, hazard ratio; ITT, intention-to-treat; LenPembro, lenvatinib with pembrolizumab; IpiNivo, ipilimumab with nivolumab; OS, overall survival; RCC, renal cell carcinoma.
Notes: *98.89% CI; †99.8% CI; All other range bars are 95% CI.
Source: 1. Choueiri 2021 (91); 2. Motzer 2021 (101); 3. Motzer 2022 (92); 4. Ipsen, DOF 2023 (102); 5. Rini 2019 (81); 6. EMA 2019 (103); 7. Powles 2020 (96); 8. Rini 2021 (104); 9. Motzer 2018 (80); 10. Motzer 2019 (79); 11. Motzer 2020 (105); 12. Albiges 2020 (106); 13. Motzer 2021(107); 14. Motzer 2021 (95); 16. Choueiri 2023 (100).

The clinical benefits of cabozantinib with nivolumab extend into the real-world setting. For instance, a recent observational study demonstrated the generalisability of these described improvements to a real-world clinical practice setting (108).

Finally, the indirect treatment comparison (ITC) conducted by the company using the 32.9-month follow-up data demonstrated the superiority of cabozantinib with nivolumab over monotherapy TKIs (sunitinib and pazopanib) in PFS and OS in an all-risk aRCC population using a Bayesian fractional polynomial approach. Albeit none of the comparisons were statistically significant. Although it was not possible to include tivozanib in the ITC, due to the accepted clinical equivalence, it can also be accepted that cabozantinib with nivolumab would provide improved PFS and OS compared to tivozanib (109). Further, the ITC also demonstrated that cabozantinib with nivolumab improves PFS and OS (neither were significant) when compared to AxiAve, which, unlike cabozantinib with nivolumab, is not recommended by ESMO guidelines (37, 77, 78, 109). As a note, cabozantinib with nivolumab is also superior to IpiNivo in both PFS and OS (not significant) in an intermediate/poor sub-group comparison (109). Ipsen is in the process of updating the ITC to include the latest data from the Checkmate 9ER trial which contains the median 44-month follow-up data. This will be provided to the EAG during April 2023.

Providing an all-risk patient population with aRCC access to first line treatment with cabozantinib with nivolumab offers potential for improved clinical benefits and maintenance of HRQoL compared to currently available TKIs and combination treatments, many of which are limited to risk subgroups.

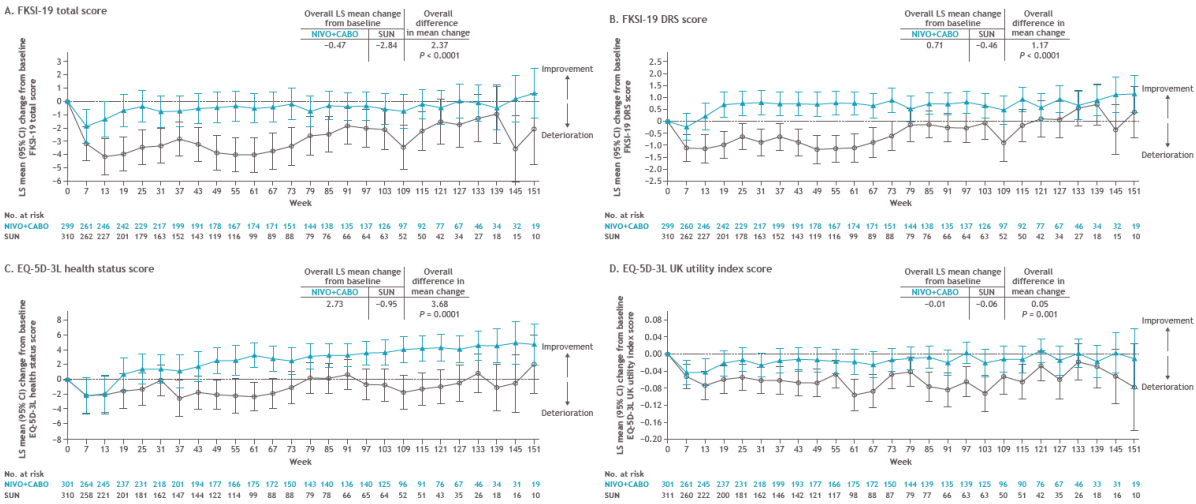
A.3 Cost-effectiveness

A.3.1 Health-related quality of life data from clinical trials

As described in section A.1.3.1.2 Burden of disease, an aRCC diagnosis is accompanied by a notable decrement in HRQoL. In oncology indications, it is well known and accepted that patients who exhibit a positive response to treatment and remain progression-free for a sustained period of time may experience a notable improvement in their HRQoL (110). The combination of cabozantinib with nivolumab builds upon the benefits of each individual treatment, offering a sustained treatment effect, leading to subsequent improvements in PFS, OS and HRQoL.

Assessments of HRQoL during CheckMate 9ER were conducted using the following patient-reported outcome (PRO) instruments: the preference-based 3-level EQ-5D (EQ-5D-3L) as well as its visual analogue scale (EQ-VAS) (111), and the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) (90, 91, 94). The methodology and results of the analysis for FKSI-19 and EQ-VAS and EQ-5D have been previously reported in the literature (94). In brief the estimated changes from baseline show that cabozantinib with nivolumab maintained or improved HRQoL from baseline through week 151, while decreased scores were observed with sunitinib (Figure 16). Between-treatment comparisons in overall change from baseline scores through week 151 showed statistical significance ($p<0.05$) in favour of cabozantinib with nivolumab over sunitinib for all scores except FWB (FKSI-19 total score and DRS, EQ-5D-3L VAS, and UK utility index; Figure 16; DRS-P LS mean [95% CI], 1.54 [0.83–2.25], $p<0.0001$; FWB, 0.29 [−0.11 to 0.68], $p=0.1523$)

Figure 16: Estimated changes from baseline through week 151 in PRO scores (MMRM analysis)



Key: CI, confidence interval; LS, least squares; MMRM, mixed models for repeated measures; PRO, patient-reported outcome; SE, standard error.

Source: Cella 2022 (94)

This section focuses on and presents evidence related to the collection and analysis of EQ-5D-3L from CheckMate 9ER trial, as EQ-5D-3L utility indices can be directly used in the economic assessment of cabozantinib with nivolumab for the treatment of aRCC. EQ-5D-3L is a generic five-item scale PRO instrument designed to assess the HRQoL of patients with advanced kidney cancer. The UK utility index values bounded between 0 and 1 are derived using the UK preference weights, where a higher utility index score indicates better outcomes (111). Utility indices derived by EQ-5D can be directly used as an input in model-based cost-utility analyses.

The company's analysis of the EQ-5D-3L data (median follow-up 32.9 months) collected in the CheckMate 9ER estimated a mean (standard error) [SE] utility of [redacted] for the progression-free state and [redacted] for progressed disease state. The methods used to measure and value the health effects based on EQ-5D-3L in CheckMate 9ER trial are detailed in the following sections.

A.3.1.1 Data collection

The CheckMate 9ER protocol specified patient completion of the EQ-5D-3L questionnaire at different time points during the trial duration. EQ-5D-3L collection time points varied between treatment arms:

- For patients receiving cabozantinib with nivolumab: On Day 1 of Week 1 of each 2-week study cycle, at the first two safety follow-up visits (approximately 30 days and approximately 100 days after the last nivolumab dose), and every survival follow-up visit (to occur every 3 months from safety follow-up 2)

- For patients receiving sunitinib: On Day 1 of Week 1 of each 6-week study cycle, at the first two safety follow-up visits (approximately 30 days and approximately 100 days after the last sunitinib dose), and every survival follow-up visit (to occur every 3 months from safety follow-up 2)

The UK EQ-5D-3L tariff was used to derive utility values from patient questionnaire responses in the CheckMate 9ER trial, consistent with section 4.3 of the NICE Methods Manual 2022 (112).

A3.1.2 Completion rates and baseline scores (EQ-5D-3L utility)

A total of 651 patients were randomised to cabozantinib with nivolumab (N=323) or sunitinib (N=328). PRO completion rates in both treatment arms were high (>90%) at baseline. Completion rates, declined overtime, but remained high in both treatment arms through week 115 (>75% except for week 109, where it was 73% in the sunitinib arm). Baseline EQ-5D-3L scores were comparable between the treatment groups and showed relatively low symptom burden, with scores similar (FKSI-19) or slightly lower (EQ-5D-3L) than UK population norms (Table 21).

Table 21: EQ-5D-3L baseline scores and population norms

Baseline EQ-5D-3L, mean (SD)	Cabozantinib with Nivolumab (n=323)	Sunitinib (n=328)	Population norms
UK utility index; range 0-1	0.78 (0.25)	0.73 (0.29)	0.86 (0.23) [a]

[a]Based on data from a sample of the general UK adult population.
Key: EQ-5D-3L, 3 Level version of EQ-5D; SD, Standard deviation; UK, United Kingdom

Source: Cella et al., 2022 (94)

A.3.2 Analysis of utility

A.3.2.1 Multivariate mixed-model analysis

To solve for the trial-based utility values, mixed-models for repeated measures (MMRM) were built based on the dependent variables selected using the manual stepwise backward elimination method. As the same patient needed to complete the questionnaire multiple times throughout the study period, a MMRM was chosen to properly account for the hierarchical nesting of the data (113, 114). The chosen mixed model used an unstructured time and covariance structure, to avoid model misspecification and reduce the risk of bias introduced by data which are missing completely at random (MCAR) or missing at random (MAR). Further, a MMRM model was preferred as it considers the repetition of measurements at different time points for each patient, making it possible to consider the evolution of intra-individual values, longitudinally, resulting in more robust utility estimates.

The MMRM analysis of EQ-5D-3L was applied to the all-risk population as this reflects the marketing authorisation and the HRQoL benefits are expected to be consistent across risk groups, as demonstrated for clinical benefits in the CheckMate 9ER trial.

Note that the use of utility values resulting from the MMRM model should be preferred to those of raw utility values because:

1. The mixed model takes into consideration the repetition of measurements (administration of questionnaires at different times to each of the patients).

2. It allows introduction of covariates of interest that would be associated with differences in EQ-5D (i.e., progression event, AEs, etc.), by assigning a relative weight to each covariate.

3. It provides an unbiased estimation when data are MCAR or MAR, which can be common for longitudinal data collected in clinical trials (115).

A.3.2.2 Missing values

Although completion rates were high (section A3.1.2 Completion rates and baseline scores (EQ-5D-3L utility)), some patients did not complete their EQ-5D-3L questionnaires at subsequent follow-up visits. Missing data has the potential to introduce statistical bias that can lead to invalid inferences, exaggerated type 1 error, or reduced power. Therefore, the patients' missing EQ-5D utilities were imputed. The MMRM model was used to predict the utility of patients with missing EQ-5D responses in the trial. Although the EQ-5D value of these patients is unknown and therefore the utility is unknown, the variables required by the MMRM such as AE status, progression status of these patients are known. Thus, their known covariates' information was used to predict their utility.

A.3.2.3 Model selection steps

Selection of the final model involved the manual stepwise backward elimination method to ensure the best statistical approach was chosen:

Step 1. Start with the EQ-5D non-missing measurements dataset, using EQ-5D-3L utility value as the outcome variable, and including all variables in the model: First measurement of EQ-5D-3L index value, week number of the visit, treatment, adverse event, progression status, age, race, gender. The best fitting model was selected based on the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) (116).

Step 2. Refine the model by removing variables one by one.

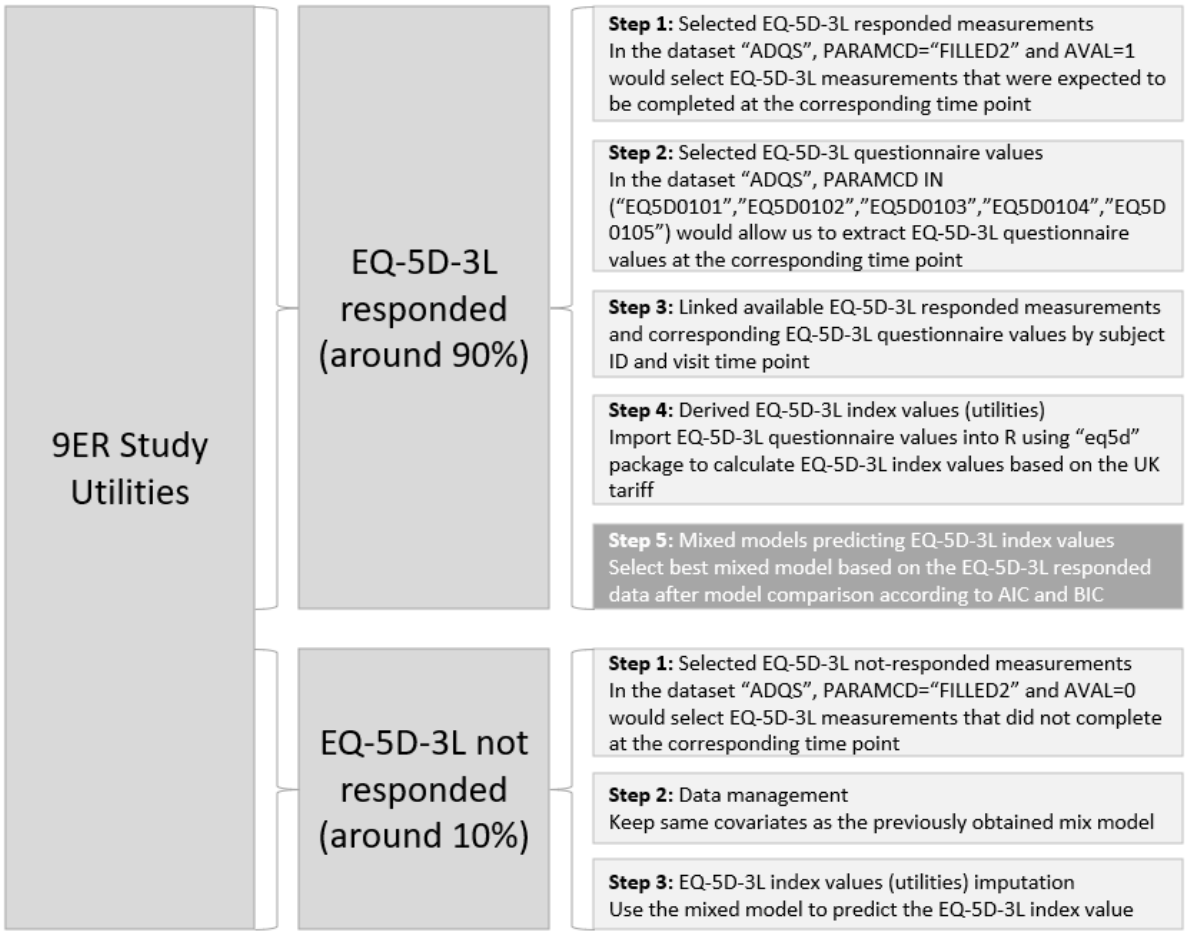
Step 3. Assess the model fit using the lowest AIC/BIC. If the model has lower AIC and BIC values, then this is selected to replace the previous best fitting model. Otherwise, it means that the variable should not be eliminated, but other variables should be tested to continue the iteration

Step 4. Repeat Step 2 and Step 3 until all variables have been tested.

These steps were repeated until the removal of variables did not result in a model with improved fit in terms of AIC and BIC.

Figure 17 illustrates the stepwise approach used in the analysis for patients with and without missing EQ-5D data.

Figure 17: Procedure to develop a mixed model for estimation of missing EQ-5D values



Key: ADQS, questionnaires analysis dataset; AVAL, analysis value; EQ-5D-3L, 3 Level version of EQ-5D; SD, standard deviation; PARAMCD, parameter code; UK, United Kingdom

A.3.2.4 Selected model for EQ-5D-3L utility change

The final MMRM model included the following fixed-effect variables: baseline EQ-5D-3L index, week of visit, treatment, AE, progression status and age, and the following random-effect variables: week of visit, AE, progression status (Table 22). Treatment effect did not show significance in the MMRM selection process, thus in the estimation of health state utilities for the purpose of informing the economic evaluation of cabozantinib with nivolumab the same set of utilities can be between treatment arms. This assumption aligns with prior aRCC NICE technology appraisals

and is consistent with NICE preference when there is insufficient robust evidence to support an alternative approach (6, 56, 112).

Table 22: Estimates from the final model predicting EQ-5D-3L index value change from first measurement

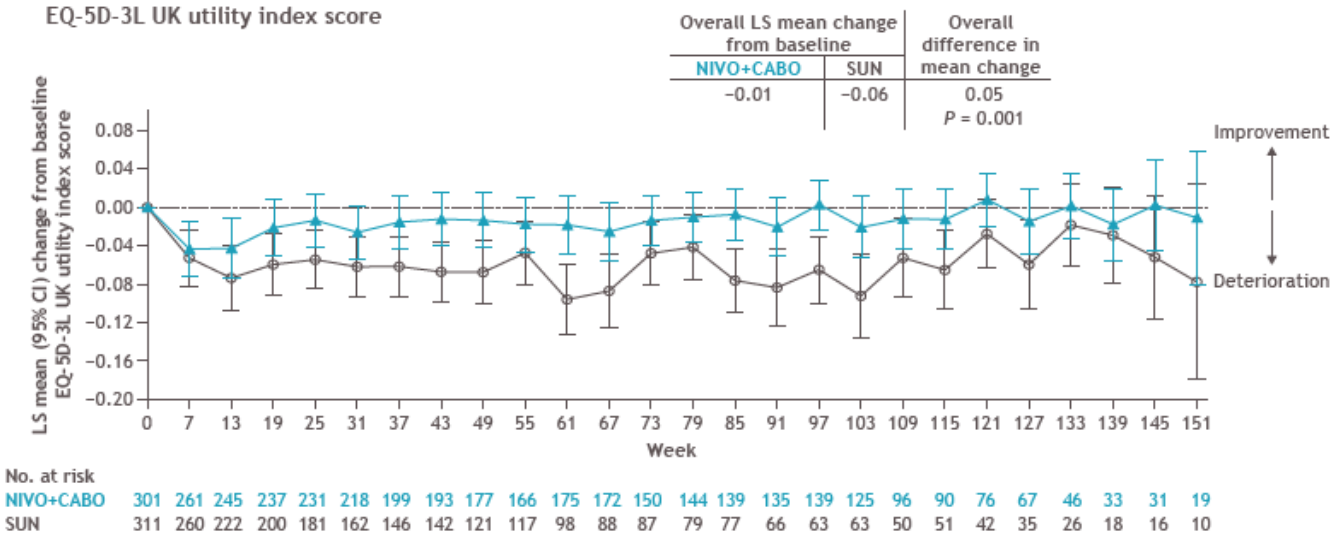
Model 6 (N=10025)			Raw model without fixed and random effect parameters	
Fixed Effects	**Estimate**	**Standard Error**	**Estimate**	**Standard Error**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
First measurement of EQ-5D-3L index value	[redacted]	[redacted]		
Week number of the visit	[redacted]	[redacted]		
Treatment	[redacted]	[redacted]		
AE	[redacted]	[redacted]		
Progression status	[redacted]	[redacted]		
Age	[redacted]	[redacted]		
Error Variance				
Level-1	[redacted]	[redacted]	[redacted]	[redacted]
Level-2 Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Week number of the visit	[redacted]	[redacted]		
AE	[redacted]	[redacted]		
Progression status	[redacted]	[redacted]		
Model Fit				
AIC	[redacted]		[redacted]	
BIC	[redacted]		[redacted]	

Key: AIC, Akaike information criterion; AE, adverse event ; BIC, Bayesian information criterion
Values based on SAS Proc Mixed. Entries show parameter estimates with standard errors in parentheses
Estimation Method = ML; Satterthwaite degrees of freedom
Notes: bold = statistically significant, $p<0.05$

A.3.2.5 EQ-5D-3L utility change from baseline

At baseline, mean (standard deviation) [SD] EQ-5D-3L UK utility index values for the cabozantinib with nivolumab and sunitinib treatment arms were 0.78 (0.25) and 0.73 (0.29), respectively (Table 21). EQ-5D-3L-UK utility index scores generally remained stable for patients in the cabozantinib with nivolumab arm (-0.01), whereas patients in the sunitinib arm again had a slight trend towards decreased scores (-0.06) (Figure 18) (94).

Figure 18: Estimated changes from baseline through week 151 in EQ-5D-3L scores (MMRM analysis)



Key: CI, confidence interval; EQ-5D-3L, 3 Level version of EuroQol-5D; LS, least square; MRMM, mixed-models for repeated measures; NIVO+CABO, cabozantinib with nivolumab; SUN, sunitinib; UK, United Kingdom
Notes: Change from baseline was assessed using descriptive statistics and a mixed model repeated measures analysis, which controlled for treatment arm, timepoint, baseline patient reported outcomes score, IMDC prognostic score, PD-L1 tumour expression and region. No. at risk denotes intention-to-treat patients with baseline plus at least one post-baseline HRQoL assessment with non-missing patient reported outcome data. Time 0 indicates baseline.
Source: Cella et al., 2022 (94)

A.3.2.6 Estimated utility values by progression status

As it is anticipated that patients who exhibit a positive response to treatment and remain progression-free for a sustained period of time may experience a notable improvement in their HRQoL (110), EQ-5D-3L utility indexes were estimated based on the CheckMate 9ER study accounting for patients' progression status. These utility values can form inputs for the model-based economic assessment of cabozantinib with nivolumab for the treatment of aRCC patients.

Analysis of the EQ-5D-3L data collected in the CheckMate 9ER by progression status yielded an estimated mean (SE) utility of [redacted] for the progression-free patients and [redacted] for patients with progressed disease (Table 23).

A.3.2.7 Adverse reactions

Evidence on 3-4 AEs was collected in the CheckMate 9ER study. The MMRM model that was used to estimate utility values from the CheckMate 9ER study included AE

as a variable. Hence, it was leveraged to estimate the disutility associated with any grade 3-4 AE. The estimated EQ-5D-3L utility index decrement associated with any Grade 3-4 AE was [redacted] as estimated by the MMRM model.

Table 23 below summarises the final mean (SE) utility values utilised in the analysis for both the progression-free and progressed states, and the grade 3/4 TEAE disutility.

Table 23: Summary of utility values estimated by the MMRM approach

State	Utility Value
Progression-free state (Mean, [SE])	[redacted]
Progressed state (Mean, [SE])	[redacted]
Disutility Grade 3/4 TEAEs (SE)	[redacted]
Key: SE, standard error; TEAE, treatment-emergent adverse events	

A.3.3 Mapping

As per the NICE technology appraisal (TA) guidelines, mapping of questionnaire responses is not required for the economic evaluation of cabozantinib with nivolumab. The EQ-5D-3L generic preference measure was used in the CheckMate 9ER Trial and the UK EQ-5D-3L tariff was used to derive utility values from patient questionnaire responses. The use of this measure is in line with NICE recommendations for utility calculation in cost-effectiveness analyses (61, 112, 117).

A.3.4 Health-related utility data from the literature

A pragmatic search was conducted to identify technology appraisals reporting HRQoL or utility data for patients with previously untreated, advanced and/or metastatic RCC that could be utilised in scenario analyses.

Table 24 provides a comprehensive account of the recent history of NICE appraisals for newly available treatments for previously untreated aRCC, with a particular focus on the methods and data employed for HRQoL assessment. Six NICE appraisals

have been conducted since March 2018, each of which sought to capture patient HRQoL. A range of methods have been used in preceding technology appraisals when determining the source, specificity to treatment arm and dependency on treatment status for utility values. As described in the above section, the selected base case methodology for deriving utility values aligns with the selected model structure, multiple preceding appraisals and remains consistent with the NICE reference case and committee feedback on health state utilities selection (5, 6, 55, 76, 112).

Table 24: Utility data reported in previous NICE technology appraisals in advanced renal cell carcinoma

TA no.	Appraisal	Treatment arm	PFS utility	PPS Utility	Comment
TA512	Tivozanib	All	0.726	0.649	Health state utility values were accepted by the committee. Company adjusted PFS utility to account for treatment related adverse events, rejected and removed from the committee base case.
TA542	Cabozantinib for untreated aRCC	All	0.726	0.649	CABOSUN did not collect EQ-5D data. Hence, the utility values utilised by the company and EAG were sourced from TA512.
TA581	Ipilimumab with Nivolumab for untreated aRCC	Ipilimumab with Nivolumab	On treatment: 0.793 Off treatment: 0.749	On treatment: 0.794 Off treatment: 0.702	A regression model was used to derive EQ-5D utilities from Checkmate 214. Utility values dependent on treatment arm and treatment status.
		Sunitinib	On treatment: 0.754 Off treatment: 0.707	On treatment: 0.763 Off treatment: 0.707	
TA645	Avelumab with axitinib for untreated aRCC	All	0.753	0.683	PFS on treatment and PPS off treatment utility values were derived from patient EQ-5D-5L questionnaire responses in the JAVELIN Renal 101 study, which were mapped to EQ-5D-3L, and utilities generated.
TA650	Pembrolizumab with axitinib for untreated aRCC	Utility values redacted in publicly available submission documents			EQ-5D data collection in KEYNOTE-426 gave overly optimistic estimates. PPS utilities from the published literature or KEYNOTE-426 were acceptable for decision making.

TA858	Lenvatinib with pembrolizumab for untreated aRCC	Lenvatinib with Pembrolizumab	Redacted	N/A	Submission utilised PFS utility values specific for each treatment arm. PPS utility was assumed to be the same for all treatment arms.
		Sunitinib	Redacted	N/A	
		All	N/A	Redacted	

Key: aRCC, Advanced Renal Cell Carcinoma; EAG, Economic Assessment Group; EQ-5D, EuroQol-5D; EQ-5D-3L, 3 Level version of EuroQol-5D; EQ-5D-5L, 5 Level version of EuroQol-5D; NICE, National Institute of Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal; TKI, tyrosine kinase inhibitor.
Source: TA512 (5), TA542 (55), TA581 (117), TA645 (6), TA650 (7), TA858 (76)

A.3.5 Intervention and comparators' costs and resource use

Cost and resource use estimates presented below for the intervention cabozantinib with nivolumab align with appropriate key sources of data as described in the NICE reference case. The unit costs for drug acquisition costs have been sourced from the British National Formulary (BNF) list prices (17). Costs associated with intervention-specific resource use were sourced from Personal Social Services Research Unit (PSSRU) or NHS reference cost documentation (118, 119). Because previous NICE TAs have shown consistency in information used related to the NHS resource burden associated with aRCC treatment, these sources have been also used to inform some cost items for consistency with precedence (6, 55, 60, 117).

A.3.5.1 Intervention costs

The drug acquisition cost of cabozantinib with nivolumab was calculated by combining the unit cost, dosage, and dose intensity. Table 25 provides the total drug acquisition cost per month for the intervention using list prices for cabozantinib with nivolumab, in line with the dosing regimens described in Section A.2.3.1 Study design.

The RDI for cabozantinib with nivolumab was estimated separately for each treatment based on patient level data from the CheckMate 9ER study. The estimated mean RDI for nivolumab was [redacted]%. This was estimated based on the cumulative length of delay in the nivolumab dosing as estimated in the cabozantinib with nivolumab arm of CheckMate 9ER. The mean RDI for cabozantinib was calculated as [redacted]% by factoring in the mean number of cabozantinib doses received and the planned number of cabozantinib doses per patient in the all-risk population of the cabozantinib with nivolumab arm.

A.3.5.2 Administration costs

As per the guidance, monthly administration costs should be applied for treatments administered intravenously or orally. Cabozantinib is administered as a 40mg tablet once daily when in combination with nivolumab; with the treatment regime assumed to incur an initial cycle cost associated with the delivery of an oral chemotherapy and a subsequent cycle cost reflecting 12 minutes of pharmacist dispensing time (56).

Intravenous administration of nivolumab is assumed to be delivered in the outpatient setting, incurring a cost associated with the delivery of a chemotherapy cycle as detailed in the NHS reference cost listing and as provided in Table 26 (119). Nivolumab in the combination of cabozantinib with nivolumab can be administered every 2 weeks at a flat 240mg dose or every 4 weeks at 480mg. Studies have reported the consistency in safety profile and pharmacokinetic exposure between nivolumab 240mg Q2W and 480mg Q4W across multiple tumour types, including RCC. The 480mg option is assumed to be preferred as it represents a convenient and flexible option for patients that minimises hospital attendance, offers increased freedom and ultimately optimises patient care (120). The estimation of total nivolumab cost in Table 26 utilises the cost of a 240mg vial and assumes the 480mg dosing schedule of two vials every 4 weeks.

As described in Section A.2.8.1 Treatment exposure, the maximum treatment duration for nivolumab is 2 years from cabozantinib with nivolumab treatment initiation.

Total intervention costs are presented in Table 26 based on list prices. It is important to note that there is a confidential patient access scheme in place for nivolumab, approved by the Department of Health and Social Care, as well as a confidential simple patient access scheme is available for cabozantinib.

Table 25: Treatment & administration information associated with first-line treatment with cabozantinib with nivolumab

Treatment option	Package	Cost per pack (£)	Cost per mg (£)	Dosage per administration (mg) [2]	Dose intensity (%)[3]	Administration	Monthly administrations†	Stopping rule (month)	Total cost per month (£)**
Cabozantinib	30 units of 40 mg	5,143.00[1]	4.29	40mg QD	[redacted]	Oral	30.4		[redacted] ▪
Cabozantinib (PAS)	30 units of 40 mg	[redacted]	[redacted]	40mg QD	[redacted]	Oral	30.4		[redacted] ▪
Nivolumab	240 mg vial	2,633.00[2]	10.97	480mg Q4W	[redacted]	IV	1.1	24*	[redacted]

Key: £, Great British Pound; IV, Intravenous; mg, milligram; Q4W, Every 4 weeks; QD, Every day

Notes: * = As per NICE guidance, nivolumab has a stopping rule after the maximum treatment period of 2 years (from the first dose). ** = Total cost per month includes treatment administration costs. ▪ = Total costs per month for cabozantinib are presented as the monthly costs incurred following the first month of treatment, during which an additional cost of delivering the first cycle of oral chemotherapy would be considered due to the delivery of the first cycle of oral chemotherapy, as detailed in Table 26 below. Calculations of total cost per month considers more than the two decimals presented in the table. † = Calculations consider 365.242 days per year.

Source:[1] = Cabozantinib 40mg tablets, BNF 2023 (17); [2] = Opdivo 240mg/24ml concentrate for solution for infusion vials; BNF 2023 (18). [3] = Check-Mate-9ER: 1L RCC Phase 3 Study(90) [4] = 9ER patient level data analysis, June 2021 data cut. (93).

A.3.5.3 End of Life Costs

Whilst it is expected that the costs associated with patient care in the last three months of life will rise, the evidence collected in the CheckMate 9ER did not allow quantification of the cost of end-of-life care for aRCC patients and thus no data have been provided.

Table 26: Unit costs associated with the technology

Items	Intervention (confidence interval)		Source	Reference
Technology cost	Cabozantinib	£5,143.00	30 units of CABOMETYX 40 mg (cabozantinib). 1 box of 30 film-coated tablets	BNF 2023 (17)
	Cabozantinib (PAS)	[redacted]	30 units of CABOMETYX 40 mg (cabozantinib). 1 box of 30 film-coated tablets (PAS price discount of [redacted])	Company Data on file
	Nivolumab (240mg)	£2,633.00	240 mg vial. OPDIVO 10 MG/ML. PERF FL10ML	BNF 2023 (18)
Technology cost per administration	Cabozantinib	£171.43	Derived from the cost per mg and dosage per administration of cabozantinib	N/A
	Nivolumab	£5,266.00	Derived from the cost per mg and dosage per administration of nivolumab	N/A
Administration costs	Cabozantinib	£245.00 (at first attendance) £9.60 (cycle thereafter)	Initial cost at first cycle: Deliver exclusive oral chemotherapy SB11Z Cycle thereafter: Cost of 12 minutes pharmacist time (56)	NHS National schedule of reference costs 2021 (119)
	Nivolumab	£471.00	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle.	NHS National schedule of reference costs 2021 (119)
Average administration	Cabozantinib	£0.32	Derived from the administration cost per	N/A

Items	Intervention (confidence interval)		Source	Reference
cost (per administration)			cycle and number of units per pack.	
	Nivolumab	£471.00	Derived from the administration cost and number of administrations per cycle.	N/A
Total cost of technology treatment	Cabozantinib	[redacted] /month	Derived from the technology and administration costs per cycle, RDI and number of monthly administrations	N/A
	Cabozantinib (PAS)	[redacted] /month	Derived from the technology and administration costs per cycle, RDI and number of monthly administrations (PAS price discount of [redacted])	Company Data on file
	Nivolumab	[redacted] /month	Derived from the technology and administration costs per cycle, RDI and number of monthly administrations	N/A

Key: £, Great British Pound; BNF, British National Formulary; mg, milligram; ml, millilitre; NHS; National Health Service; PAS, patient access scheme

A.3.6 Uncertainty

There is reasonably high certainty in the clinical and HRQoL benefits of treatment with cabozantinib with nivolumab for the management of aRCC as supported by a high-quality CheckMate 9ER trial with extended follow-up period. This is in contrast to the evidence previously appraised by NICE for an all-risk aRCC population. For instance, TA645 for AxiAve relied on data with a 12-month median follow-up, which

is considerably shorter compared to the 32.9 months of follow-up presented here (and the availability of median 44-month follow-up data) and presumably led to high uncertainty and its CDF recommendation. Further, a review of the point estimates and confidence intervals for primary and secondary endpoints across the data-cuts published by the comparator trials shows a high degree of consistency (and hence higher certainty) in the results of CheckMate 9ER versus some of its comparators for overall survival (Figure 14, Figure 15).

A.3.7 Benefits not captured in the quality-adjusted life year (QALY) calculation

Cabozantinib with nivolumab is expected to provide additional indirect health benefits not fully captured in the quality-adjusted life year (QALY) measure on account of cabozantinib's oral administration route when used as an alternative to one of the IO components of an IO-IO combination. The additional health benefits are relevant within the initial immunotherapy loading period (i.e., initial 4 weeks) and again for patients treated with cabozantinib beyond the IO 2-year stopping rule. The use of cabozantinib with nivolumab would be expected to reduce the environmental impact of treatment, due to a reduction in the need for hospital appointments related to treatment administration, which aligns with the NHS sustainability plan (121).

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health technology appraisal

Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [ID6186]

Document A

Company evidence submission

(Updated to include median 44-month follow-up data for the CheckMate-9ER trial)

April 2023

File name	Version	Contains confidential information	Date
ID6186_Company updated 44-month evidence submission_AIC_CIC_12April2023_Final_Updated ACIC_24Aug2023	Version 1	Yes	12th April 2023

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List of Abbreviations

AE	Adverse event
BICR	Blinded independent central review
CaboNivo	Cabozantinib with nivolumab
CI	Confidence interval
CR	Complete response
CRF	Case report form
DoR	Duration of response
EQ-5D-3L	3 Level version of EuroQol-5D (EQ-5D)
ESMO	European Society for Medical Oncology
HR	Hazard ratio
HRQoL	Health-related quality of life
IMAE	Immune-mediated adverse events
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
MAIC	Matching-adjusted indirect comparison
mo	Months
N.A.	Not applicable
N.E.	Not estimable
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate

OS	Overall survival
PD	Progressed disease
PR	Partial response
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
QALY	Quality adjusted life year
QoL	Quality of life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	Statistical analysis plan
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse events
TTD	Time to treatment discontinuation
TTR	Time to treatment response

1. Clinical effectiveness results of the relevant studies

The results in this section are presented for all randomised patients from the CheckMate-9ER trial (n = 651) [1].

Table 1 provides an overview of the available data cut offs for this trial. From March 2020 till date, follow-up (median) was done at 18.1, 23.5, 32.9, and 44.0 months. At the time of primary analysis (database 4 lock date: 27 May 2022), the median study follow-up was 44.0 (36.5–56.5) months, the data for which is presented in this document.

The Appendix 1, Table 12 provides information on what data has now been provided from CheckMate-9ER using the median 44-month follow up data compared to that provided on 3rd April which contained the 32.9 months median follow-up data.

Table 1. Overview of CheckMate-9ER trial cut-off points and database analysis

		Database lock 1	Database lock 2	Database lock 3	Database lock 4
PLAN	**Planned DBL date**	30 March 2020	August 2020	Feb 2021	N.A.
	Planned Analysis	Final PFS Interim #1 OS	Interim #2 OS	Final OS	Additional PFS and OS
Actual DBL		30 March 2020	10 Sept 2020	24 Jun 2021	27 May 2022
Actual Analysis		Final PFS Interim #1 OS Final ORR*	–	Final OS	Extended follow-up: Additional OS and PFS data reported
mFU (for OS)		18.1 months	23.5 months	32.9 months	44.0 months
Min FU			16	25.4 (2 year)	36.5 (3 year)
Key Publications/Posters/Abstracts presented at congress for each DBL					
QoL data		Choueiri et al. NEJM, 2021 [2] Porta et al. Poster 668P ESMO, 2021 (MAIC) [3]	Cella et al. Lancet Oncol, 2022 [4]	Cella et al. Poster ASCO GU, 2022 [4]	
Efficacy data		Choueiri et al. NEJM, 2021 [2]	Motzer et al. Poster 308. ASCO, GU 2021 [5] Apolo et al. Poster 4553. ASCO, 2021 [6]	Motzer et al. Lancet Oncol, 2022 [7]	Ipsen, Data on File, 2023 [1]

*Due to successful demonstration of PFS and OS superiority (as per SAP)

Key: ASCO GU, American Society of Clinical Oncology genitourinary; DBL, database lock; ESMO, European Society for Medical Oncology; FU, follow-up; m, median; min, minimum; N.A., not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SAP, statistical analysis plan.

Source: Ipsen, Data on File, 2023 [1]

1.1 Primary efficacy outcome: Progression-free survival

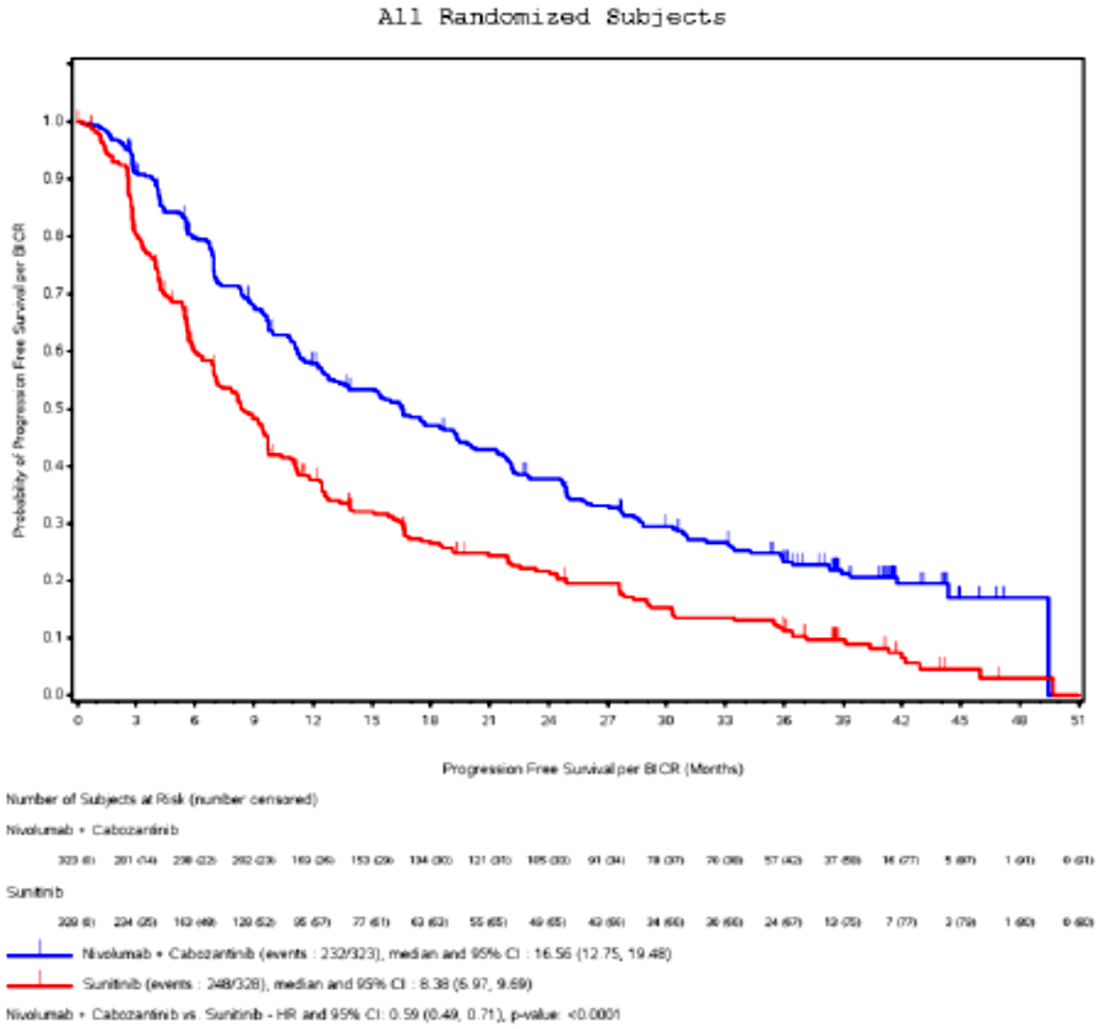
Table 2 presents a summary of PFS per blinded independent central review (BICR) assessment. A total of 480 BICR-assessed PFS events were observed at data cut-off: 232 in the cabozantinib with nivolumab arm and 248 in the sunitinib arm [1].

PFS was significantly improved with cabozantinib with nivolumab versus sunitinib with a doubling of PFS (median [95% confidence interval {CI}: 16.56 [12.75 – 19.48] versus 8.38 [6.97 – 9.69] months), resulting in a hazard ratio (HR) of 0.59 (95% CI: [0.49 – 0.71], p-value: <0.0001) [1]. Throughout the study, PFS rates were consistently higher with cabozantinib with nivolumab compared with sunitinib; at 6 months, the PFS rates were 79.6% versus 59.9%, at 9 months, PFS rates were 67.9% versus 48.3%, at 12 months were 57.8% versus 37.6%, and at 24 months were 37.8% versus 21.7%, respectively [1]. Separation of the Kaplan–Meier (KM) curves occurred early (in favour of cabozantinib with nivolumab), with no crossing of the curves (Figure 1). Overall, the PFS results show an extension in progression-free living with cabozantinib with nivolumab among treatment-naïve patients with advanced or metastatic renal cell carcinoma (RCC) compared with currently available first-line tyrosine kinase inhibitor (TKI) monotherapy.

Table 2: Summary of progression-free survival by blinded independent central review assessment

	Cabozantinib with Nivolumab (n = 323)	**Sunitinib (n = 328)**
Median PFS, months (95% CI) [a]	16.56 (12.75, 19.48)	8.38 (6.97, 9.69)
Hazard ratio (95% CI) [b]	0.59 (0.49, 0.71), p-value: <0.0001	
Key: CI, confidence interval; IRT, Interactive Response Technology; PFS, progression-free survival; RCC, renal cell carcinoma. **Notes:** [a], based on Kaplan–Meier estimates; [b], stratified Cox proportional hazards model. Hazard ratio is cabozantinib with nivolumab over sunitinib. **Source:** Ipsen, Data on File, 2023 [1]		

Figure 1: Kaplan–Meier curve of progression-free survival per blinded independent central review



Key: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Source: Ipsen, Data on File, 2023 [1]

1.2 Secondary efficacy outcome: Overall survival

Table 3 presents a summary of OS. In the randomised population, the minimum and median follow-up for OS across both treatment arms was 36.5 and 44.0 months, respectively [1].

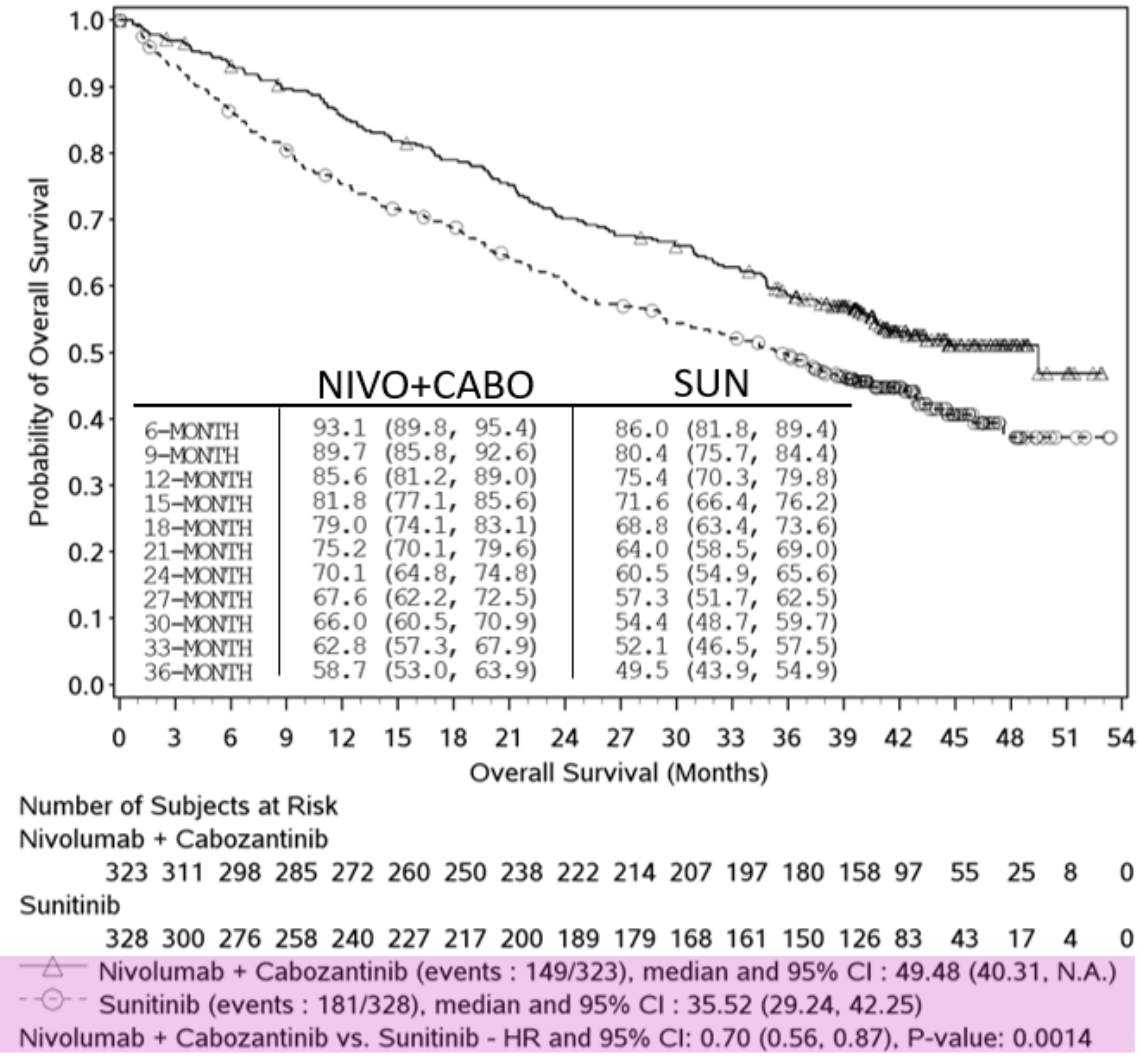
OS was significantly improved with cabozantinib with nivolumab versus sunitinib, with a HR of 0.70 (95% CI: 0.56 - 0.87), p-value: 0.0014. Median OS was 49.48 (95% CI: 40.31 –N.E.) months with cabozantinib with nivolumab and 35.52 (95% CI: 29.24 – 42.25) months with sunitinib, as shown in Figure 2 [1]. Throughout the study,

OS rates were consistently higher with cabozantinib with nivolumab compared with sunitinib; at 6 months, the OS rates were 93.1% versus 86.0%, at 9 months the OS rates were 89.7% versus 80.4%, at 12 months were 85.6% versus 75.4%, at 24 months were 70.1% versus 60.5%, respectively [1].

Table 3: Summary of overall survival

	Cabozantinib with Nivolumab (n = 323)	**Sunitinib (n = 328)**
Median OS, months (95% CI) [a]	49.48 (40.31, N.E.)	35.52 (29.24, 42.25)
Hazard ratio (98.89% CI) [b]	0.70 (0.56, 0.87)	
Key: CI, confidence interval; N.E., not estimable; OS, overall survival.		
Notes: [a], based on Kaplan–Meier estimates; [b], stratified Cox proportional hazards model. Hazard ratio is cabozantinib with nivolumab over sunitinib		
Source: Ipsen, Data on File, 2023 [1]		

Figure 2: Kaplan–Meier curve of overall survival



Key: CI, confidence interval; HR, hazard ratio; N.E., not estimable
Source: Ipsen, Data on File, 2023 [1]

1.3 Secondary efficacy outcome: Objective response rate

Table 4 presents a summary of response rates. The ORR was significantly higher with cabozantinib with nivolumab versus sunitinib with an absolute increase of 28.0% (56.0% [95% CI: 50.4, 61.5] versus 28.0% [95% CI: 23.3, 33.2]). A higher proportion of patients in the cabozantinib with nivolumab arm achieved complete response (CR) and a partial response (PR) compared with patients in the sunitinib arm (CR: 13.3% versus 4.9%; PR: 42.7% vs 23.2%), and a lower proportion of patients had progressive disease (PD: 6.5% vs 14.0%). The data was similar for 32.9-month cut-off (previous data).

Table 4: Summary of response rates per blinded independent central review

Outcome	Cabozantinib with nivolumab (N=323)	Sunitinib (N=328)
ORR %, (95% CI)[a]	181/323 (56.0%) (50.4, 61.5)	92/328 (28.0%) (23.3, 33.2)
Odds ratio estimate (95% CI)[b, c]	3.37 (2.41–4.72)	
p-value	<0.0001	
Best Overall Response		
CR, n (%)	43 (13.3)	16 (4.9)
PR, n (%)	138 (42.7)	76 (23.2)
SD, n (%)	103 (31.9)	135 (41.2)
PD, n (%)	21 (6.5)	46 (14.0)
Not evaluable/Not assessed, n (%)[d]	18 (5.6)	54 (16.5)
Median time to response (range), mo	2.83 (1.0–24.4)	4.32 (1.7–30.4)
Median duration of response (95% CI), mo[e]	22.08 (17.97, 26.02)	16.07 (11.07, 19.35)

Per RECIST 1.1, confirmation of response required
[a], CR+PR, confidence interval based on the Clopper and Pearson method. [b],Stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (>= 1% versus < 1% or indeterminate), and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT. [c], Strata adjusted odds ratio (Cabozantinib with nivolumab over Sunitinib) using Mantel-Haenszel method. [d], Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified. [e,] Median computed using Kaplan–Meier method. **Key:** CR, complete response; IMDC, International Metastatic RCC Database Consortium; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease
Source: Ipsen, Data on File, 2023 [1]

1.4 Secondary efficacy outcome: Time to response and duration of response

The median time to response (TTR) was shorter for confirmed responders treated with cabozantinib and nivolumab compared to those treated with sunitinib (2.83 versus 4.32 months; Table 5). In addition, the median duration of response (DoR) was longer for confirmed responders treated with cabozantinib with nivolumab compared with those treated with sunitinib (22.08 [95% CI: 17.97, 26.02] versus 16.07 [95% CI: 11.07, 19.35]) [1]. Table 5 presents a Kaplan–Meier plot of DoR.

Table 5: Time to and duration of response per blinded independent central review

Outcome	Cabozantinib with nivolumab (n=180)	Sunitinib (n=93)
Time to objective response (months)		
Mean	3.98	6.10
Median	2.83	4.32
Min, Max	1.0, 24.4	1.7, 30.4
Q1, Q3	2.76, 4.11	2.83, 7.13
Standard deviation	3.22	4.76
Duration of response (months)		
Min, Max [a]	1.4+, 45.4	1.6+, 42.6
Median (95% CI), mo[b]	22.08 (17.97, 26.02)	16.07 (11.07, 19.35)
N event/N responders (%)	121/181 (61.9)	69/92 (75.0)

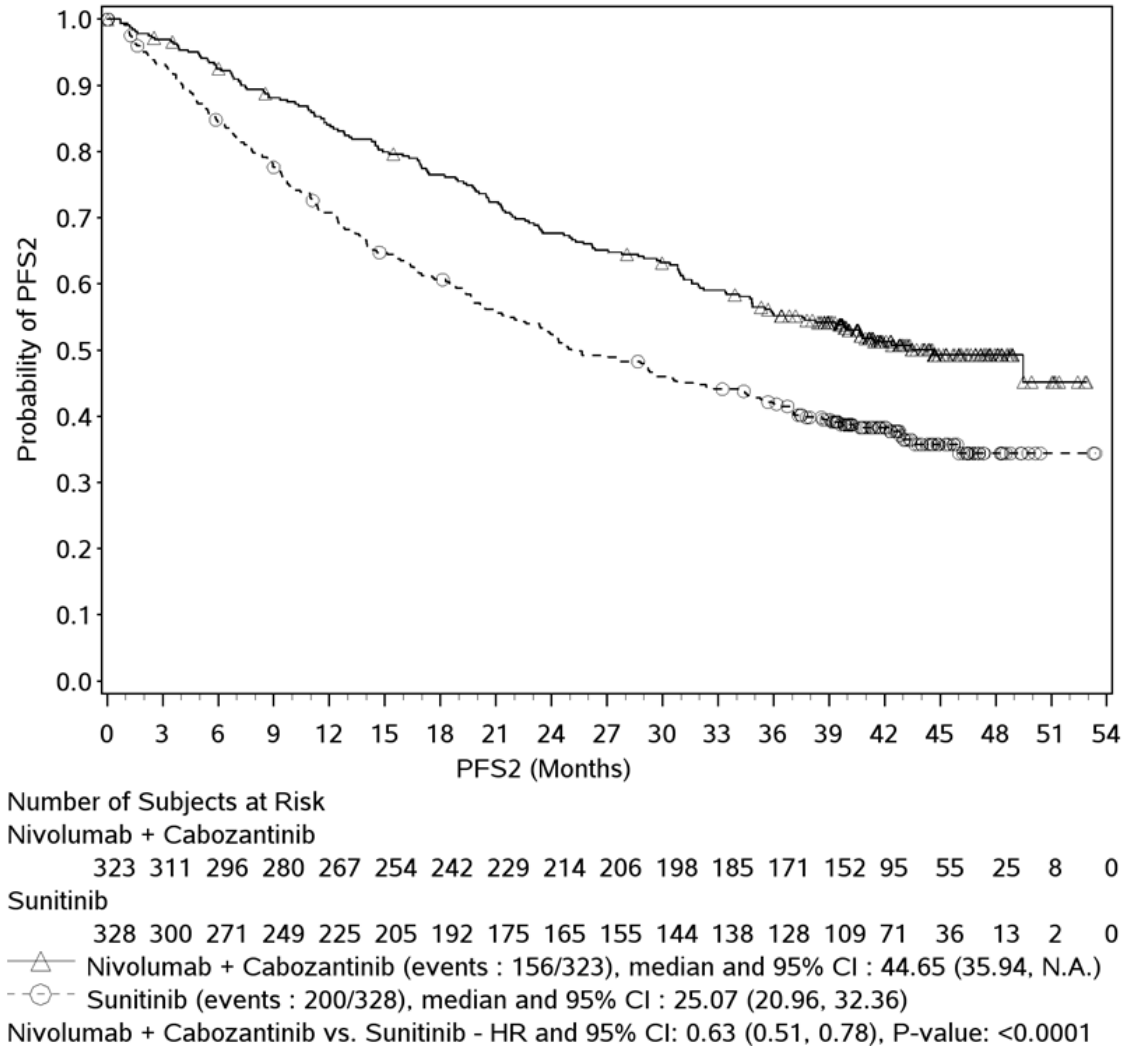
[a], Symbol + indicates a censored value; [b], median computed using Kaplan-Meier method.
Key: CI, confidence interval; max, maximum; min, minimum; mo, months; N, number
Source: Ipsen, Data on File, 2023 [1]

1.5 Exploratory efficacy outcome: Progression-free survival-2 (PFS-2) per investigator assessment

For the analysis of progression-free survival on next line of treatment (PFS-2), patients who were alive and without progression after the next line of treatment were censored at their last known alive date.

A total of 356 investigator-assessed PFS-2 events were observed: 48.3% in the cabozantinib with nivolumab arm and 61.0% in the sunitinib arm. The median (95% CI) PFS-2 per investigator was 44.65 (35.94, N.A.) months in the cabozantinib with nivolumab arm, and 25.07 (20.96, 32.36) months in the sunitinib arm. HR of the cabozantinib with nivolumab arm over the sunitinib arm was 0.63 (95% CI: 0.51, 0.78), with p<0.0001 [1] (Figure 3).

Figure 3: Kaplan–Meier plot of investigator-assessed progression-free survival-2



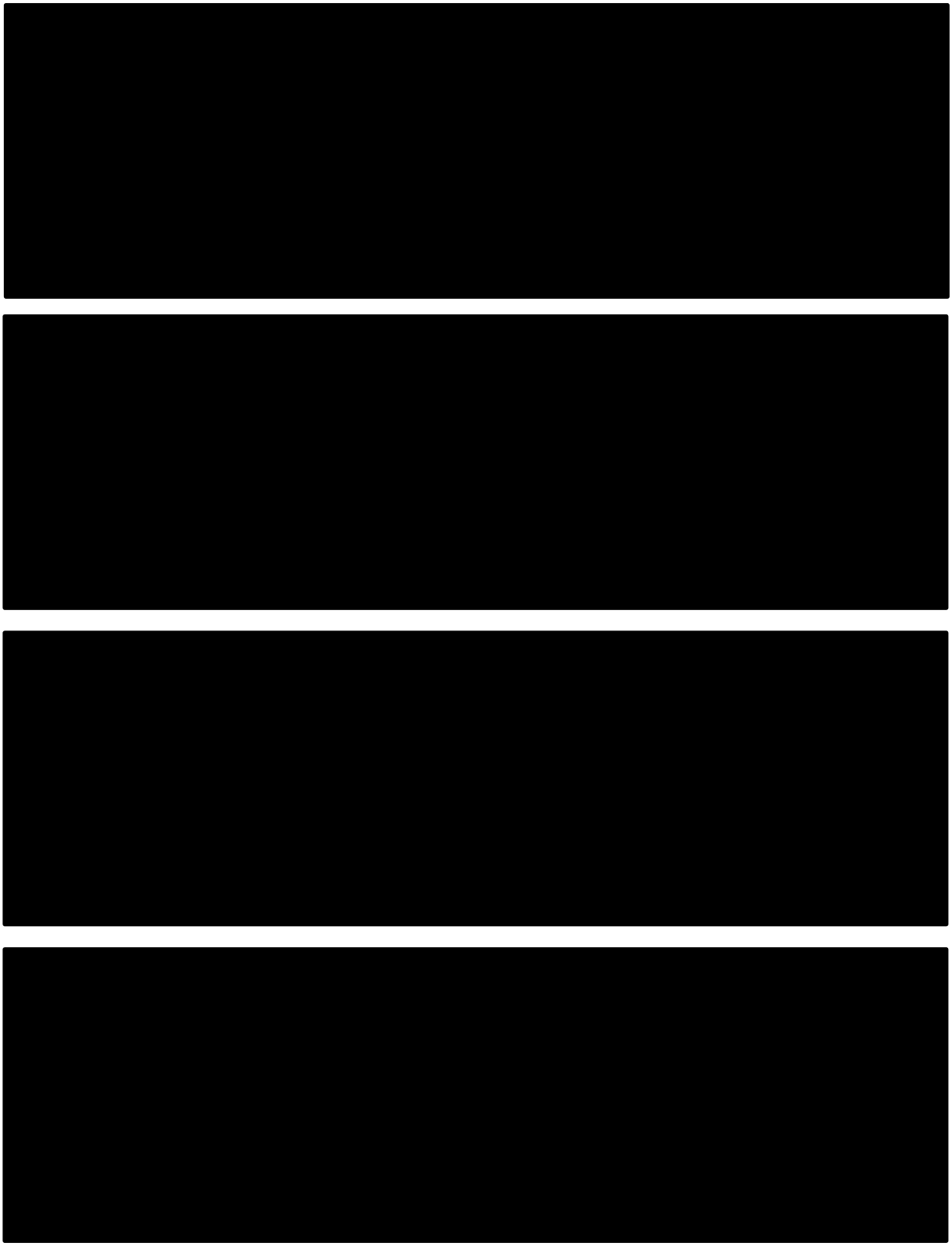
Key: CI, confidence interval; PFS2, progression-free survival on next line of treatment.
Notes: Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test. Symbols represent censored observations.
Source: Ipsen, Data on File, 2023 [1]

2. Subgroup analysis

Overall, cabozantinib with nivolumab showed a consistently favourable treatment effect versus sunitinib in pre-planned subgroup analyses (analysed for PFS, OS and ORR for all the subgroups), [redacted].

2.1 Progression-free survival

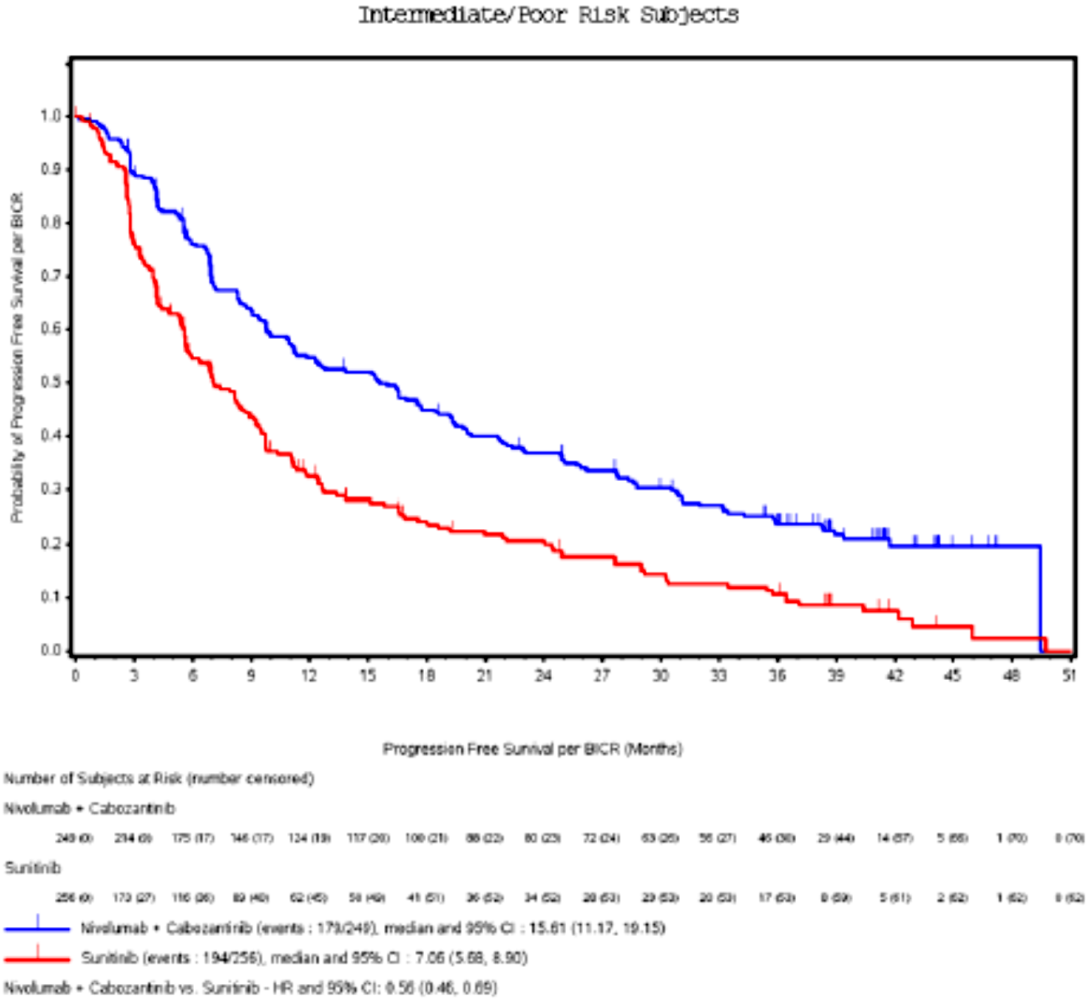
Figure 4: Forest Plot of Treatment Effect on Progression Free Survival per BICR in Pre-Defined Subsets - Primary Definition - All Randomised Subjects



Note: HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Key: CI, confidence interval; HR, hazard ratio; PFS, progression free survival; IRT, Interactive Response Technology; CRF, Case Report Form
Source: Ipsen, Data on File, 2023 [1]

For intermediate/poor International Metastatic RCC Database Consortium (IMDC) risk group, PFS was significantly improved with cabozantinib with nivolumab versus sunitinib with a doubling of PFS (median [95%CI: 15.61 [11.17 – 19.15] versus 7.05 [5.68 – 8.90] months), resulting in a HR of 0.56 (95% CI: 0.46 – 0.69) [1] (Figure 5).

Figure 5: Kaplan–Meier curve of progression-free survival per blinded independent central review for intermediate/poor independent data safety monitoring committee risk group



Key: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Source: Ipsen, Data on File, 2023 [1]

2.2 Overall survival

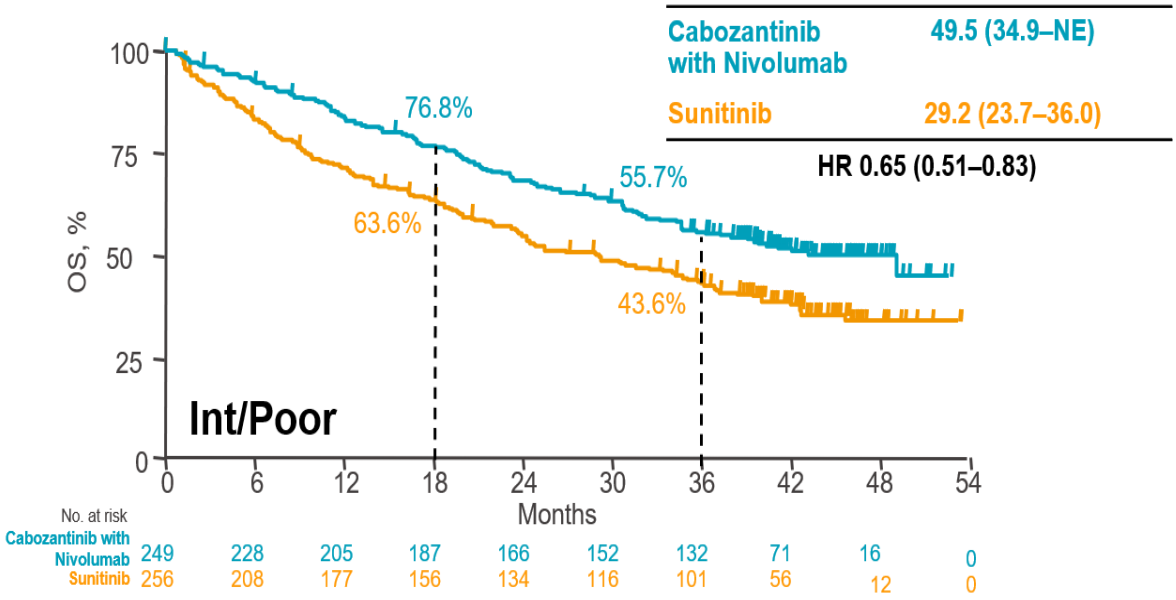
In all selected subgroups, cabozantinib with nivolumab demonstrated a positive trend in overall survival compared to the sunitinib arm,

Figure 6.

Figure 6: Overall Survival in Select Subgroups

For intermediate/poor IDMC risk group, OS was significantly improved with cabozantinib with nivolumab versus sunitinib with a doubling of OS (median [95% CI: 49.5 [34.9 – N.E.] versus 29.2 [23.7 – 36.0] months), resulting in a HR of 0.65 (95% CI: 0.51 – 0.83) [1] (Figure 7).

Figure 7: Kaplan–Meier curve of overall survival per blinded independent central review for intermediate/poor independent data safety monitoring committee risk group



Key: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: Ipsen, Data on File, 2023 [1]

2.3 Objective response rate

ORR was also observed for all IMDC-risk groups for cabozantinib with nivolumab versus sunitinib arms (Table 6).

Table 6: Confirmed ORR per blinded independent central review and BOR by IMDC-risk group

Outcome	Favourable		Intermediate		Poor		I/P	
	Cabo Nivo (n=74)	SUN (n=72)	Cabo Nivo (n=188)	SUN (n=188)	Cabo Nivo (n=61)	SUN (n=68)	Cabo Nivo (n=249)	SUN (n= 256)
ORR n (%), (95% CI)	50 (67.6) (55.7, 78.0)	33 (45.8) (34.0, 58.0)	106 (56.4) (49.0, 63.6)	52 (27.7) (21.4, 34.6)	25 (41.0) (28.6, 54.3)	7 (10.3) (4.2, 20.1)	131 (52.6) (46.2, 58.9)	59 (23.0) (18.0, 28.7)
Complete response, n (%)	12 (16.2)	7 (9.7)	28 (14.9)	8 (4.3)	3 (4.9)	1 (1.5)	31 (12.4)	9 (3.5)
Partial response, n (%)	38 (51.4)	26 (36.1)	78 (41.5%)	44 (23.4)	22 (36.1)	6 (8.8)	100 (40.2)	50 (19.5)
Stable disease, n (%)	22 (29.7)	28 (38.9)	56 (29.8)	80 (42.2)	25 (41.0)	27 (39.7)	81 (32.5)	107 (41.8)
Progressive disease, n (%)	2 (2.7)	2 (2.8)	15 (8.0)	29 (15.4)	4 (6.6)	15 (22.1)	19 (7.6)	44 (17.6)
Not evaluable/ not assessed, n (%) [a]	0	9 (12.5)	11 (5.9)	26 (13.8)	7 (11.5)	19 (27.9)	18 (7.2)	45 (17.6)

Key: BOR, best overall response; CaboNivo, cabozantinib with nivolumab; CI, confidence interval; IMDC, International Metastatic renal cell carcinoma Database Consortium; I/P, intermediate/poor; ORR, objective response rate; SUN, sunitinib

Source: Ipsen, Data on File, 2023 [1]

3. Adverse reactions

Unless otherwise specified, all results in this section are presented for the treated population (n = 640), for the CheckMate 9ER study. There were no other relevant studies which stated additional adverse events (AE), except the ones covered in this section below.

3.1 Treatment exposure

Table 7 presents a summary of the treatment exposure during the latest follow-up for CheckMate 9ER study, 44.0 (36.5–56.5) months. The median duration of treatment (defined as last dose date – start dose date + 1 day) was 21.8 months for cabozantinib with nivolumab and 8.9 months for sunitinib [1].

In the latest analysis (mFU 44 months), 62.8% and 54.4% of patients had at least 1 dose reductions for cabozantinib and sunitinib respectively, with no dose reductions allowed for nivolumab [1].

Two additional patients discontinued treatment due to an any-grade treatment-related AE since the previous database lock (mFU 32.9 mo) and one patient discontinued either cabozantinib or nivolumab, and one patient discontinued sunitinib [1].

Table 7: Summary of treatment exposure in CheckMate 9ER (mFU 44 months)

	Cabozantinib with Nivolumab (n = 320)	Sunitinib (n = 320)
Median duration of therapy (IQE), months	21.8 (8.8–34.0)	8.9 (2.9–20.7)
Patients with at least 1 dose reduction (Cabozantinib or Sunitinib), % a	62.8	54.4
Treatment discontinuation, n (%) b	263 (82.2)	288 (90.0)
Treatment discontinuation due to disease progression, %	48.1	62.8
Any-grade treatment-related AEs leading to discontinuation, n (%) c	88 (27.5) [d]	34 (10.6)
Nivolumab only, n (%)	31 (9.7)	-
Cabozantinib only, n (%)	31 (9.7)	-
Cabozantinib and Nivolumab, both, n (%)	21 (6.6)	-
Cabozantinib and Nivolumab, sequential, n (%)	5 (1.6)	-

[a]No dose reductions were allowed for Nivolumab but were permitted for Cabozantinib and Sunitinib per protocol. [b]Reasons were reported per investigator at the time of discontinuation and included disease progression, study drug toxicity, death, adverse event unrelated to study drug, request to discontinue treatment, withdrawal of consent, poor/non-compliance, administrative reasons by sponsor, maximum clinical benefit, completion of treatment per protocol, other reason. [c]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients. [d]Includes events leading to discontinuation of either Nivolumab or Cabozantinib at any time; as the assessments for discontinuation of Nivolumab and Cabozantinib were made separately for each drug, it was acceptable to continue treatment with only the study drug that was not related to the observed toxicity. Patients in the Cabozantinib and Nivolumab group were considered off treatment if both Cabozantinib and Nivolumab are discontinued.

Source: Ipsen, Data on File, 2023 [1]

3.1.1 Time to treatment discontinuation

The median (95% CI) time to treatment discontinuation (TTD) based on Kaplan-Meier analysis was [redacted] and [redacted] months for the cabozantinib with nivolumab and sunitinib arms, respectively [1], as depicted in Figure 8: Kaplan–Meier plot of time to treatment discontinuation (cabozantinib and nivolumab considered dependently)

In this analysis, patients in the cabozantinib with nivolumab arm were considered as off-treatment if both nivolumab and cabozantinib were discontinued.

Figure 8: Kaplan–Meier plot of time to treatment discontinuation (cabozantinib and nivolumab considered dependently)

Key: CI, confidence interval.
Source: Ipsen, Data on File, 2023 [1]

3.1.2 Subsequent therapy

In the intention to treat (ITT) population, subsequent anti-cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 35.9% patients in

cabozantinib with nivolumab arm and 45.1% patients in the sunitinib arm, as summarised in Table 8.

Table 8: Subsequent therapy summary (median follow-up 44 months)

	Cabozantinib with Nivolumab (n = 323)	**Sunitinib (n = 328)**
Any subsequent therapy[a]	116 (35.9)	148 (45.1)
Subsequent radiotherapy	46 (14.2)	40 (12.2)
Subsequent surgery	25 (7.7)	18 (5.5)
Subsequent systemic therapy	81 (25.1)	133 (40.5)
Any PD-(L)1 inhibitor	21 (6.5)	101 (30.8)
Nivolumab	17 (5.3)	93 (28.4)
Pembrolizumab	7 (2.2)	7 (2.1)
Atezolizumab	0	1 (0.3)
Durvalumab	0	4 (1.2)
Any CTLA4 inhibitor	8 (2.5)	20 (6.1)
Ipilimumab	8 (2.5)	19 (5.8)
Tremelimumab	0	1 (0.3)
Any VEGF(R) inhibitor	69 (21.4)	63 (19.2)
Axitinib	29 (9.0)	20 (6.1)
Sunitinib	21 (6.5)	8 (2.4)
Pazopanib	13 (4.0)	8 (2.4)
Lenvatinib	10 (3.1)	3 (0.9)
Cabozantinib	7 (2.2)	30 (9.1)
Sorafenib	2 (0.6)	7 (2.1)
Tivozanib	2 (0.6)	0
Sorafenib tosilate	1 (0.3)	0
Tivozanib hydrochloride monohydrate	0	1 (0.3)
Other	20 (6.2)	18 (5.5)
Everolimus	12 (3.7)	10 (3.0)
Investigational antineoplastic drugs	4 (1.2)	4 (1.2)
Belzutifan	1 (0.3)	0
BMS 986179	1 (0.3)	0
Gimeracil; oteracil potassium; tegafur	1 (0.3)	0
MK 4280	1 (0.3)	0
Talazoparib	1 (0.3)	0

Investigational drug	0	1 (0.3)
Other monoclonal antibodies and anybody drug conjugates	0	1 (0.3)
Savolitinib	0	2 (0.6)
Temsirolimus	0	1 (0.3)

[a] Patient may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if patient never treated).
Source: Ipsen, Data on File. April 2023 [1]

Subsequent therapy followed similar trends as previously reported; most commonly, PD-1/PD-L1 inhibitor-based subsequent therapy was used in the sunitinib arm and VEGF-targeted subsequent therapy was used in the cabozantinib with nivolumab arm (Table 8).

Table 8: Subsequent therapy summary (median follow-up 44 months)

	Cabozantinib with Nivolumab (n = 323)	**Sunitinib (n = 328)**
Any subsequent therapy[a]	116 (35.9)	148 (45.1)
Subsequent radiotherapy	46 (14.2)	40 (12.2)
Subsequent surgery	25 (7.7)	18 (5.5)
Subsequent systemic therapy	81 (25.1)	133 (40.5)
Any PD-(L)1 inhibitor	21 (6.5)	101 (30.8)
Nivolumab	17 (5.3)	93 (28.4)
Pembrolizumab	7 (2.2)	7 (2.1)
Atezolizumab	0	1 (0.3)
Durvalumab	0	4 (1.2)
Any CTLA4 inhibitor	8 (2.5)	20 (6.1)
Ipilimumab	8 (2.5)	19 (5.8)
Tremelimumab	0	1 (0.3)
Any VEGF(R) inhibitor	69 (21.4)	63 (19.2)
Axitinib	29 (9.0)	20 (6.1)
Sunitinib	21 (6.5)	8 (2.4)
Pazopanib	13 (4.0)	8 (2.4)
Lenvatinib	10 (3.1)	3 (0.9)
Cabozantinib	7 (2.2)	30 (9.1)
Sorafenib	2 (0.6)	7 (2.1)
Tivozanib	2 (0.6)	0

Sorafenib tosilate	1 (0.3)	0
Tivozanib hydrochloride monohydrate	0	1 (0.3)
Other	20 (6.2)	18 (5.5)
Everolimus	12 (3.7)	10 (3.0)
Investigational antineoplastic drugs	4 (1.2)	4 (1.2)
Belzutifan	1 (0.3)	0
BMS 986179	1 (0.3)	0
Gimeracil; oteracil potassium; tegafur	1 (0.3)	0
MK 4280	1 (0.3)	0
Talazoparib	1 (0.3)	0
Investigational drug	0	1 (0.3)
Other monoclonal antibodies and anybody drug conjugates	0	1 (0.3)
	0	2 (0.6)
Savolitinib	0	1 (0.3)
Temsirolimus		

[a] Patient may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if patient never treated).
Source: Ipsen, Data on File. April 2023 [1]

Time to subsequent therapy was also observed for patients who completed 2 years of nivolumab therapy (in a post-hoc analysis) with median of [redacted] months ([redacted]) (Figure 9).

Figure 9: Time to subsequent therapy for patients who completed 2 years of nivolumab (post-hoc analysis)

Notes: Time to subsequent therapy was defined in patients who are completed 2 years of nivolumab treatment as (1) the survival time from end of therapy in patients who never received subsequent therapy, and (2) the time from end of therapy until subsequent therapy in patients who received subsequent therapy. An event was defined as receiving subsequent therapy or death. Symbols represent censored observations

[a]Among patients who discontinued nivolumab treatment after 2 years, 101 (88%) continued to receive cabozantinib treatment.
Source: Ipsen, Data on File, 2023 [1]

3.2 Adverse events

3.2.1 Summary of treatment-related adverse events

Table 9 presents a summary of treatment-related adverse events (TRAEs). The most commonly observed TRAEs showed similar results as with previous reported data. Also, TRAEs were consistent between treatment arms (cabozantinib with nivolumab versus sunitinib): diarrhoea (59.4% versus 46.3%), palmar-plantar erythrodysaesthesia syndrome (38.8% versus 41.9%), hypothyroidism (36.9% versus 30.6%), hypertension (33.1% versus 34.1%), and fatigue (27.5% versus 31.6%). In the cabozantinib with nivolumab arm, the most frequently reported grade 3–4 drug-related AEs were hypertension (12.8%), palmar-plantar erythrodysaesthesia syndrome (7.8%), diarrhoea (7.2%) and increased ALT (5.9%). In the sunitinib arm, the most common grade 3–4 drug-related AEs were hypertension (12.5%), palmar-plantar erythrodysaesthesia syndrome (8.1%), fatigue (4.7%) and diarrhoea (4.7%) [1].

Table 9: Summary of any-grade TRAEs in ≥ 20% of treated patients of either arm (with 30 days follow-up), mFU 44 months

Event	Cabozantinib with Nivolumab (n = 320)		Sunitinib (n = 320)	
	Any grade	Grade ≥3[a]	Any grade	Grade ≥3[a]
	No. of patients (%)			
Patients with any event	311 (97.2)	214 (66.9)	298 (93.1)	177 (55.3)
Diarrhoea	190 (59.4)	23 (7.2)	148 (46.3)	15 (4.7)
Palmar-plantar erythrodysaesthesia	124 (38.8)	25 (7.8)	134 (41.9)	26 (8.1)
Hypothyroidism	118 (36.9)	1 (0.3)	98 (30.6)	1 (0.3)
Hypertension	106 (33.1)	41 (12.8)	109 (34.1)	40 (12.5)
ALT increased	91 (28.4)	19 (5.9)	23 (7.2)	4 (1.3)
Fatigue	88 (27.5)	8 (2.5)	101 (31.6)	15 (4.7)
AST increased	86 (26.9)	12 (3.8)	36 (11.3)	3 (0.9)
Nausea	77 (24.1)	1 (0.3)	87 (27.2)	0
Dysgeusia	69 (21.6)	0	67 (20.9)	0
Decreased appetite	69 (21.6)	4 (1.3)	55 (17.2)	2 (0.6)
Rash	66 (20.6)	6 (1.9)	22 (6.9)	0
Mucosal inflammation	67 (20.9)	3 (0.9)	83 (25.9)	8 (2.5)

[a]Zero patients had a grade 5 event with cabozantinib with nivolumab and 1 patient had a grade 5 event with sunitinib.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Ipsen, Data on File, 2023 [1]

3.2.2 Most common adverse events

Almost all patients in both treatment arms experienced an AE (Table 10). In the latest follow-up (mFU 44.0 months), 45.9% subjects in the cabozantinib with nivolumab arm and 55.3% of subjects in the sunitinib arm had died. The frequency of deaths attributed to study drug toxicity was low and similar between the cabozantinib with nivolumab and sunitinib arms. Disease progression was the most common cause of death in both arms [1].

Table 10 provides a summary of the most commonly observed all-cause AEs reported in ≥ 20% of patients in either treatment arm during the CheckMate 9ER study [1]. Similar results were observed for most commonly observed AEs in this follow-up study (mFU 44.0 months) as with previous study data cut-off points.

The most commonly observed any grade all-cause AEs were consistent between treatment arms (cabozantinib with nivolumab versus sunitinib): diarrhoea (65.6% versus 50.3%), palmar-plantar erythrodysaesthesia syndrome (40.6% versus 41.9%), hypertension (39.4% versus 37.5%), hypothyroidism (37.5% versus 32.5%), and fatigue (34.1% versus 35.6%). In the cabozantinib with nivolumab arm, the most frequently reported grade 3–4 drug-related AEs were hypertension (15.6%), diarrhoea (8.8%), palmar-plantar erythrodysaesthesia syndrome (7.8%), and increased ALT (6.6%). In the sunitinib arm, the most common Grade 3–4 drug-related AEs were hypertension (13.4%), palmar-plantar erythrodysaesthesia syndrome (8.1%), fatigue (5.6%) and diarrhoea (4.7%) [1] (Table 10).

Table 10: Summary of any-grade all-cause AEs in ≥ 20% of treated patients of either arm (with 30 days follow-up), mFU 44 months

Event	Cabozantinib with Nivolumab (n = 320)		Sunitinib (n = 320)	
	Any grade	Grade ≥3[a]	Any grade	Grade ≥3[a]
No. of patients (%)				
Patients with any event	319 (99.7)	268 (83.8)	317 (99.1)	243 (75.9)
Diarrhoea	210 (65.6)	28 (8.8)	161 (50.3)	15 (4.7)
Palmar-plantar erythrodysaesthesia	130 (40.6)	25 (7.8)	134 (41.9)	26 (8.1)
Hypertension	126 (39.4)	50 (15.6)	120 (37.5)	43 (13.4)
Hypothyroidism	120 (37.5)	1 (0.3)	104 (32.5)	1 (0.3)
Fatigue	109 (34.1)	11 (3.4)	114 (35.6)	18 (5.6)
Decreased appetite	102 (31.9)	6 (1.9)	67 (20.9)	4 (1.3)

ALT increased	103 (32.2)	21 (6.6)	30 (9.4)	8 (2.5)
Nausea	98 (30.6)	2 (0.6)	104 (32.5)	1 (0.3)
AST increased	97 (30.3)	13 (4.1)	43 (13.4)	4 (1.3)
Dysgeusia	76 (23.8)	0	71 (22.2)	0
Rash	77 (24.1)	7 (2.2)	28 (8.8)	0
Asthenia	76 (23.8)	15 (4.7)	59 (18.4)	11 (3.4)
Mucosal inflammation	72 (22.5)	3 (0.9)	84 (26.3)	8 (2.5)
Pruritus	71 (22.2)	2 (0.6)	15 (4.7)	0
Arthralgia	77 (24.1)	2 (0.6)	44 (13.8)	1 (0.3)
Back Pain	73 (22.8)	7 (2.2)	44 (13.8)	7 (2.2)
Vomiting	67 (20.9)	6 (1.9)	68 (21.3)	2 (0.6)

[a]24 patients had a grade 5 event with cabozantinib with nivolumab and 18 patients had a grade 5 event with sunitinib.
Includes events reported between first dose and 30 days after last dose of study
Source: Ipsen, Data on File, 2023 [1]

3.2.3 Summary of immune-mediated adverse events

Table 11 presents a summary of the immune-mediated adverse events (IMAEs) assessed during CheckMate 9ER. IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (i.e., with extended follow-up). These analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate aetiology and an immune mediated component.

Overall, the majority of IMAEs were grade 1–2 in severity. The most common in both treatment arms was hypothyroidism/thyroiditis (cabozantinib with nivolumab: 27.8%; sunitinib: 9.7%). Grade 3 or worse IMAEs were uncommon in all patients treated in

the cabozantinib with nivolumab arm (Table 11); the most common were increased alanine aminotransferase (9 [2.8%]), diarrhoea (8 [2.5%]), and hepatotoxicity (7 [2.2%]). In the sunitinib group, grade 3 or worse IMAEs were reported for hypothyroidism and hepatotoxicity (each, 1 [<1.0%] of 320).

Table 11: Any-grade immune-mediated adverse events in CheckMate 9ER, in > 1% of treated patients, mFU 44 months

Event	Cabozantinib with Nivolumab (n = 320)		Sunitinib (n = 320)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	No. of patients (%)			
Hypothyroidism[a]	89 (27.8)	1 (0.3)	31 (9.7)	1 (0.3)
Hyperthyroidism[a]	30 (9.4)	2 (0.6)	1 (0.3)	0
Rash	27 (8.4)	5 (1.6)	1 (0.3)	0
Diarrhoea	18 (5.6)	8 (2.5)	0	0
Hepatotoxicity	12 (3.8)	7 (2.2)	6 (1.9)	1 (0.3)
Pneumonitis	13 (4.1)	5 (1.6)	1 (0.3)	0
ALT increased	13 (4.1)	9 (2.8)	1 (0.3)	0
Adrenal insufficiency[a]	12 (3.8)	6 (1.9)	0	0
AST increased	9 (2.8)	5 (1.6)	1 (0.3)	0
Maculo-papular rash	9 (2.8)	0	1 (0.3)	0
Hepatitis	5 (1.6)	3 (0.9)	0	0
Increased blood bilirubin	5 (1.6)	0	1 (0.3)	0

Overall, 22% of 320 patients treated with cabozantinib with nivolumab received corticosteroids[b] to manage any-grade immune-mediated AEs; 13% and 5% of patients received corticosteroids[b] continuously for ≥ 14 days and ≥ 30 days, respectively.

Zero patients had a grade 5 event.

Includes AEs of any grade occurring in ≥ 1% of CaboNivo treated patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose,

regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component.

[a] Endocrine immune-mediated AEs
[b] Greater than or equal to 40 mg of prednisone daily or equivalent.

Source: Ipsen, Data on File, 2023 [1]

Appendix 1

Table 12: Checklist of the median 44-month follow-up data for the CheckMate-9ER trial provided in this updated submission compared with the median 32-month follow-up data submitted on 03/04/23

32.9-month data submitted to NICE 03/04/23	44-month data submitted 12/04/23
A.2.6 Clinical effectiveness results of the relevant studies	
A.2.6.1 Primary efficacy outcome: Progression-free survival (BICR)	Yes
A.2.6.2 Secondary efficacy outcome: Overall survival	Yes
A.2.6.3 Secondary efficacy outcome: Objective response rate	Yes
A.2.6.3.1. Best overall response	Yes
A.2.6.4 Secondary efficacy outcome: Time to response and duration of response	Yes
	Progression-free survival-2 (PFS-2) per investigator assessment
A.2.7 Subgroup analysis	
PFS Forest plot inc. risk groups	Yes
OS Forest plot inc. risk groups	Yes
ORR tables inc. risk groups	Yes
Intermediate/Poor Risk results for PFS (K-M plot), OS (K-M plot) and ORR	Yes
A.2.8 Adverse reactions	
A.2.8.1 Treatment exposure	Yes
A.2.8.1.1 Time to treatment discontinuation	Yes
A.2.8.1.2 Infusion interruptions and infusion rate reductions of nivolumab	No
A.2.8.1.3 Dose delays and dose reductions	No
A.2.8.1.4 Subsequent therapy	Yes. Additional data also provided for Time to subsequent therapy for patients who completed 2 years of nivolumab
A.2.8.2 Adverse events	

A.2.8.2.1 Summary of treatment-emergent adverse events	Yes
A.2.8.2.2 Most common adverse events	Yes
A.2.8.2.3 Adverse events leading to discontinuation of study treatment	No
A.2.8.2.4 Summary of immune-mediated adverse events	Yes
A.2.8.3 Safety overview	No additional information provided
A.2.9 Ongoing studies	No additional information provided
A.2.10 Interpretation of clinical effectiveness and safety evidence	No additional information provided
A.2.10.1 Principal findings from the clinical evidence	No additional information provided
A.2.10.2 Strengths and limitations of the evidence base	No additional information provided
A.3 Cost-effectiveness	
A.3.1 Health-related quality of life data from clinical trials	No additional information provided
A.3.1.1 Data collection	No additional information provided
A3.1.2 Completion rates and baseline scores (EQ-5D-3L utility)	No additional information provided
A.3.2 Analysis of utility	No additional information provided
A.3.2.1 Multivariate mixed-model analysis	No additional information provided
A.3.2.2 Missing values	No additional information provided
A.3.2.3 Model selection steps	No additional information provided
A.3.2.4 Selected model for EQ-5D-3L utility change	No additional information provided
A.3.2.5 EQ-5D-3L utility change from baseline	No additional information provided
A.3.2.6 Estimated utility values by progression status	No additional information provided
A.3.2.7 Adverse reactions	No additional information provided
A.3.3 Mapping	No additional information provided
A.3.4 Health-related utility data from the literature	No additional information provided
A.3.5 Intervention and comparators' costs and resource use	No additional information provided
A.3.5.1 Intervention costs	No additional information provided
A.3.5.2 Administration costs	No additional information provided
A.3.5.3 End of Life Costs	No additional information provided

A.3.6 Uncertainty	No additional information provided
A.3.7 Benefits not captured in the quality-adjusted life year (QALY) calculation	No additional information provided

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Health technology appraisal

Renal Cell Carcinoma Pathways Pilot [ID6186]

Patient organisation submission on the disease and current treatment pathway

Thank you for agreeing to give us your organisation's views on renal cell carcinoma and the current treatment pathway.

You can provide a unique perspective that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Action Kidney Cancer
3. Job title or position	Policy and Medical Affairs
4a. Brief description of the organisation (including who funds it). How many members does it have?	Action Kidney Cancer was founded in 2006 by two cancer patients/survivors, who started by providing practical and bespoke support to individual patients for access to life-extending systemic anti-cancer treatments for advanced or metastatic kidney cancer. Empowering patients to take an active role in their own health care, and in decisions affecting the choice, provision, and quality of cancer services throughout the UK, remains the top priority for Action Kidney Cancer. Over the years, Action Kidney Cancer has grown considerably, with a membership of over 1400 kidney cancer patients and carers on its confidential community forum. In addition, our website regularly has over 300 visits per day from people looking for information about kidney cancer, advice, and support. Action Kidney Cancer is unique; originally it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Action Kidney Cancer remains patient-led, and the group is now a registered charity, which enables it to better meet the growing needs of the kidney cancer community in the UK. The charity employs 5 part-time, home-based contractors in England and Scotland. Before the COVID-19 pandemic, funding came from trusts, foundations, and the pharmaceutical industry (around 55%), as well as fundraising activities/events organised by the public and kidney cancer community (45%). Since the pandemic, the latter has almost halved.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	When gathering the information for this submission, we specifically asked for patient and carer experience of the current treatment pathway for advanced or metastatic kidney cancer through our confidential community forum. Over 1400 patients and carers use this forum to communicate on a regular basis, and we receive in the order of 5-600 interactions and comments a day on our closed Facebook group.

Living with the condition **6a. What is it like to live with the condition?** **6b. What do carers experience when caring for someone with the condition?**	**6a. What is it like to live with the condition?** Advanced/metastatic renal cell carcinoma (RCC) is a devastating disease and is currently incurable. Most people with this disease are forced to give up work because of the symptoms of the cancer, or the toxicity of current systemic anti-cancer treatments, which can be very debilitating. This brings enormous financial pressures for patients and their families, sometimes resulting in psychosocial problems, depression and loss of confidence and self-worth. Most patients with advanced/metastatic RCC will have surgery to remove their tumour. This can be open or laparoscopic surgery, or radical or partial nephrectomy. Open surgery is a major operation to remove the whole kidney or part of the kidney along with the tumour. Patients may be hospitalised for up to 10 days following surgery, during which time they start rehabilitation. This requires physiotherapy to encourage the patient to walk and pain relief with opiates while they recover from surgery. Recovery and rehabilitation can take up to 6 weeks before patients can get back to daily activities, such as shopping, driving, exercise, gardening, housework and returning to work. This has a major impact on their lives and reduces their quality of life while they are in recovery. It also has a financial implication to both the patient and the family and carer if the patient is not able to work during recovery from surgery, especially if complications arise and recovery takes longer than expected. Nephrectomy is generally a safe procedure. But, as with any operation, nephrectomy carries a potential risk of short-term complications, such as bleeding, infection, injury to nearby organs, uncomfortable bloating after laparoscopic surgery, and other serious problems. Long-term complications from a nephrectomy relate to potential problems of living with less than two complete, fully functioning kidneys. Although overall kidney function decreases after a nephrectomy, the remaining kidney tissue usually works well enough for a healthy life. However, problems that may occur with long-term reduced kidney function include hypertension and chronic kidney disease, which could eventually result in dialysis and the additional costs of this to the state. Patients need to be mindful of these long-term complications and may need to adjust their lifestyles and diet to reduce the risk of developing them. This can also impact their quality of life, as well as the quality of life of their family and carers.

This is a quote from a patient about their experience of life after a nephrectomy:

> *"Life after nephrectomy is unpredictable. Initially there is a feeling of absolute relief that the tumour that grew inside you (without your knowledge), had been cut out… and that they had "got it all". But that feeling of thankfulness for the skill of the surgeons and the care of your hospital team is soon replaced by the fear of what might happen at your first routine scan. Patients are told that kidney cancer is a "difficult" cancer to treat, and there is always a sneaky all-pervading worry that a routine scan will pick up a spread of cancer and that what remains of your life will be changed irrevocably. So, you cope with the day-to-day problems of chronic constipation, the pain from the incisional hernia, and the general fatigue because it is nothing compared to being told that your kidney cancer has spread. Every six months for up to 10 years, you go back to your hospital for routine follow-up scans; you teeter on a cliff edge as you hope and pray for a scan report containing the magic words "all clear" and then, if you're lucky, you get the next six months of feeling positive and confident until the next scan appointment comes round.*
>
> *"Some patients …. manage very well for many years and stay clear of kidney cancer, but my situation changed drastically when one afternoon after some routine tests, the nurse told me that my kidney function was reduced and that I would need to change my diet because my remaining kidney was failing. Having only one kidney and being told you have kidney failure in that remaining kidney was something I didn't expect to hear. Over the passage of time my remaining kidney has failed and I am now going through a workup for dialysis and there may be a possibility that I could eventually get a kidney transplant.*
>
> *"So surviving kidney cancer is not always straightforward, after a diagnosis of kidney cancer, nothing is ever the same again."*

Following surgery, patients with advanced/metastatic RCC will be given systemic anti-cancer treatments to either prevent recurrence of the cancer (adjuvant therapy) or to treat metastatic spread of the cancer. These treatments include immune checkpoint inhibitors and vascular endothelial growth factor receptor (VEGFR) inhibitors.

The tolerability of both immune checkpoint inhibitors and VEGFR inhibitors are of particular concern to patients, especially if they impact quality of life. This is especially evident for the combination therapies, where clinical trials have shown that more than 90% of patients experience at least one adverse event to first-line treatment. Some of the more common side effects are:

- Extreme fatigue
- Rash and itching
- Severe hand and foot syndrome which can leave patients unable to walk
- Chronic diarrhoea or constipation
- Pneumonitis requiring hospital treatment and cessation of treatment
- Severe mouth ulcers causing problems eating and drinking
- Nausea and vomiting, which can also cause problems taking the medication
- High blood pressure (hypertension)
- Hyperthyroidism
- Immune-related adverse events affecting the thyroid gland and gut
- Muscle pain and/or joint pain

All the above side effects severely affect the quality of life of the patient, as well as impacting on the lives of family members and carers. Most side effects require additional medicines to help patients manage their treatment, adding to the cost of treatment overall.

This is especially pertinent with immune-related adverse events from immune checkpoint inhibitors, which can be life-threatening, chronic, and sometimes difficult to treat requiring additional intravenous infusions of immunosuppressants. This results in more frequent hospital appointments and the associated travel time, time off work, loss of earnings and costs for the patient and their family or carer.

Other less serious side effects can still affect the patient's quality of life, e.g., headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. Some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients. Some of the current first-line treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels.

In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment because of severe or life-threatening adverse events. This leaves patients, their family members and carers feeling anxious and concerned that the cancer will progress while they have a dose reduction or are off treatment due to side effects, thereby impacting quality of life.

Immune checkpoint inhibitor treatments are administered as intravenous infusions, requiring regular trips to hospital and the use of chemotherapy chairs. Some patients may need to travel some distance to regional

cancer centres, take time off work, or have a partner travel with them for treatment. The practicality and cost of this in terms of travel expenses and loss of income is of concern to some patients, family members and carers. However, balanced against the extra travel and time is the improved side effect profile and enhanced quality of life with immune checkpoint inhibitors. Most patients feel much better able to cope with life, and some return to work. Half a day in hospital is preferable to the debilitating side effects of VEGFR inhibitors.

Finally, not all treatments have been approved for use through NHS England, and there are other treatments available in Scotland, Europe and North America that could potentially be more beneficial to RCC patients in terms of survival outcomes and tolerability. From a psychological point of view, knowing that you have stage 4 cancer and knowing that there are possibly more effective treatments that you are not able to access is very difficult for patients. Family members and carers also find this hard to deal with, as they live with a guilt of not being able to do all they can for their loved one. Access to a choice of treatments would enable patients and their families to know that they had tried their best to beat the cancer, leading to better family relationships and a subsequent improvement in quality of life and wellbeing for the patient.

Here is a quote from a patient who was on immunotherapy for advanced/metastatic RCC:

> *"When I was advised about the difficulty of my treatment, I realised there may be things after it I may not ever be able to do the same. The muscle and joint pain still goes on at times even though the severity gets easier. I was able to talk with my medical team, peer support, a counsellor and my family about being present for my young family as they grow up. Having some control in my treatment choices allowed me to be in charge of what could happen to me."*

6b. What do carers experience when caring for someone with the condition?

Family members and carers support the patient throughout their whole cancer journey, from diagnosis through treatment and beyond. They accompany their loved one to clinic visits, support them through the diagnosis of advanced/metastatic RCC, provide support and encouragement during rehabilitation after surgery, and help them manage the debilitating side effects of treatment. They want to do all they can for their loved one to help them manage the disease and its impact on their quality of life. As a result, their own psychosocial wellbeing and quality of life is severely impacted, and the disease and its treatment can become all-encompassing for the family.

In addition to the impact on quality of life of family members and carers, there are the cost implications of the patient having to give up work and regular and frequent clinic visits (every 2-3 weeks), especially for immune

	checkpoint inhibitor treatments. Clinic visits for immunotherapy infusions often take place in regional cancer centres, requiring patients and their accompanying family members or carers to travel long distances, sometimes with an overnight stay. This has financial implications for the family in terms of travel and accommodation expenses and time off work.

6c. What are important outcomes of treatment for someone with the condition? **6d. Does this change as the disease progresses through the treatment pathway?**	**6c. What are important outcomes of treatment for someone with the condition?** The most important outcomes of treatment for both the patient, family members and carers are living for as long as possible with a good quality of life. Being able to go back to doing the things that they could do before their diagnosis, such as working, enjoying holidays, and socialising with family and friends, without the constant worry of the cancer returning or progressing. **6d. Does this change as the disease progresses through the treatment pathway?** These outcomes do not change as the disease progresses. Patients are constantly looking for treatments that will keep their cancer under control for as long as possible and with minimal side effects and impact on their quality of life. We know of patients who have completed their fourth line of treatment and are desperate to find another treatment on compassionate grounds, or a clinical trial with a drug with a new mode of action after having tried immune checkpoint inhibitors and VEGFR inhibitors that have failed to control their cancer.

Current treatment of the condition in the NHS **7a. What treatments and care are currently available on the NHS for advanced renal cell carcinoma?** **7b. Does this align with decision nodes and treatments included in the NICE pathways scope for renal cell carcinoma?** **7c. What factors are important for treatment decision making?** **7d. What do you think of the current treatments and care available for the condition on the NHS?**	**7a. What treatments and care are currently available on the NHS for advanced renal cell carcinoma?** The current treatment pathway for early stage or locally advanced (stage 1-3) RCC is surgery (either radical or partial nephrectomy) or ablation for tumours less than 4 cm in size (cryoablation, radiofrequency ablation, stereotactic ablative radiotherapy, or microwave ablation). For people with locally advanced disease, surgery or ablation can be followed by a year of adjuvant treatment with pembrolizumab to keep the cancer from returning. For advanced or metastatic RCC (stage 4 or inoperable stage 3) surgery is followed by immunotherapy combinations, such as nivolumab plus ipilimumab, pembrolizumab plus lenvatinib or avelumab plus axitinib (through the Cancer Drugs Fund) or targeted therapies, such as sunitinib, pazopanib, cabozantinib or tivozanib in the first-line setting. When these treatments start to fail and the cancer progresses, patients move on to second and then third line systemic anti-cancer treatments. Second- and third-line systemic anti-cancer treatments include targeted therapies such as lenvatinib plus everolimus, cabozantinib, axitinib, or everolimus (or sunitinib, pazopanib or tivozanib following first line nivolumab/ipilimumab) or the immunotherapy drug, nivolumab. Only everolimus is available in the fourth line. When everolimus fails, best supportive care is recommended. Targeted therapies are oral medicines with similar modes of action (VEGFR inhibitors or mTOR inhibitors that block angiogenesis). Immunotherapies are immune checkpoint inhibitors (anti-PD-1, anti-PD-L1 or CTLA-4), which are administered as a bi- or triweekly intravenous infusions, requiring outpatient hospital treatment (chemotherapy chair resources) and the associated travel time, time off work and expense for the patient and carer. **7b. Does this align with decision nodes and treatments included in the NICE pathways scope for renal cell carcinoma?** This mostly aligns with the decision nodes and treatments included in the NHS pathways scope for RCC. However, we know of several patients who have had successful treatment with IL 2, which is not included in the pathway because it is currently not approved for use by the NHS. This treatment is probably the only systemic anti-cancer treatment that can produce durable remission of advanced/metastatic RCC, and we strongly advise that it be considered for inclusion in the pathway. Also, we recommend a fifth line of treatment for advanced/metastatic RCC as active surveillance and supportive care, including psychosocial support when all lines of systemic anti-cancer treatment have been exhausted.

	‘Best supportive care’ does not fully explain the support and psychosocial needs of patients who come to the end of the line with respect to their cancer treatment and have nowhere to turn. **7c. What factors are important for treatment decision making?** Factors important for decision-making are comorbidities, such as certain cardiovascular diseases (for VEGFR inhibitors), autoimmune conditions (for immune checkpoint inhibitors), obesity and smoking status for surgery and the presence of brain metastases (how many there are and how to treatment them: SABR or whole brain radiotherapy or anti-cancer systemic treatments). Access to anti-cancer systemic treatments in the second line and beyond is complicated and dependent on what the patient had as their first-line treatment. For example, nivolumab can only be given to patients as a second- or third-line treatment if they have not previously been treated with a PD-1 or PD-L1 inhibitor (nivolumab, pembrolizumab or avelumab), and a first line VEGFR inhibitor can be given to patients in the second line if they have previously been treated with nivolumab plus ipilimumab. This requires careful planning on behalf of the medical oncologist with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatment for advanced/metastatic RCC. **7d. What do you think of the current treatments and care available for the condition on the NHS?** Treatments (both surgical and systemic) for advanced/metastatic RCC continue to improve, and patients are living longer than ever before. However, the systemic anti-cancer treatments, especially the combinations, although effective, can be toxic and very difficult to tolerate. This requires careful management of side effects, involving the patient and their family or carer in all decisions about their care and treatment (shared decision-making) to get the best out of these treatments and enable the patient to live their best life. Access to systemic anti-cancer treatments in the second line and beyond is complicated and dependent on what the patient had as their first-line treatment. This requires careful planning on behalf of the medical oncologist with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatment for advanced/ metastatic RCC. It is very disappointing that none of the current systemic treatments are available beyond the fourth line. This leaves patients with best supportive care as their only option. They are unable to control their cancer, leading to progression and inevitably death. This is very difficult for patients to come to terms with, especially when they

	know that RCC patients in other parts of the world, or those lucky enough to have private health insurance can access multiple lines of treatment to keep their cancer at bay. Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities. International discussion forums exist where patients talk to one another daily. Patients are more aware of the experiences of others, including their access to innovative treatments, quality of life, and treatment successes and failures. News about lack of access to effective medicines ripples out to other patients and families, destroying their hope and positivity. Information about treatments is readily available to patients around the world on websites. Patients and clinicians expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so that patients in England have the same choices as patients in other countries and to improve outcomes. Patients are aware that current systemic anti-cancer treatments are life-extending, but they continue to look for drugs with different modes of action, which can give improved overall survival with better quality of life. As already mentioned, some patients and family members need access to psychological support from the point of diagnosis and throughout their kidney cancer journey to help them deal with the anxiety and depression caused by having an incurable terminal disease. Psychological support services are difficult to access on the NHS and there are long waiting times of 3 months or more. Many patients go without this support when it would help to improve their quality of life. There is no agreed consensus for the treatment of oligometastatic RCC, and the definition of oligometastatic disease is tenuous. Patients with oligometastatic disease can be treated with ablative techniques, such as stereotactic ablative radiotherapy (SABR) to remove metastases from, for example, the brain, but the use of SABR for oligometastatic disease is not included in this disease pathway. Patients are having to wait too long (6 weeks or more) for scan results during treatment and follow-up. Fear of recurrence, progression, and anxiety about scan results (scanxiety) remain the most common unmet needs reported by patients. This is an extremely stressful time for both the patient and their family and carers. Metrics need to be put in place to reduce waiting times to an acceptable level, for example 2 weeks. Not every patient has access to a clinical nurse specialist (CNS). Access to a CNS who can provide advanced psychological support skills may be necessary to respond to the many kinds of psychological distress experienced by patients with advanced/metastatic RCC, including their family and carers. Also, the CNS can chase the radiology department to get the scan report in time for the clinic appointment to prevent further distress and additional hospital appointments for scan results.

	There is evidence of the benefits that CNSs can offer people living with advance/metastatic cancer in terms of improving their quality of life, their experience of care, and potentially their survival. A CNS can help to; reduce the number of emergency admissions; reduce the length of hospital stays; organise and administer follow-up appointments; reduce the number of medical consultations; and provide support to patients with the management of side effects enabling them to stay on treatment for longer resulting in better outcomes and improved quality of life. Not all patients have a Personalised Care and Support Plan to ensure that their physical, practical, emotional, and social needs are identified and addressed at the earliest opportunity. A Personalised Care and Support Plan developed with the patient and their family or carer will help the clinical team to understand the patient's care and support needs, their life and family situation.

8. If there are disadvantages for patients of current NHS treatments for this condition (for example, how they are given or taken, side effects of treatment, and any others) please describe these.	**8. If there are disadvantages for patients of current NHS treatments for this condition (for example, how they are given or taken, side effects of treatment, and any others) please describe these.** The main disadvantages of current NHS treatments for advanced/metastatic RCC include: • The toxicity of current systemic anti-cancer treatments, especially the first-line combination treatments where over 90% of patients in clinical trials reported an adverse event to treatment. • The seriousness of adverse events to immune checkpoint inhibitors, especially immune-related adverse events that leave patients with chronic autoimmune conditions that can be life-threatening and require lifelong treatment, for example hyperthyroidism and ulcerative colitis. Some autoimmune conditions are difficult to treat and require additional infusions of immunosuppressants. • The effect of the toxicity of systemic anti-cancer treatments on the quality of life of the patients and the family and carers, for example, severe hand and foot syndrome which can leave patients unable to walk, chronic diarrhoea prohibiting patients from leaving the house on bad days, pneumonitis requiring hospitalisation and cessation of treatment, severe mouth ulcers causing problems eating and drinking, nausea and vomiting, which can also cause problems taking the medication. • Additional medicines to help patients manage the side effects to the systemic anti-cancer treatments. • Costs for additional medicines to mitigate the side effects of systemic anti-cancer treatments. • The effect of less serious side effects to systemic anti-cancer treatments on the patient's quality of life, for example, headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. • The need for a dose reduction or treatment holidays to mitigate severe side effects, which are more frequent and severe with the combination therapies. In some cases, treatment can affect a patient's quality of life to such an extent that some patients are even advised to stop treatment because of severe adverse events. • The anxiety and worry caused by dose reductions, treatment holidays or cessation of treatment because the cancer might recur or progress. This impacts the quality of life of the patient, their family, and carers. • Changes to the appearance of the patients caused by some systemic anti-cancer treatments can be distressing. White, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients. • Immune checkpoint inhibitor treatments are administered as intravenous infusions, requiring regular trips to hospital and the use of chemotherapy chairs. Some patients may need to travel some

	distance to regional cancer centres, take time off work, or have a partner travel with them for treatment. The practicality of this is of concern to some patients and their families or carers. • The expense of combination treatments to the NHS, and the budgetary constraints of the NHS. NICE and the manufacturer need to work collaboratively to negotiate an acceptable patient access scheme to ensure advanced/metastatic RCC patients can benefit from the latest clinically effective drug combination or a drug with a new mode of action.

Patient population

9. Would living with the condition, and outcomes such as the prognosis of someone with the condition change because of specific characteristics of the disease? Would treatment decisions be different for people in these subgroups? If so, please describe them and explain why (and note if this may differ for different types of treatments [i.e. classes of drugs]) Consider, for example, prognostic markers, or genetic alterations if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	There are several different subtypes of RCC, which do not respond well to current treatments, for example, papillary type 1 and type 2, chromophobe and collecting duct RCC. Currently, these subtypes are treated in the same manner as clear cell RCC, but their prognosis is poor. There is evidence that papillary RCC responds well to cabozantinib, and pembrolizumab plus axitinib: only cabozantinib is available in the first line setting for advanced/metastatic RCC. Some patients develop RCC with sarcomatoid features. This type of RCC is very aggressive and difficult to treat, and current available treatments have had limited success in improving outcomes for these patients. There are several different types of hereditary RCC, including Von Hippel–Lindau (VHL) disease, hereditary leiomyomatosis and renal cell carcinoma (HLRCC), hereditary papillary renal cell carcinoma (HPRCC), and Birt–Hogg–Dubé (BHD). RCC resulting from these hereditary conditions are treated with currently available systemic anti-cancer treatments. VHL can result in multiple RCC tumours in both kidneys. Patients with this condition can have a series of malignant and benign tumours their whole lives, requiring surgical and systemic anti-cancer treatment when tumours arise. This will not result in the typical treatment pathway of surgery, followed by different lines of treatment, because each kidney tumour would be considered a primary tumour. The VHL gene is involved in many other forms of cancer. Manifestations commonly occur on the retina, brain and spinal cord, pancreas, inner ear, and adrenals, as well as the kidneys. Belzutifan has shown promise for the treatment of VHL RCC, but is not currently available through the NHS, although it has been given an "Innovation Passport" through the Medicines and Healthcare products Regulatory Agency's (MHRA) new Innovative Licensing and Access Pathway (ILAP).

Equality

9. Are there any potential equality issues that should be taken into account when considering this condition? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	There is a rare subtype of RCC called renal medullary carcinoma that only affects young black men with sickle cell disease. These patients are disadvantaged because current treatments are not effective against this subtype of RCC.

Other issues

10. Are there any other issues that you would like the committee to consider?	Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that novel treatments are made available to patients in order that they have the best possible care. If these treatments are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. Poor UK survival rates might possibly be due to the restrictions in clinical choice brought about by UK regulatory authorities. In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available. Without treatment alternatives in all lines of treatment, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life. Current systemic anti-cancer treatment options are not effective for everyone. Undue restrictions in accessing novel treatments would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in all lines of treatment would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.

Key messages

11. In up to 5 bullet points, please summarise the key messages of your submission.	• Access to systemic treatments in the second line and beyond is complicated and dependent on what the patient had as their first-line treatment. This requires careful planning on behalf of the medical oncologist with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatment for advanced/ metastatic RCC. • The toxicity of current systemic anti-cancer treatments, especially the first-line combination treatments where over 90% of patients in clinical trials reported an adverse event to treatment, is a concern and seriously affects the quality of life of patients. Management of adverse events also adds to the cost of treatment, particularly for patients who experience immune-related adverse events resulting in autoimmune conditions requiring life-long treatment with intravenous immunosuppressants. • Immune checkpoint inhibitor treatments are administered as intravenous infusions, requiring regular trips to hospital and the use of chemotherapy chairs. Some patients may need to travel some distance to regional cancer centres, take time off work, or have a partner travel with them for treatment. The practicality of this is of concern to some patients and their families or carers. • The expense of combination treatments to the NHS, and the budgetary constraints of the NHS. NICE and the manufacturer need to work collaboratively to negotiate an acceptable patient access scheme to ensure RCC patients can benefit from the latest clinically effective drug combination or a drug with a new mode of action. • It is very disappointing that none of the current systemic anti-cancer treatments are available beyond the fourth line. This leaves patients with best supportive care as their only option. They are unable to control their cancer, leading to progression and inevitably death.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Health technology appraisal

Renal Cell Carcinoma Pathways Pilot [ID6186]

Professional organisation submission on the disease and current treatment pathway

Thank you for agreeing to give us your organisation's views on the current treatment pathway for renal cell carcinoma.

You can provide a unique perspective on current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	On behalf of BAUS
3. Job title or position	Professor of Surgical Oncology, University of Cambridge; Consultant Urologist, Addenbrooke's Hospital
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition? Yes If you are an expert in the clinical evidence base for a technology, please specify which technology you are an expert in: N/A Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Association of Urological Surgeons (BAUS) is a registered charity whose object is to promote the highest standard in the practice of urology for the benefit of patients by fostering education, research and clinical excellence. Membership of the association is open to all those engaged in delivering urological care to patients. The Association's primary sources of income are the membership subscriptions and income from educational meetings and conferences. Full accounts and further information are available at: www.baus.org.uk
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition and current treatment

6. What is the main aim of treatment for renal cell carcinoma? Does this change as the disease progresses through the treatment pathways? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Stages 1-3c – cure Stage 4 – prolong life of a high quality
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	By this you mean due to systemic anti-cancer therapy (SACT). This is not an area of our expertise as urologists as SACT is the realm of medical oncolgists
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Better knowledge and treatment of localised kidney cancer.

9a. How is the condition currently treated in the NHS? **Does this align with decision nodes and treatments included in the NICE pathways scope for renal cell carcinoma?**	The figure of the pathway for RCC is accurate in the NICE scope document.
9b. Are any clinical guidelines used in the treatment of the condition, and if so, which? Are any commissioning policies relevant to treatment of renal cell carcinoma, if so which?	EAU/ESMO/ASCO There is no NICE guideline, although one has been commissioned and will provide a renewed focus on the best management of this forgotten cancer.
9c. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No, it is not well defined and treatment varies across centres. This variation has been established by a recent NHS Digital related audit commissioned by Kidney Cancer UK and will soon be illustrated on a yearly basis by the National Kidney Cancer Audit.

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Equality

10a. Are there any potential equality issues that should be taken into account when considering this condition?	Yes, variation in care across the UK.

Key messages

12. In up to 5 bullet points, please summarise the key messages of your submission.	• Pathway is good in the NICE scope document and this pathway should be useful for other HTAs in the years to come • Variation has been illustrated across the UK • NICE guideline has been commissioned and is welcome for guiding management of RCC in the future. • NKCA will show if variation is reducing in the years to come •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Health technology appraisal

Renal Cell Carcinoma Pathways Pilot [ID6186]

Patient organisation submission on specific technology/ies under consideration

Thank you for agreeing to give us your organisation's views on the technology/ies being considered in this pathways appraisal and its/their possible use in the NHS.

You can provide a unique perspective on the technology/ies that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

Technology/ies under consideration:

- Cabozantinib with nivolumab (Ipsen)

Point in the treatment pathway:

- Untreated advanced or metastatic renal cell carcinoma

About you

1.Your name	[redacted]
2. Name of organisation	Action Kidney Cancer
3. Job title or position	Policy and Medical Affairs
4a. Brief description of the organisation (including who funds it). How many members does it have?	Action Kidney Cancer was founded in 2006 by two cancer patients/survivors, who started by providing practical and bespoke support to individual patients for access to life-extending systemic anti-cancer treatments for advanced or metastatic kidney cancer. Empowering patients to take an active role in their own health care, and in decisions affecting the choice, provision, and quality of cancer services throughout the UK, remains the top priority for Action Kidney Cancer. Over the years, Action Kidney Cancer has grown considerably, with a membership of over 1400 kidney cancer patients and carers on its confidential community forum. In addition, our website regularly has over 300 visits per day from people looking for information about kidney cancer, advice, and support. Action Kidney Cancer is unique; originally it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Action Kidney Cancer remains patient-led, and the group is

	now a registered charity in England and Scotland, which enables it to better meet the growing needs of the kidney cancer community in the UK. The charity employs 5 part-time, home-based contractors in England and Scotland. Before the COVID-19 pandemic, funding came from trusts, foundations, and the pharmaceutical industry (around 55%), as well as donations and fundraising activities/events organised by the public and kidney cancer community (45%). Since the pandemic, the latter has almost halved.
4b. Has the organisation received any funding from the company/ies bringing the technology/ies to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	When gathering the information for this submission, we specifically asked for patient and carer experience of taking part in the CheckMate 9ER study looking at cabozantinib plus nivolumab versus sunitinib as a first-line treatment for advanced or metastatic renal cell carcinoma (RCC) through our confidential community forum. Failing that we asked for patient experience of using a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) plus an immune checkpoint inhibitor combination as a first-line treatment for advanced or metastatic RCC. We also have a dedicated immunotherapy Facebook group specifically set-up to

	help us collate experiences from patients using these types of medication. Over 1400 patients and carers use these channels to communicate on a regular basis, and we receive in the order of 5-600 interactions and comments a day on our closed Facebook group.

Current treatment of the condition **6a. What treatments and care are currently available on the NHS for untreated advanced or metastatic renal cell carcinoma?** **6b. What do you think of the current treatments and care available for the condition on the NHS?**	**6a. What treatments and care are currently available on the NHS for untreated advanced or metastatic renal cell carcinoma?** The current treatment pathway for early stage or locally advanced (stage 1-3) renal cell carcinoma (RCC) is surgery (either radical or partial nephrectomy) or ablation for tumours less than 4 cm in size (cryoablation, radiofrequency ablation, or stereotactic ablative radiotherapy). For people with locally advanced disease, surgery or ablation can be followed by adjuvant treatment with pembrolizumab. For advanced or metastatic RCC (stage 4 or inoperable stage 3) surgery is followed by immunotherapy combinations, such as nivolumab plus ipilimumab, pembrolizumab plus lenvatinib or avelumab plus axitinib (through the Cancer Drugs Fund) or targeted therapies, such as the VEGFR inhibitors sunitinib, pazopanib, cabozantinib or tivozanib in the first-line setting. Targeted therapies are oral medicines with similar modes of action (VEGFR inhibitors or mTOR inhibitors that block angiogenesis). Immunotherapies are immune checkpoint inhibitors (anti-PD-1, anti-PD-L1 or CTLA-4), which are administered as a bi- or triweekly intravenous infusions, requiring outpatient hospital treatment (infusion chair resources) and the associated travel time, time off work and expenses for the patient and their family or carer. We have extracted the following details from statements submitted to Action Kidney Cancer by patients living with advanced or metastatic RCC. Using currently available systemic anti-cancer treatments, many patients (more than 90% in clinical trials) suffer with at least one of the following side effects, all of which can severely affect the quality of life of the patient and impact the lives of their family members or carers: • Chronic diarrhoea leading to weight loss • Severe hand and foot syndrome which can leave patients unable to walk • High blood pressure (hypertension) • Extreme fatigue • Nausea and vomiting, which can cause problems taking the medication • Severe mouth ulcers (stomatitis) causing problems eating, drinking, talking and sleeping • Loss of taste/unpleasant taste sensation (dysgeusia) causing problems eating and drinking • Decreased appetite leading to weight loss, anorexia and cachexia • Hypothyroidism • Liver damage • Muscle pain/joint pain • Constipation

	• Immune-related adverse events, such as:
	  ○ Hypothyroidism or hyperthyroidism
	  ○ Rash and itching
	  ○ Impairment of liver function (hepatoxicity) or liver damage
	  ○ Pneumonitis requiring hospital treatment and cessation of treatment
	  ○ Adrenal insufficiency
	  ○ Inflammation of the liver
	
	Most of the above side effects require additional medicines to help patients manage their treatment, adding to the cost of treatment overall. Many patients also require opioid prescriptions to manage tumour pain.
	
	This is especially pertinent with immune-related adverse events from immune checkpoint inhibitors, which can be life-threatening, chronic, and sometimes difficult to treat requiring additional intravenous infusions of immunosuppressants. This results in more frequent hospital appointments and the associated travel time, time off work, loss of earnings and costs for the patient and their family or carer.
	
	Other less serious side effects, which still affect the patient's quality of life, are headache, loss of taste/ taste disturbances (dysgeusia), hair loss and change of hair colour, depression, loss of libido, and inability to drive.
	
	In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment because of severe or life-threatening side effects. These side effects are more frequent and severe with the combination therapies, with 70% or more patients reporting severe or life-threatening adverse events in clinical trials. This leaves patients, their family members and carers feeling anxious and concerned that the cancer will progress while they have a dose reduction or are off treatment due to side effects, thereby impacting quality of life.
	
	Although less serious than some of the side effects to current first-line treatments available via NHS England, some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients.
	
	6b. What do you think of the current treatments and care available for the condition on the NHS?
	
	Systemic anti-cancer treatments for advanced/metastatic RCC continue to improve, and patients are living longer than ever before. However, the systemic anti-cancer treatments, especially the combinations, although effective, can be toxic and very difficult to tolerate. This requires careful management of side effects, involving the patient and their family or carer in all decisions about their care and treatment (shared decision-making) to get the best out of these treatments and enable the patient to live their best life.

	Immune checkpoint inhibitor treatments are administered as intravenous infusions, requiring regular trips to hospital and the use of infusion chairs. Some patients may need to travel some distance to regional cancer centres, take time off work, or have a partner travel with them for treatment. The practicality and cost of this in terms of travel expenses and loss of income is of concern to some patients, family members and carers. However, balanced against the extra travel and time is the improved side effect profile and enhanced quality of life with immune checkpoint inhibitors. Most patients feel much better able to cope with life, and some return to work. Half a day in hospital is preferable to the debilitating side effects of VEGFR inhibitors. Finally, not all treatments have been approved for use through NHS England, and there are other treatments available in Scotland, Europe and North America that could potentially be more beneficial to RCC patients in terms of survival outcomes and tolerability. From a psychological point of view, knowing that you have stage 4 cancer and knowing that there are possibly more effective treatments that you are not able to access is very difficult for patients. Family members and carers also find this hard to deal with, as they live with a guilt of not being able to do all they can for their loved one. Access to a choice of treatments in the first line would enable patients and their families to know that they had tried their best to beat the cancer, leading to better family relationships and a subsequent improvement in quality of life and wellbeing for the patient. Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities. International discussion forums exist where patients talk to one another daily. Patients are more aware of the experiences of others, including their access to innovative treatments, quality of life, and treatment successes and failures. News about lack of access to effective medicines ripples out to other patients and families, destroying their hope and positivity. Information about treatments is readily available to patients around the world on websites. Patients and clinicians expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so that patients in England have the same choices as patients in other countries to improve outcomes. Patients are aware that these treatments are life-extending, but they continue to look for systemic anti-cancer treatments with different modes of action, which can give improved overall survival with better quality of life. Access to systemic treatments in the second line and beyond is complicated and dependent on what the patient had as their first-line treatment. For example, nivolumab can only be given to patients as a second- or third-line treatment if they have not previously been treated with a PD-1 or PD-L1 inhibitor (nivolumab, pembrolizumab or avelumab), and a first line TKI can be given to patients in the second line if they have previously been treated with nivolumab plus ipilimumab. This requires careful planning on behalf of the medical oncologist with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatment for advanced or metastatic RCC.

Advantages of the technology/ies under consideration **7a. If there are advantages of the technology/ies over current treatments on the NHS please describe these.** For example, the effect on quality of life, ability to continue work, education, self-care, and care for others?	**7a. If there are advantages of the technology over current treatments on the NHS, please describe these** The cabozantinib plus nivolumab combination has been approved for use in the USA and European Union by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively. The results from the phase 3 CheckMate 9ER trial with 651 patients with previously untreated advanced or metastatic RCC showed significant improvement in survival and response to treatment with the cabozantinib plus nivolumab combination compared to the standard of care with sunitinib. After an average follow-up of 32.9 months, median overall survival was 37.7 months for the combination treatment and 34.3 months with sunitinib. Median progression-free survival was double that seen with sunitinib (16.6 months versus 8.3 months, respectively). The safety profile of the cabozantinib plus nivolumab combination is no worse than that for the individual drugs alone. In clinical trials, quality of life (patient-reported outcomes) with the cabozantinib plus nivolumab combination was maintained throughout therapy as opposed to a decrease in quality of life seen with sunitinib. With regards to the disease-related symptom subscale, combination therapy improved scores over time, whereas sunitinib therapy was associated with deterioration. Compared with sunitinib, the combination significantly delayed the time to deterioration of patient-reported outcome scores. These results suggest a benefit for cabozantinib plus nivolumab compared with sunitinib in the treatment of patients with advanced or metastatic RCC in the first-line setting. This improved quality of life enables patients to contribute both socially and economically to society. Nivolumab can cause immune-related adverse events, which can affect any organ or tissue in the body. These immune-related adverse events may leave the patient with chronic autoimmune conditions that can be life-threatening and require lifelong treatment, for example hypothyroidism and ulcerative colitis. Some autoimmune conditions are difficult to treat and require additional intravenous infusions of immunosuppressants. However, if identified early they can be managed effectively to ensure the safe use of nivolumab. The following quotes are taken from patients with advanced or metastatic RCC being treated with an immune checkpoint inhibitor plus VEGFR inhibitor combination treatment: *"I was first diagnosed with a tumour on my right kidney ……. in Summer 2016. A CT scan showed …. a 4cm tumour that went onto the Vena Cava…… opted for a full Nephrectomy…. October of the same year……March 2017 it was noted to be in my lymph nodes in the renal bed. I was offered standard TKI treatment……. but the Oncologist offered to refer me to a London cancer centre to explore more options. I volunteered for the trial ……. June 2017.*

	"……. the side effects of the first [infusion] was [sic] quite extreme with flu-like symptoms and aches pains, these soon wore off……. I only noted 2 minor side effects of the [VEGFR inhibitor] at this stage and this was spots in my hair and a slight sore throat. However, these were in no way affecting my quality of life. I actually went on a 3-week road trip around Europe without any problems. *"September 2017 I was put up to 7mg twice a day. This caused some worse side effects with sore mouth, a worse sore throat, sore feet, and slight diarrhoea. Again, this did not affect my quality of life too much and I was put [up] to 10mg twice a day in Feb 2018. I have managed to stay on 10mg twice a day, but the side effects can be extreme. I have daily diarrhoea up to 5 times a day, this has led to other connected effects such as ……. haemorrhoids, my feet can be so sore that I cannot walk, I suffer with sore mouth at times, the most unusual side effect is that my muscles can get really tight and make my body ache. I have suffered with breathlessness, headaches, my thyroid has suffered, and I am now on 150mg of Thyroxine daily. However, I have managed to stay on 10mg twice a day and continue to work and lead a normal life (relatively). I don't really experience tiredness, but I have noticed my memory has suffered slightly.* *"…….in the summer I have hardly any side effects, the diarrhoea remains but sore feet, mouth, spots in the hair etc. all clear up. As soon as it gets cold again and I come into contact with bugs and viruses the side effects seem to get worse again.* *"The results have been great, so far! [The metastasis in the lymph nodes has reduced from 27mm to 5mm]."* When compared to other first-line immunotherapy combinations, cabozantinib plus nivolumab is not as good as lenvatinib plus pembrolizumab at extending progression-free survival but performs better than avelumab plus axitinib and nivolumab plus ipilimumab. Cabozantinib plus nivolumab has a similar safety profile to other checkpoint inhibitor plus VEGFR inhibitor combinations. These are better tolerated than a combination of two checkpoint inhibitors (nivolumab plus ipilimumab), where around 70% of patients reported immune-related adverse events in clinical trials.

7b. If multiple technologies are being considered, do the advantages differ between any of the technologies being considered?	Not applicable
7c. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	The most important advantages of treatment with the cabozantinib plus nivolumab combination for both the patient, their family and carers are the improvement in survival compared to standard treatment with sunitinib, and the quality of life of the patient during treatment. Patients and their families and carers want to live for as long as possible with a good quality of life. They want to be able to go back to doing the things that they could do before their diagnosis, such as working, enjoying holidays, and socialising with family and friends, without the constant worry of the cancer returning or progressing.
7d. Do the technology/ies help to overcome or address any of the disadvantages of current treatments? If so, please describe these	It is difficult to say, because cabozantinib plus nivolumab has only been directly compared to sunitinib in clinical trials. When compared to sunitinib, the combination treatment doubles median progression-free survival and extends median overall survival by nearly 3 and a half months. Also, patient-reported outcomes were maintained or improved compared to sunitinib, indicating that quality of life was improved in those patients taking the cabozantinib plus nivolumab combination. The disadvantages of the other combination treatments available in the first line mostly pertain to tolerability and subsequent quality of life on treatment. There are fewer immune-related adverse events with an immunotherapy-VEGFR inhibitor combination than with an immunotherapy-immunotherapy combination, such as ipilimumab plus nivolumab, and a subsequent improvement in quality of life.

Disadvantages of the technology/ies under consideration **8a. If there are disadvantages of the technology/ies over current treatments on the NHS please describe them.** For example, are there any risks with the treatments? If you are concerned about any potential side effects you have heard about, please describe them and explain why	**8a. If there are disadvantages of the technology over current treatments on the NHS please describe them** Advanced or metastatic RCC is a devastating disease and it currently incurable. Most patients with advanced/metastatic RCC are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings enormous financial pressures for the patients and their families, sometimes resulting in psychological problems, depression, loss of confidence and self-worth. Nivolumab is given intravenously over 30 minutes every 2-4 weeks until disease progression or drug intolerance. This requires hospital visits every 2-4 weeks and the provision of infusion chairs. Cabozantinib is an oral drug, which can be taken at home. Standard first-line treatment with oral VEGFR inhibitors only require a monthly hospital visit to replenish supplies of medication. Patients will typically be travelling some distance to a regional cancer centre for the nivolumab infusions and to collect cabozantinib supplies. Some patients may need to take time off work, or have a partner travel with them to treatments, the practical aspects of which can impact the quality of life of both patient and carer. However, balanced against the extra travel and time is the improved side effect profile and enhanced quality of life. Most patients feel much better able to cope with life, and some return to work. In addition, the side effects of both immunotherapies and VEGFR inhibitors are of particular concern to patients, especially if they impact quality of life. This is especially pertinent with immune-related adverse events from immunotherapies. These immune-related adverse events may leave the patient with chronic autoimmune conditions that can be life-threatening and require lifelong treatment, for example hypothyroidism and ulcerative colitis. Some autoimmune conditions are difficult to treat and require additional intravenous infusions of immunosuppressants. Most side effects require additional medicines to help patients manage their treatment, adding to the cost of treatment overall. Other less serious side effects can still affect the patient's quality of life, e.g., headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. Some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients. Some of the current first-line treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment because of severe adverse events. This leaves patients, their family and carers feeling anxious and concerned that the cancer will progress while they have a dose reduction or are off treatment due to side effects, thereby impacting quality of life.

	We understand that combination treatments are expensive, and we appreciate the budgetary constraints of the NHS. Nonetheless, NICE and the manufacturer need to work collaboratively to negotiate an acceptable patient access scheme to ensure RCC patients can benefit from this latest clinically effective combination.
8b. If multiple technologies are being considered, do the disadvantages differ between any of these technologies?	Not applicable
8c. If you have stated more than one disadvantage, which one(s) do you consider to be the most important, and why?	For patients, the most important disadvantages of treatment with a combination of cabozantinib plus nivolumab are tolerability and administration of the treatment, and the subsequent impact on the quality of life of the patient and their family and carers. Patients will typically be travelling some distance to a regional cancer centre for the treatment. Some patients may need to take time off work, or have a partner travel with them, the practical and cost implications of which can impact quality of life and is of concern to some patients and families. Most patients with advanced/metastatic RCC are forced to give up work because of the debilitating effects of the treatment. This brings enormous financial pressures for the patients and their families, sometimes resulting in psychological problems, depression, loss of confidence and self-worth. The side effects of the combination treatment are of particular concern to patients, especially if they impact quality of life. This is especially pertinent with immune-related adverse events from immunotherapies. These immune-related adverse events may leave the patient with chronic autoimmune conditions that can be life-threatening and require lifelong treatment. Some autoimmune conditions are difficult to treat and require additional intravenous infusions of immunosuppressants. Most side effects require additional medicines to help patients manage their treatment, adding to the cost of treatment overall.

Patient population

9. Are there any groups of patients who might benefit more from the technology/ies than others or any that may benefit less? If so, please describe them and explain why (and note if this differs between any of the technologies under consideration, if more than one technology is being considered). Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different technologies.	Patients with significant co-morbidities, such as cardiovascular disease or pre-existing autoimmune conditions, such as hypothyroidism or ulcerative colitis would benefit less from this combination than other patients with advanced/metastatic RCC. Access to the cabozantinib plus nivolumab combination is restricted to selected patients with these co-morbidities because treatment with the combination might result in serious or life-threatening adverse events or exacerbate these pre-existing co-morbidities. Treatment with immunotherapy, such as nivolumab, can exacerbate autoimmune conditions requiring life-long treatment with intravenous immunosuppressants. Treatment with VEGFR inhibitors, such as cabozantinib, can worsen hypertension and cardiac function (left ventricular systolic function).

Equality **10. Are there any potential equality issues that should be taken into account when considering this condition and the technology/ies that haven't previously been raised in any submissions by your organisation, if a previous form was submitted? Please explain if you think any groups of people with this condition are particularly disadvantaged.** Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	There is a rare subtype of RCC called renal medullary carcinoma that only affects young black men with sickle cell disease. These patients are disadvantaged because black men with this condition were not included in clinical trials with cabozantinib plus nivolumab, and there is no evidence that this combination can improve outcomes in this group of patients.

Other issues

11. Are there any other issues that you would like the committee to consider?	Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy, Austria and the Czech Republic. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that novel treatments are made available to patients in order that they have the best possible care. If these treatments are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. Poor UK survival rates might be due to the restrictions in clinical choice brought about by UK regulatory authorities. In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available. Without treatment alternatives in all lines of treatment, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life. Current systemic anti-cancer treatment options are not effective for everyone. Undue restrictions in accessing novel treatments would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first line would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.

Key messages

12. In up to 5 bullet points, please summarise the key messages of your submission.	• The cabozantinib plus nivolumab combination is safe and effective to use as a first-line treatment of people with advanced/metastatic RCC and has already been approved for use by the FDA in the USA and the EMA in Europe. • The cabozantinib plus nivolumab combination is well tolerated, as well as proven to be more effective at extending progression-free survival and improving overall response rates compared to standard first-line treatment with sunitinib. • Adding the cabozantinib plus nivolumab combination as a choice in the first line enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life. • The extended progression-free survival and relative toxicity of the cabozantinib plus nivolumab combination enhances quality of life and enables patients to contribute socially and economically to society. • The cabozantinib plus nivolumab combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Health technology appraisal

Renal Cell Carcinoma Pathways Pilot [ID6186]

Professional organisation submission on specific technology/ies under consideration

Thank you for agreeing to give us your organisation's views on the technology/ies being considered in this pathways appraisal and its/their possible use in the NHS.

You can provide a unique perspective on the technology/ies in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

Technology/ies under consideration:

- Cabozantinib with nivolumab (Ipsen)

Point in the treatment pathway:

- Untreated advanced or metastatic renal cell carcinoma

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	On behalf of BAUS
3. Job title or position	Professor of Surgical Oncology, University of Cambridge; Consultant Urologist, Addenbrooke's Hospital
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or the technology/ies? No, I am a urologist and metastatic disease is treated mainly by medical oncologists If you have specific experience or expertise of a technology and there are multiple technologies being appraised, please specify which technology you are an expert in: Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Association of Urological Surgeons (BAUS) is a registered charity whose object is to promote the highest standard in the practice of urology for the benefit of patients by fostering education, research and clinical excellence. Membership of the association is open to all those engaged in delivering urological care to patients. The Association's primary sources of income are the membership subscriptions and income from educational meetings and conferences. Full accounts and further information are available at: www.baus.org.uk
5b. Has the organisation received any funding from the manufacturer(s) of the technology/ies and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Ipsen took stand space at the Annual Scientific Meeting of BAUS in June 2022, the charge for that was £6,696. Ipsen have booked a stand at the June 2023 meeting and an invoice was issued in December 2022 for £3,780.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

What is the expected place of the technology/ies in current practice?

6a. How is untreated advanced or metastatic renal cell carcinoma currently treated in the NHS?	Mainly with a variety of systemic anti-cancer therapies (SACT)
6b. Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO/EAU/ASCO
6c Are there any commissioning policies in place that are relevant to the treatment of the condition, and if so, which?	Not our area of expertise
6d. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes in centres of excellence. The exact SACT and the sequence of these used at different points in the pathways will vary from expert to expert as there is currently no predictive tool/marker for each agent.
6e. What impact would the technology/ies have on the current pathway of care?	Provide a welcome additional 1st line IO/TKI option in addition to the existing axi/ave which is thought to be less effective than some of the combinations which have followed and not been commissioned.

7a. Will the technology/ies be used (or is it/are they already used) in the same way as current care in NHS clinical practice? If so and there are multiple technologies, does this differ for any of the technologies under consideration?	Not our area of expertise
7b. How does healthcare resource use differ between the technology/ies and current care? If there are multiple technologies being considered, are there any expected differences in healthcare resource use between any of the technologies under consideration?	Not our area of expertise
7c. In what clinical setting should the technology/ies be used? (For example, primary or secondary care, specialist clinics.) If there are multiple technologies being considered, is the setting expected to differ between the technologies under consideration?	Secondary care clinics.
7d. What investment is needed to introduce the	Nil, would replace existing less effective treatment - axi/ave.

technology/ies? (For example, for facilities, equipment, or training.) If multiple technologies are being considered, is this expected to differ between the technologies under consideration?	
8a. Do you expect the technology/ies to provide clinically meaningful benefits compared with current care? If so and there are multiple technologies, please specify including whether this will differ by the technologies under consideration.	Not our area of expertise
8b. Do you expect the technology/ies to increase length of life more than current care? If so, please specify which.	Not our area of expertise
8c. Do you expect the technology/ies to increase health-related quality of life more than current care? If so, please specify which.	Not our area of expertise

9. Are there any groups of people for whom the technology/ies would be more or less effective (or appropriate) than the general population?	Not our area of expertise

The use of the technology/ies

10. Will the technology/ies be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for the use of the technology/ies? (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Not our area of expertise
11. Will any rules (informal or formal) be used to start or stop treatment with the technology/ies? Do these include any additional testing?	As there are no predictive factors the use will be down to expert opinion and hence not involve extra testing.

12. Do you consider that the use of the technology/ies will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? If so and there are multiple technologies, which technology and how?	Not our area of expertise
13a. Do you consider the technology/ies to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? If so and there are multiple technologies, which technology and why?	Not our area of expertise
13b. Is the technology/ies a 'step-change' in the management of the condition? If so and there are multiple technologies, which technology?	Not a step change, rather a marginal gain.
13c. Does the use of the technology/ies address any particular unmet need of the patient population? If	Not our area of expertise

so and there are multiple technologies, which technology?	
14. Do any side effects or adverse effects of the technology/ies affect the management of the condition and the patient's quality of life? If so, how.	Not our area of expertise

Sources of evidence (please comment on each technology if multiple technologies are being considered)

15a. Do the clinical trials on the technology/ies reflect current UK clinical practice?	Not our area of expertise
15b. If not, how could the results be extrapolated to the UK setting?	Not our area of expertise
15c. What, in your view, are the most important outcomes, and were they measured in the trials?	Not our area of expertise
15d. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not our area of expertise
15e. Are there any adverse effects that were not apparent in clinical	Not our area of expertise

trials but have come to light subsequently?	
16. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not our area of expertise
17. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA858, TA830 or TA780?	Not our area of expertise
18. How do data on real-world experience compare with the trial data?	Not our area of expertise

Equality

19a. Are there any potential equality issues that should be taken into account when considering the technology/ies?	Most phase 3 trials do not include a real world population and this trial will be no different.
19b. Consider whether these issues are different from issues with current care and why.	They are not as the preceding trials will be the same.

Key messages

20. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a wish in the community for a better IO/TKI option than axi/ave. • • • •

Thank you for your time.

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Treatments for renal cell carcinoma [ID6186]: A Pathways Pilot Appraisal Assessment Report

Produced by

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Dawn Lee	Project lead, lead for production of the decision model, input to design of observational data analysis, conduct of the economic literature searches, writing and editorial input
Madhusubramanian Muthukumar	Development of excel interface for the decision model inputs, screening and data extraction of evidence identified in the economic literature searches and input to production of the decision model, economic writing
Alan Lovell	Production of the literature search strategies, identification of potential observational data sources and contact with relevant data holders, writing the literature search methods
Caroline Farmer	Screening evidence identified in the clinical literature searches, identification of clinical experts for consultation, quality assurance of clinical data extraction, production of write up of clinical evidence and treatment pathway
Darren Burns	Production of the decision model
Justin Matthews	Conduct and writeup of fractional polynomial network meta-analysis. Input to design of observational data analysis

Helen Coelho	Screening evidence identified in the clinical literature searches, clinical data extraction, production of write up of treatment pathway
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Amanda Brand	Quality assessment of clinical trials
Louise Crathorne	Review of real-world evidence, patient and clinical commentary sections and proof reading
Zain Ahmad	Clinical and economic data extraction, and production of expert elicitation survey
Sophie Robinson	Advising on literature search methods, quality assurance of the literature search strategies
Edward CF Wilson	Production of the decision model
G.J. Melendez-Torres	Guarantor of the report. Conduct of statistical analysis, screening and data extraction for clinical literature searches and production of write up of clinical evidence and treatment pathway

All [redacted] data has been highlighted in blue and underlined, all [redacted] data is highlighted in yellow and underlined

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List of Key Issues

List of Abbreviations

Acronym	Definition
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
AG	Assessment group
AIC	Akaike information criterion
ALT	Alanine aminotransferase
aRCC	Advanced RCC
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BM	Bone metastases
BMJ	British Medical Journal
BMS	Bristol Myers Squibb
BNF	British National Formulary
BRL	Brazilian Real
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
ccRCC	Clear cell renal cell carcinoma
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CPI	Consumer Price Index
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
DAPS	Direct access pathology services
DBL	Database lock
DCR	Disease control rate
DES	Discrete event simulation
DF	Degrees of freedom
DFS	Disease-free survival
DIC	Deviance information criterion

Acronym	Definition
DICE	Discretely integrated condition event
DM	Distance metastases
DoR	Duration of response
DSU	Decision Support Unit
DVT	Deep vein thrombosis
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EHR	Electronic health record
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EPAR	European public assessment report
ERG	Evidence review group
ESMO	European Society for Medical Oncology
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
FACT	Functional Assessment of Cancer Therapy quality of life questionnaire
FAD	Final appraisal determination
FDA	U.S. Food and Drug Administration
FE	Fixed effects
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index - Disease Related Symptoms
FP	Fractional polynomials
G-BA	Federal Joint Committee (Germany)
GBP	Great British Pounds
GFR	Glomerular filtration rate
GG	Generalised gamma
GP	General practitioner
GU	Genito urinary
HAS	Haute Autorité de Santé (France)
HCRU	Healthcare resource use
HES	Hospital Episode Statistics
HFS	Hand foot syndrome
HR	Hazard ratio
HRG	Health resource group
HRQoL	Health-related quality of life
HSE	Health Survey England
HTA	Health technology assessment
IA	Investigator assessment
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
ICTRP	International Clinical Trials Registry Platform
IFN	Interferon

Acronym	Definition
IL	Interleukin
IMDC	International Metastatic RCC Database Consortium
INAHTA	International Network of Agencies for Health Technology Assessment
INR	International normalized ratio
IO	Immuno-oncology
IPD	Individual patient-level data
IPW	Inverse probability weighting
IQR	Interquartile range
IRIN	irinotecan
IRRC	Independent radiology review committee
IRT	Interactive Response Technology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
IVI	Innovation and Value Initiative
IxRS	Interactive voice or web response systems
KM	Kaplan Meier
KPS	Karnofsky performance status
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LOT	Line of treatment
LR	Local recurrence
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MA	Meta-analyses
MCM	Mixture-cure model
MDG	Modified de Gramont
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model repeated measures
MoA	Mechanism of action
MRC	Medical Research Council
mRCC	Metastatic renal cell carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
MTA	Multiple technology appraisal
NA	Not applicable
NB	Net benefit
NCCN	National Comprehensive Cancer Network
nccRCC	Non-clear cell renal cell carcinoma
NCRAS	National Cancer Registration and Analysis Service
NDRS	National Disease Registration Service
NE	Not evaluable
NEJM	New England Journal of Medicine

Acronym	Definition
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NHSE	National Health Service, England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
NOS	Not otherwise specified
NR	Not reported
NSCLC	Non-small cell lung cancer
OD	Once daily
OLS	Ordinary least squares
ONS	Office for National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
OWSA	One way sensitivity analysis
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD	Progressive disease
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazards
PICOS	Population, Intervention, Comparison, Outcomes and Study
PO	Per os (orally)
PPS	Post progression survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QC	Quality control
QD	Every day
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dosing intensity
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
REMARCC	Registry for Metastatic Renal Cell Carcinoma
RWD	Real-world data
RWE	Real-world evidence

Acronym	Definition
SABR	Stereotactic ablative radiotherapy
SACT	Systemic Anti-Cancer Therapy
SCLC	Small-cell lung cancer
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TA	Technology appraisal
TE	Treatment effect
TKI	Tyrosine kinase inhibitor
TSD	Technical support document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
ToT	Time on treatment
TTP	Time to progression
TTR	Time to response
TWSA	Two-way sensitivity analysis
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
ZIN	Zorginstituut Nederland National Health Care Institute

Key issues summary

The decision problem: summary of the EAG's key issues

Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments

Report sections	
Description of issue and why the EAG has identified it as important	Clinical advice to the EAG and consideration of relevant evidence highlights that optimal treatment sequencing following novel treatments at first line (i.e. IO/IO or IO/TKI combinations) remains an area of uncertainty. In addition, evidence for optimal treatment choice and sequencing in favourable risk patients at first-line remains an area of clinical debate.
What alternative approach has the EAG suggested?	The EAG has received clinical advice as to most likely treatment sequences. However, additional clinical evidence is needed to ascertain which treatments are most likely to be received, and most effective, as novel treatments continue to emerge in first line; as well as optimal treatment choice for favourable risk patients.
What is the expected effect on the cost-effectiveness estimates?	Current estimates of cost effectiveness, particularly in second line and for favourable risk patients, may evolve as this evidence develops. Optimal treatment sequencing may also impact overall estimates of OS in first line, but the direction of impact on cost-effectiveness estimates is unclear.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 2: Company's definition of relevant comparators

Report sections	
Description of issue and why the EAG has identified it as important	The company argued that, at first line, avelumab plus axitinib is a relevant comparator, and excluded tivozanib. The EAG disagrees with this position as avelumab plus axitinib is not considered to be routinely commissioned while it is accessed through the Cancer Drugs Fund; further, tivozanib is a relevant treatment at first line.
What alternative approach has the EAG suggested?	The EAG has included avelumab plus axitinib in clinical effectiveness analyses for completeness in line with the scope of the pathways decision problem (rather than the decision problem specific to cabozantinib plus nivolumab), but has not included this treatment in economic analyses for cabozantinib + nivolumab in keeping with NICE guidance. The EAG has also included tivozanib where possible in first-line analyses acknowledging limitations in the ability to conduct indirect treatment comparisons.
What is the expected effect on the cost-effectiveness estimates?	The EAG's cost-effectiveness estimates will more closely reflect NICE guidance.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 3: Company's definition of relevant outcomes

Report sections	
Description of issue and why the EAG has identified it as important	The company argued in its original submission that time to next treatment was not a relevant outcome. When these data were provided, the definition used was non-standard, precluding meaningful comparisons to other studies.
What alternative approach has the EAG suggested?	The EAG has suggested defining time to next treatment in a way similar to other studies; i.e. considering the time from initiation of first-line treatment to the first of uptake of a second systemic treatment where this has been recorded, death or loss to follow-up. These data are not yet available.
What is the expected effect on the cost-effectiveness estimates?	The EAG's economic modelling will be able to draw on data for this outcome to produce more consistent and high-fidelity cost-effectiveness estimates.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 4: Company's definition of relevant subgroups

Report sections	
Description of issue and why the EAG has identified it as important	The company argued in its original submission that cabozantinib plus nivolumab should be assessed in the all-risk group. The EAG notes that risk group is known to be an important prognostic factor, an important effect modifier across a range of RCC treatments, and a key factor in previous NICE appraisals, as well as a salient factor in clinical decision-making. As a result, subgroup-specific evidence is highly probative. Moreover, in subgroup-specific network meta-analyses, the EAG found that patterns of effect were different by risk group.
What alternative approach has the EAG suggested?	The EAG has considered cost-effectiveness both in an all-risk population as well as in intermediate/poor risk populations and favourable risk populations separately, reflecting practice in prior appraisals for RCC.
What is the expected effect on the cost-effectiveness estimates?	The EAG expects that cost-effectiveness estimates will more closely reflect clinical realities and the existing treatment pathway, supporting more robust decision-making.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 5: CheckMate 9ER: Consistency of reporting

Report sections	
Description of issue and why the EAG has identified it as important	The company submitted an interim report of clinical effectiveness, with a subsequent update provided due to data quality issues. However, the EAG did not find that the explanation of changes provided was sufficiently comprehensive to provide confidence in the data quality. For example, data relating to adverse events had minor changes that were not explicitly described as updated.
What alternative approach has the EAG suggested?	It was not possible for the EAG to resolve this issue within its appraisal using the available data. A clear explanation of all changes made

Report sections	
	between data cuts provided would increase confidence in the analyses provided.
What is the expected effect on the cost-effectiveness estimates?	It is unclear if an explanation would impact data inputs to the EAG's economic model; however, confidence in data quality is essential to minimise decision risk.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice

Report sections	
Description of issue and why the EAG has identified it as important	The EAG's inspection of the company's trial data found that the trial enrolled a relatively small number of UK patients, and that the rate of patients continuing to receive treatment post-progression was both higher than expected and not in keeping with clinical treatment patterns in the UK. In addition, patients with intermediate and poor risk receiving sunitinib had higher restricted mean survival times for both OS and PFS in the CheckMate 9ER trial than the comparable real world evidence source preferred by the EAG, with a similar trend seen for OS in the favourable risk group as well. Patients receiving sunitinib also had comparatively lower use of nivolumab as a subsequent treatment than expected.
What alternative approach has the EAG suggested?	It was not possible for the EAG to resolve this issue within its appraisal using the available data. A clearer justification of why post-progression treatment rates were higher than expected would contextualise concerns about generalizability. Analyses accounting for post-progression treatment would be valuable to better understand the impact of post-progression treatment rates, and mix of post-progression treatments.
What is the expected effect on the cost-effectiveness estimates?	Clearer understanding of time on treatment post-progression would impact treatment costs estimated in an economic model. The direction of this impact is unclear pending an explanation from the company.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 7: CheckMate 9ER: Effect modification by risk group

Report sections	
Description of issue and why the EAG has identified it as important	The EAG's inspection of the company's trial data found that there was some evidence of effect modification by risk group for OS and PFS; for example, the hazard ratio for OS comparing cabozantinib plus nivolumab against sunitinib in favourable-risk patients (HR=1.07) is more than twice as high as for patients with poor risk (HR=0.46), with a similar trend in evidence for PFS (HR=0.72 vs HR=0.37). This is important because it reinforces the value of risk group as a key consideration in this appraisal and its salience in clinical and cost-effectiveness decision-making.
What alternative approach has the EAG suggested?	The EAG reiterates that cost-effectiveness modelling should also consider risk group as a key factor, including production of cost-effectiveness estimates by risk group.
What is the expected effect on the cost-	Estimates for the cost-effectiveness of cabozantinib plus nivolumab are likely to be very different by risk group.

Report sections	
effectiveness estimates?	

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 8: Evidence base: quality and sufficiency of included randomised trials

Report sections	
Description of issue and why the EAG has identified it as important	The EAG's appraisal of the randomized trials included in its syntheses identified significant limitations in the quality of included trials, including CheckMate 9ER; of the 17 prioritised trials, nine were appraised as being at high risk of bias and eight were appraised as being at an unclear risk of bias. The majority of comparisons in first-line and second-line networks were informed by only one trial, meaning that many comparisons between novel treatments were based on indirect evidence only, and inconsistency in networks could not be assessed. Moreover, risk group-specific analyses drew on comparatively sparse data, which were often unevenly presented; in particular, pembrolizumab plus lenvatinib could not be included in risk group-specific fractional polynomial NMAs for PFS due to redacting of data in TA858.
What alternative approach has the EAG suggested?	The EAG has used parallel analysis methods for survival outcomes, including fractional polynomial NMA and proportional hazards NMA, to test the robustness of analyses to different assumptions where possible. However, only proportional hazards NMAs are available for survival outcomes in the favourable risk group patients in first line. However, this does not address the challenges relating to risk of bias.
What is the expected effect on the cost-effectiveness estimates?	Estimates for the cost-effectiveness of cabozantinib plus nivolumab are increased in their statistical uncertainty due to limitations and sparseness in the underpinning evidence base; in addition, it is impossible to quantify the impact of trial-level bias on cost-effectiveness estimates.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks

Report sections	
Description of issue and why the EAG has identified it as important	While the EAG did not regard that distribution of effect modifiers across the network precluded the feasibility of NMAs, it remains that differences between trials in risk group distribution, histological features, proportion with prior nephrectomy, proportion with sarcomatoid features and, to a possibly lesser degree, age could not be meaningfully addressed in NMAs. This was both because of the sparseness of networks and because of poor reporting of several of these characteristics (particularly proportion with sarcomatoid features). More generally, observational evidence suggests that over time and in the last 15 years, patients have experienced better outcomes regardless of treatment. Trials included draw from a wide range of timeframes and follow-up lengths, adding another challenge to interpretation.
What alternative approach has the EAG suggested?	The EAG used a random effects term when appropriate in its fractional polynomial NMAs, which accounted for some heterogeneity in baseline risk. However, a network meta-regression with a less sparse evidence network would have provided greater confidence in findings.

Report sections	
What is the expected effect on the cost-effectiveness estimates?	The direction of travel of cost-effectiveness estimates as a result of this uncertainty is difficult to quantify, as it in part depends on the age of the trial and trial-specific distribution of effect modifiers. However, given lower numbers of poor risk patients in trials linking tivozanib in first-line networks, estimates may be biased in favour of tivozanib.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes

Report sections	
Description of issue and why the EAG has identified it as important	Many of the prioritised trials exhibited violations of the proportional hazards assumptions, based either on statistical tests or on visual inspection. In addition, time-to-event data were drawn from the last available data cut given difficulties in identifying 'most similar' time points for analysis and to avoid discarding collected data. However, differential trial maturity is a challenge for interpretation given evidence of 'slippage' in HRs towards the null, particularly for IO/TKI combinations, over sequential follow-ups.
What alternative approach has the EAG suggested?	As above, the EAG has used parallel analysis methods for survival outcomes, including fractional polynomial NMA and proportional hazards NMA, to test the robustness of analyses to different assumptions. However, challenges in estimating hazard functions generated some inconsistencies between both analysis strategies, particularly for pembrolizumab plus lenvatinib in first-line, and generated estimates for second-line fractional polynomial NMAs that were inconsistent between outcomes. It is likely that the EAG's analyses should be revisited when all trials have reached maturity.
What is the expected effect on the cost-effectiveness estimates?	Based on evidence of slippage, it is likely that cost-effectiveness estimates for novel treatments drawing on comparatively less mature trials may be unduly optimistic.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment

Report sections	
Description of issue and why the EAG has identified it as important	Included trials primarily restricted inclusion to patients with clear cell RCC, creating questions about the applicability of analyses to other RCC histologies. In addition, adjuvant pembrolizumab is now available in routine practice, but was not available as part of routine practice when any of the included trials were conducted. Clinical advice to the EAG is that adjuvant pembrolizumab may reduce the subsequent effectiveness of IO treatments and improve prognosis for other types of treatment as patients will be scanned more regularly, leading to earlier detection and treatment of progression.
What alternative approach has the EAG suggested?	The EAG could not address these issues in this appraisal due to sparsity of evidence. However, a number of trials are emerging in different RCC histologies which will provide additional evidence in this area.

Report sections	
What is the expected effect on the cost-effectiveness estimates?	As adjuvant pembrolizumab increases in use, it is likely that effect estimates from IO treatments will vary in practice from those observed in key trials. These may eventually attenuate the cost-effectiveness of IO-based treatments, particularly in first line.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

1. OBJECTIVES OF THE PILOT PROCESS AND THIS ASSESSMENT

The NICE Pathways pilot process aims to enhance the efficiency of assessing treatments and inform access decisions by developing a comprehensive and adaptable core model for specific disease areas.

NICE selected RCC as the first pilot topic due to the expected pipeline of treatments, indicating a dynamic and evolving landscape in RCC therapies. RCC is a disease area characterised by multi-comparator decision spaces, meaning there are several treatment options available at different stages of the disease pathway. Treatment decisions in RCC are influenced by factors such as the patient's exposure to prior therapies, disease progression, and individual patient characteristics. The NICE Pathways pilot process for RCC seeks to test an evaluation framework that can effectively assess and compare various treatment options within the RCC pathway. By considering the evolving landscape of RCC therapies, the process aims to inform access decisions, optimise treatment pathways, and ultimately benefit patients with RCC.

As part of this pilot NICE requested the development of an EAG model which incorporates multiple decision nodes to assess multiple technologies in a disease pathway and inform robust access decisions. NICE has published a process statement outlining the summary of this pilot and the intended process to achieve its aims.[1] Within this pilot the aim was to develop a high-quality open-source disease model, available to all relevant stakeholders without restriction, which can be reused and built upon in future appraisals whilst maintaining confidentiality of proprietary data.

An attractive model for this type of approach is the Innovation and Value Initiative's Open-Source Value Project (IVI; Jansen et al. 2019[2]). Since the project began in 2018, IVI has developed three disease models – one in rheumatoid arthritis, one in non-small-cell lung cancer and one in major depressive disorder – that are made freely available to all users, with full open-source code posted in a public repository (GitHub).[3] As part of its development process, IVI holds regular public consultation seeking feedback on the structure and parameterisation of its analyses, and exposing its implementation to unrestricted scrutiny.

Given the scope and steps of the process the consultation stage is different to the IVI models. In particular, a user-interface will not be provided prior to the Appraisal Committee meeting and is scheduled instead for a later phase of work (see Section 4.3.1.9). However, the code will be posted in a public repository enabling full public scrutiny and as discussed additional functionality will be incorporated during Phase 2 of the pilot.

2. DECISION PROBLEM, DESCRIPTION OF THE TECHNOLOGIES AND CLINICAL CARE PATHWAY

2.1. Description of the health condition

RCC is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer, accounting for more than 80% of cases.[4] Clear cell RCC is the most common subtype, quoted as accounting for approximately 75% of cases.[4] Non-clear cell subtypes have varying frequencies, with papillary RCC comprising around 10-15% of cases, chromophobe RCC around 5%, and other subtypes representing approximately 1% each.[4] Non-classifiable RCC is a rare category and histological assessment can be challenging, especially when a nephrectomy was not performed initially or limited tissue samples are available.

Diagnosis is usually incidental, and when people present with symptoms the disease is usually advanced; the most common symptoms being upper abdomen or back pain, a palpable lump or mass in the kidney area and gross haematuria.[5,6] In metastatic disease, symptoms associated with the metastatic tumours may be present, including airway obstruction, bleeding, and dyspnoea for lung metastases, pain and fractures for bone metastases, jaundice and swelling for liver metastases, and swelling of lymph nodes for lymphatic metastases.[7-9]

RCC is typically staged from Stage 1 to Stage 4 according to how far the cancer may have spread; Stage 3 indicates that the cancer has advanced locally (within regional lymph nodes) and Stage 4 indicates that metastases beyond the regional lymph nodes are present. Treatment depends on the location and stage of the cancer.[10]

The scope for this appraisal is people with advanced RCC (aRCC) or metastatic RCC (mRCC). Although systemic treatments are mostly suitable for those with metastatic disease (Stage 4), they may be offered to people with locally advanced (Stage 3) disease where this is unresectable. Due to this, people with Stage 4 RCC or Stage 3 unresectable RCC have been included in this appraisal.

2.2. Epidemiology

Kidney cancer is the eighth most common cancer in the UK, accounting for 4% of all new cancer cases (2019).[11,12] Kidney cancer is more common in men than in women: in the UK, between 2016 and 2018, there were 1.7 times more new cases in men than in women. A quarter of cases were diagnosed in people aged 60 to 69 years, with nearly half of cases (49.7%) diagnosed in people aged ≥70 years.[11] It is also more common in people of white ethnicity.[11] Links to certain lifestyle factors such as obesity, hypertension and smoking are well-established.[13]

In 2018, 9,438 new kidney cancer cases were diagnosed in England.[14] Of those, 40.2% had Stage 1 disease, 7.6% had Stage 2 disease, 15.5% had Stage 3 disease and 20.5% had Stage 4 disease.[10] The five-year survival has been reported as 86.8%, 76.6%, 74.2% and 12.4% for Stage 1, 2, 3, and Stage 4 disease, respectively.[15] These survival rates are likely to underestimate survival for patients starting treatment now as they do not include the impact of immuno-oncology combinations that have more recently entered clinical practice.

RCC is the most common type of kidney cancer, responsible for more than 80% of all cases diagnosed in the UK.[16,17] In aRCC (Stage 3), the tumour located in the kidney may be any size if it has spread to regional lymph nodes or may have grown into major veins or perinephric tissue but has not spread to other parts of the body.[18] In mRCC (Stage 4), the tumour may have spread to areas beyond Gerota's fascia, extending into the adrenal gland on the same side of the body as the tumour and possibly to lymph nodes, but not to other parts of the body, or has spread to any other organ. Metastases in RCC most commonly occur in the lung, bone, lymph node, and liver, leading to significant morbidity as well as poor prognosis.[9]

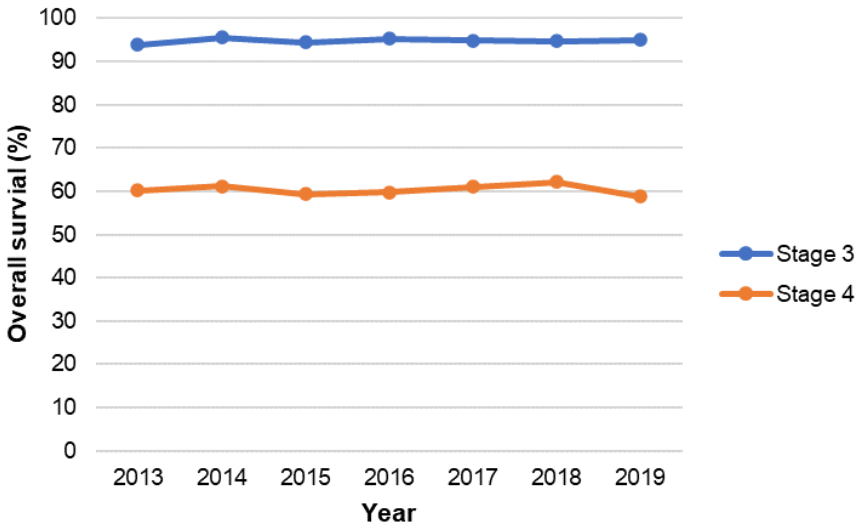
OS data for RCC were available from the Get Data Out (GDO) 'Kidney' dataset, published by the NCRAS. Yearly data (from 2013 to 2019) were recorded for Stage 1, 2, 3 and 4 clear cell RCC patients (n=252), and for RCC not otherwise specified (NOS) (n=364) (patients may be NOS either because a distinct morphology cannot be seen under the microscope [histologically confirmed], or because the tumour has been clinically diagnosed and no tissue sample has been taken [not histologically confirmed]). Survival rates were reported as Kaplan-Meier (KM) estimates at Month 3, 6, 9, 12, 24, 36, 48, 60, 72 and 84. The most complete data were for 12 months i.e. 12-month data were reported for all years. The data

indicate that patients with Stage 3 clear cell RCC have better 12-month prognosis/ highest survival rates (ranging from 93.9% to 95%) than those with Stage 3 or 4 RCC with any other histological profile. The majority of these patients will not be eligible for surgery and therefore not in scope of this appraisal.

Stage 4 clear cell RCC, is the histology in which the majority of clinical trials have been conducted. Cancer Research UK data indicate that this makes up approximately 75% of all RCC cases, whereas NCRAS data indicate that this makes up 77 % of Stage 3 and 44% of Stage 4 RCC case.[16,19] Clinical expert advice has indicated that 44% clear cell at Stage 4 is lower than typically seen in clinical practice suggesting that some patients may not have undergone a biopsy. For Stage 4 clear cell patients, 12-month survival ranged from 58.5% to 62.2% (Figure 1 and Figure 2). The most severe histological subtype with the lowest 12-month overall survival estimates were patients with Stage 4 renal cell carcinoma NOS (not histologically confirmed), ranging from 13.1% to 18.4%.

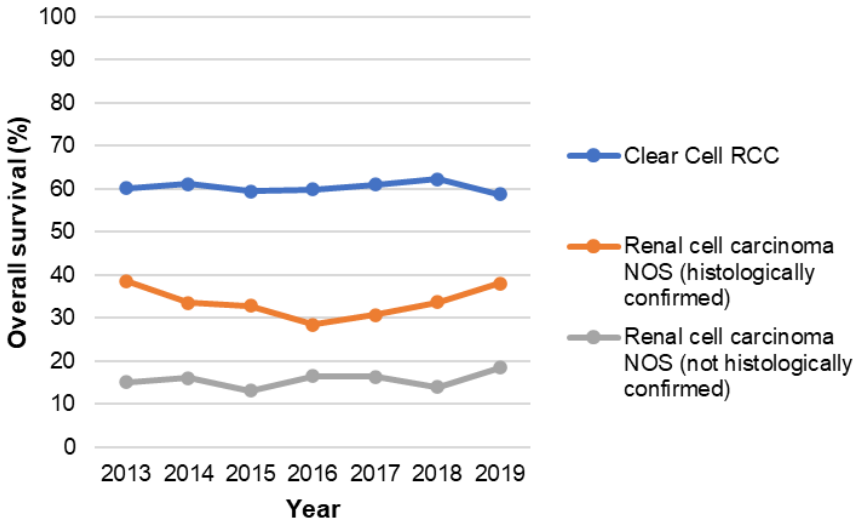
The data suggest that there has been a sustained improvement in OS from 2016 to 2019 for patients with Stage 4 RCC NOS (histologically confirmed), with OS increasing from 28.5% to 38%. Although the cause for improved survival rates is not clear, it may be due to patient enrolment in clinical trials focusing on non-clear cell histologies.

Figure 1: 12-month overall survival for Stage 3 and 4 clear cell RCC (2013-2019)



Abbreviations: RCC, renal cell carcinoma

Figure 2: 12-month overall survival for Stage 4 cancer, all histologies (2013-2019)

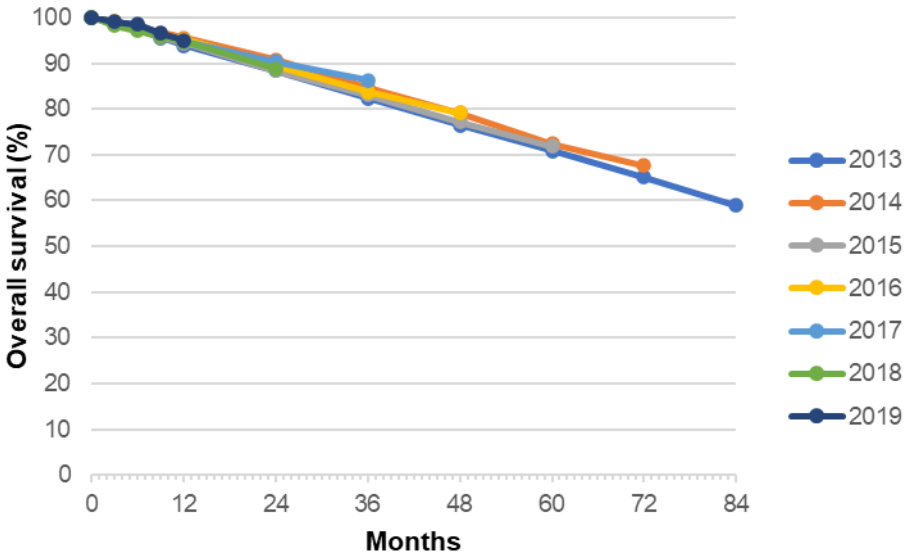


Abbreviations: RCC, renal cell carcinoma

Five-year (60 month) survival rates were recorded for years 2013, 2014 and 2015. For completeness and for validation purposes these are outlined below. OS at 60 months confirm that patients with Stage 3 clear cell RCC have the best 12-month prognosis/ highest survival rates (ranging from 70.8% to 72.4%). For Stage 4 clear cell RCC, 60-month survival ranged from 19.1% to 20.1%. Patients with Stage 4 RCC NOS (not histologically confirmed) have the poorest 12-month prognosis/lowest survival rates (ranging from 2.1% to 2.7%).

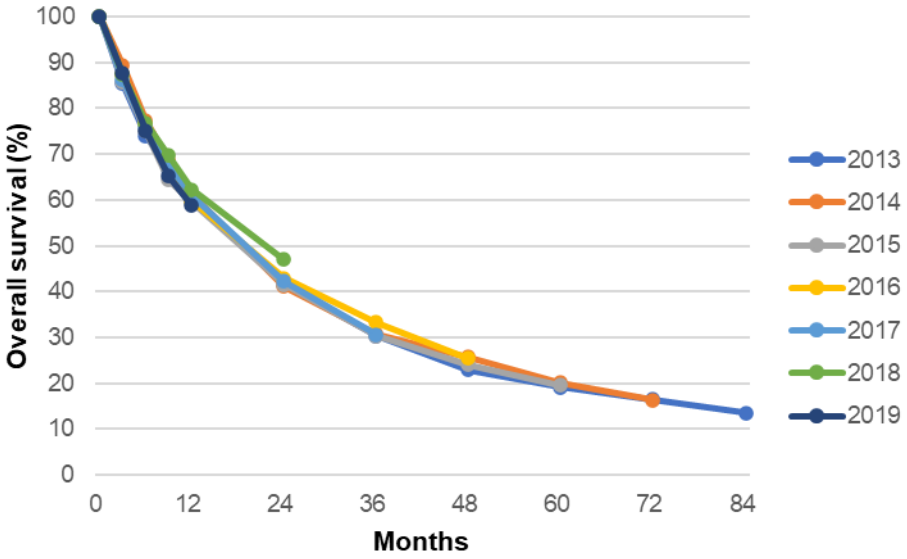
Figure 3 and Figure 4 show that the prognosis for clear cell RCC remained relatively consistent between 2013 and 2019, however, as noted earlier these survival rates are likely to underestimate survival for patients starting treatment now as they do not include the impact of immuno-oncology combinations that have more recently entered clinical practice for which any improvements are most likely to be seen in longer-term data.

Figure 3: Overall survival for patients with Stage 3 clear cell RCC (all years)



Abbreviations: RCC, renal cell carcinoma

Figure 4: Overall survival for patients with Stage 4 clear cell RCC (all years)



Abbreviations: RCC, renal cell carcinoma

2.3. Prognostic factors

Prognostic factors play a key role in aRCC by providing valuable insights into disease prognosis and guiding treatment decisions. Several important prognostic factors have been identified in aRCC.

Risk scores, such as the International Metastatic RCC Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) scores, are widely used tools that incorporate various factors including performance status, time from diagnosis to systemic therapy initiation, haemoglobin levels, calcium levels, and lactate dehydrogenase (LDH) levels. These scores help classify patients into favourable, intermediate, and poor-risk groups, providing valuable information about disease aggressiveness and treatment response (see Section 2.3.1).

Histology is another key prognostic factor, with clear cell RCC being the most common subtype and generally associated with a poorer prognosis compared to other subtypes.[20] The presence of metastasis is a well-established prognostic factor in aRCC, indicating the extent and aggressiveness of the disease.[20] Differentiating between visceral metastases and bone metastases is also important, as patients with bone metastases often exhibit a less favourable outcome and suboptimal response to certain treatments, such as tyrosine kinase inhibitors (TKIs).[20]

Nephrectomy is an additional prognostic factor in aRCC. In select patients, nephrectomy has shown benefits, especially in favourable-risk disease, with improved survival compared to those who do not undergo the procedure. In cases where nephrectomy is performed, it typically indicates that the primary tumour was localised and surgically resectable. This suggests that the disease had not spread extensively beyond the kidney at the time of diagnosis. Consequently, patients who undergo nephrectomy in these circumstances tend to have a more favourable prognosis compared to those with primary metastatic disease.[21] On the other hand, if a patient presents with primary metastatic disease, nephrectomy may not be pursued as the cancer has already spread beyond the kidney to other distant sites. The presence of metastasis often indicates a more advanced stage of the disease, and the prognosis for such patients tends to be poorer.[21]

Timely initiation of systemic therapy is also a significant prognostic factor, as delayed treatment may adversely affect outcomes. Patients who received treatment within 100 days of diagnosis had a lower OS from the start of systemic

treatment compared to those who initiated treatment 600 days or more after diagnosis.[22] Early intervention with targeted therapies or immunotherapies has been associated with better response rates and prolonged survival.

Sarcomatoid features within the tumour represent another important prognostic factor in aRCC.[20,23] Sarcomatoid RCC, characterised by spindle or giant cells resembling a sarcoma, is associated with a poorer prognosis. This variant often exhibits larger tumour size, extensive disease, and a higher likelihood of metastasis. Additionally, sarcomatoid differentiation can lead to resistance against systemic therapies, limiting treatment options and reducing overall survival rates.

Other prognostic factors in aRCC include age, tumour stage, PS,[24,25] and laboratory parameters such as haemoglobin levels, LDH levels, and calcium levels.[26] These parameters provide additional information about disease aggressiveness and can aid in treatment decision-making.

By considering these prognostic factors, clinicians can better evaluate disease prognosis, select appropriate treatment strategies, and optimise outcomes for patients with aRCC.

2.3.1. Risk status

According to expert advice received, risk status for people with aRCC who have not received systemic therapy is classified using the International Metastatic RCC Database Consortium (IMDC) risk score.[27,28] This scoring system was derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy and predicts survival based on time from diagnosis, Karnofsky performance status, and laboratory measures of haemoglobin, corrected calcium and neutrophils. Within the current treatment pathway for RCC, some treatments are only recommended for people with IMDC poor or intermediate risk status (Section 2.4). Although the relevance of IMDC prognostic criteria to frontline combination immunotherapy is still being established, these criteria are commonly used to risk-stratify patients in clinical trials and guide treatment decisions in practice.[29]

Historically, risk status was classified using another risk stratification score: the Memorial Sloan Kettering Cancer Center (MSKCC) risk score,[24,30] which was later extended to create the IMDC system to enhance its predictive accuracy. The IMDC risk score includes additional factors like absolute neutrophil count and

platelet count, which are not considered in the MSKCC model. In UK clinical practice, the IMDC risk score is preferred over the MSKCC risk score because lactate dehydrogenase concentration, which is not routinely tested in the UK, is included in the MSKCC risk score. Studies have shown a high concordance rate (83%) between the two risk scores, with disagreements primarily observed in classifying patients as intermediate or poor risk.[28,31] However, for the purpose of this appraisal, these differences are likely to have limited impact as these groups are generally combined within NICE recommendations.

In UK practice, the majority of patients with RCC are classified as intermediate or poor risk. Recent real-world data indicate rates from 59% to 89% with intermediate or poor risk status on the MSKCC risk score[32,33] and from 69% to 86% using the IMDC risk score.[34,35] Clinical expert advice indicated that approximately 70-75% of RCC patients in the UK have intermediate or poor IMDC risk status, and 25-30% are categorised as favourable risk.

Validation studies have demonstrated that different risk statuses are associated with varying median OS rates. An international study validating the IMDC score reported by Gore et al. in 2015 reported a median OS of 45.5 months for favourable risk, 18.9 months for intermediate risk and 6.2 months for poor risk using data from 4,065 participants between 2004 and 2010.[33] Another study by Yip et al. in 2017,[36] investigating real-world outcomes of 255 individuals treated with immuno-oncology agents, found that while survival data were immature for evaluating 1st line treatment, IMDC risk status was predictive at the 2nd line, with median OS rates not reached, 26.7 months, and 12.1 months ($p<0.0001$) in each of the three risk groups.

Clinical advice suggests that IMDC risk status may be particularly relevant in predicting outcomes for patients receiving treatment with TKIs, as the original risk score was developed using this patient population. Therefore, it is plausible that patients with favourable risk disease may have a higher likelihood of responding to TKI treatment compared to other options.

Risk status is not re-assessed at 2nd or later lines of treatment, and thus the impact of risk assessment on treatment decision-making tends to decrease in subsequent lines. However, it can still be useful for discussing prognosis with patients. In some cases, risk status may be assessed once at the initial diagnosis of aRCC, and that status is carried forward for the patient's subsequent treatment courses. However,

individual patient characteristics and response to treatment may evolve over time, so clinical judgment would be exercised in interpreting and applying risk assessment in later lines of therapy.

2.4. Treatment pathway

The treatment pathway for RCC can be divided into interconnected decision points based on the disease staging system and line of therapy (see Figure 5 and Figure 6). The treatment pathway is based upon people with clear cell histology (as are the majority of trials; Section 3). In practice, the same treatment algorithm is applied to the majority of people with non-clear cell histologies including papillary RCC, chromophobe RCC, collecting duct RCC (Bellini collecting duct RCC), medullary RCC - mucinous tubular and spindle cell RCC, multilocular cystic RCC, XP11 translocation RCC and unclassified RCC.37 Information on the specific histologies where treatments are commissioned in the same manner as clear-cell has been requested from NHSE and will be incorporated into the project findings when received.

2.4.1. Treatment for early stage to locally advanced RCC

Surgery (partial or radical nephrectomy) is usually possible, and is the preferred treatment, for people with early stage to locally advanced RCC and is usually curative.[38] After tumour resection, the cancer can be graded. Risk of recurrence is greater in higher-grade cancers.[39] After surgery, micro-metastases and individual tumour cells may still be present or may reoccur. They can potentially develop into larger tumours and spread to distant sites around the body.[39] This results in advanced, unresectable tumours.[39] The aim of adjuvant treatment is to prevent recurrence and potential progression to advanced (unresectable or metastatic) disease.[40] Approximately 20–40% of people who have received surgery subsequently develop metastatic RCC.[41]

One major change is the introduction of adjuvant treatment. NICE recommended pembrolizumab as an option for the adjuvant treatment of RCC at increased risk of recurrence after nephrectomy, with or without metastatic lesion resection in October 2022.[39] Receipt of pembrolizumab in the adjuvant setting may restrict later treatment options. The reason for this being that the NHS does not fund treatment with subsequent immuno-oncology treatments for people who have received treatment with a programmed cell death protein (PD-1) / programmed death-ligand 1 (PD-L1) inhibitor in the adjuvant setting in the previous 12 months. Based upon expert input patients who are treated in the adjuvant

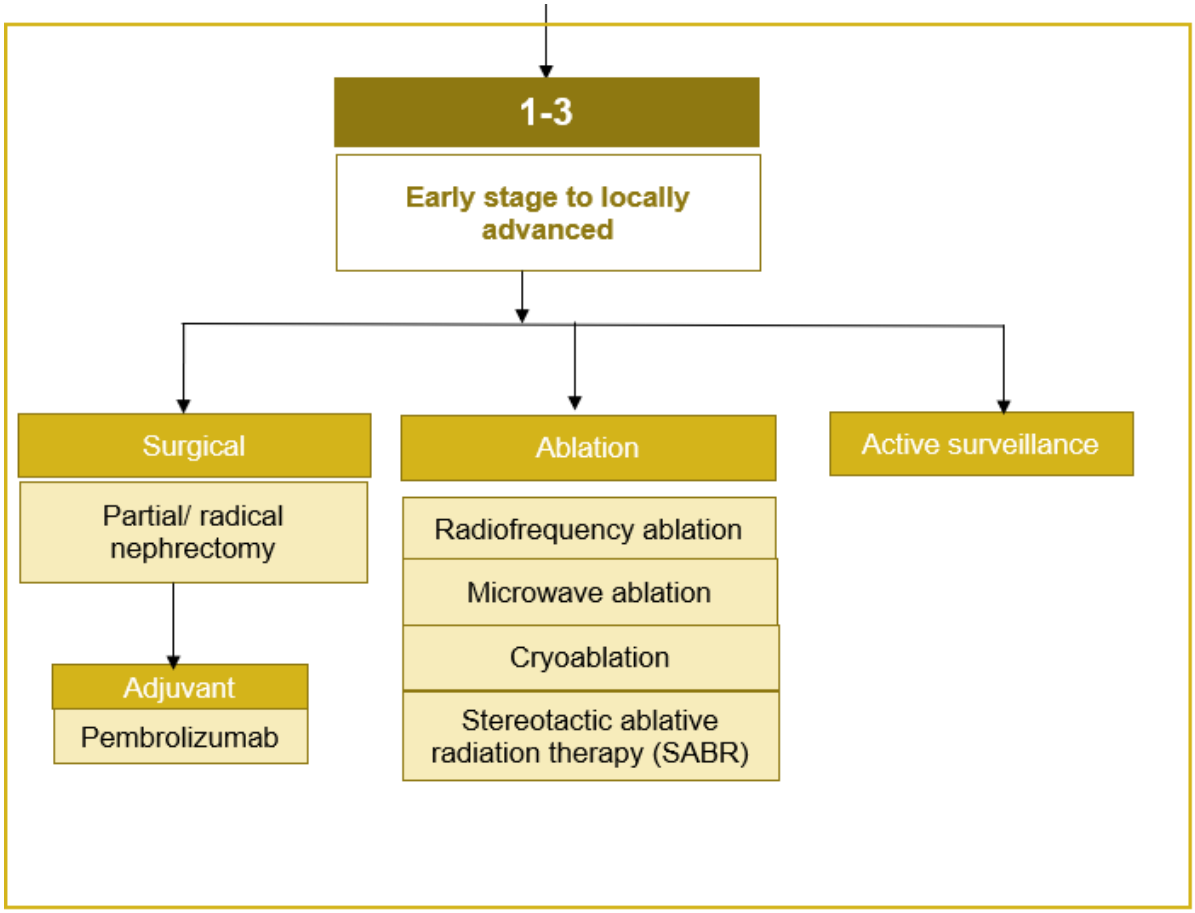
setting are likely to be assessed as favourable risk on IMDC criteria if they relapse as they are scanned frequently which means that relapses are usually detected early.

Clinical feedback to the EAG indicated that the use of adjuvant therapy is a matter of debate among clinicians. While the pembrolizumab trial in the adjuvant setting has reported positive data, trials of other PD-1 inhibitors have reported mixed results. One clinician noted that many clinicians are currently hesitant to use adjuvant treatment due to concerns about toxicity, and the lack of clear selection criteria for identifying patients who would truly benefit from it. In addition, the impact of widespread adjuvant treatment and its effect on relapse rates can significantly influence the validity of existing data. It is still considered too early to determine the uptake of adjuvant pembrolizumab and its impact on the treatment landscape. Currently the proportion of participants receiving adjuvant therapy is low. At the time pembrolizumab was appraised, uptake was expected to start at 20% of the eligible population rising to 65% in five years.[39] Based upon estimates of the eligible population size the maximum uptake is expected to be 18% of the total population. One clinician noted that it will be important to wait for a period of three to six months to assess the real-world utilisation and outcomes of adjuvant pembrolizumab. Understanding the optimal duration and potential long-term effects of adjuvant therapy is crucial for interpreting effectiveness data accurately.

Local ablation is an alternative 1st line approach of particular use in people whose renal function needs to be preserved.[42] The most commonly utilised of these techniques are radiofrequency ablation and cryoablation.[42]

Active surveillance may also be appropriate for early stage RCC, particularly where the mass is small and/or in those who are elderly or frail.[42]

Figure 5: Treatment pathway for early stage to locally advanced RCC



2.4.2. Treatment for advanced RCC

As aRCC is currently incurable, the goal of treatment is to prevent disease progression, maintain health-related quality of life (HRQoL), provide relief from cancer symptoms and extend life.

Treatment guidelines have been developed by the European Society for Medical Oncology (ESMO)[43] and the British Medical Journal (BMJ) RCC best practice guidelines (July 2022).[42] Both guidelines highlight the importance of considering patient factors such as comorbidities, treatment toxicity, and patient preferences when selecting the appropriate treatment regimen. Treatment decisions should be made in consultation with healthcare professionals, taking into account individual patient characteristics and available clinical evidence. While there are no separate NICE guidelines dedicated solely to the management of RCC currently, the NICE recommendations from various technology appraisals (TAs) do guide the treatment of RCC in the UK. Treatments recommended by NICE are summarised in Table 1 and Table 2.

Patients who receive a diagnosis of RCC are afforded a variety of treatment options ranging from active surveillance for those with low volume, indolent disease to cytoreductive nephrectomy for those who for those with favourable outcomes, to treatment with an immune checkpoint inhibitor or tyrosine kinase inhibitor (TKI).

2.4.2.1. Active surveillance or surgery

Treatment options for patients with mRCC include active surveillance and cytoreduction for patients with favourable-risk disease. A subset of patients with mRCC have indolent disease and limited metastatic burden. Initiation of systemic treatment can be postponed in this group of patients to avoid the treatment-related toxicities. In these individuals the ESMO and American Society of Clinical Oncology (ASCO) clinical practice guidelines suggest that active surveillance may be an appropriate option.[43,44] This approach involves closely monitoring the patient's condition without immediate treatment intervention. Active surveillance allows for regular assessments of disease progression and can help avoid unnecessary treatment in patients who may have slower-growing tumours or who may benefit from delayed intervention.

Surgery is only recommended in people where there is a metastasis in a single regional lymph node, but no evidence of distant metastasis.[42] The potential benefits and risks of deferred surgery for residual primary tumours or metastases after partial response to checkpoint inhibitor treatment is, however, gaining interest, considering the potential for long-lasting effects with these treatments.

2.4.2.2. Systemic treatment

The treatment landscape for RCC has evolved significantly with the introduction of targeted therapies and immunotherapies.

Vascular endothelial growth factor (VEGF) receptor-tyrosine kinase inhibitors (TKIs), encompassing a range of multikinase inhibitors, have emerged as the cornerstone of targeted therapies in the treatment of RCC. These agents target VEGF receptors, primarily 1-3, which play a critical role in tumour-induced angiogenesis and lymphogenesis. Standard treatments for RCC may include various VEGF receptor-TKIs such as sunitinib, pazopanib, tivozanib, and cabozantinib. These inhibitors act by impeding the activity of VEGFRs, thereby disrupting the signalling pathways involved in angiogenesis and lymphogenesis. VEGF receptor-TKIs can be initially classified as selective or non-selective inhibitors. Non-selective inhibitors have the capability to interact with multiple targets and exhibit different levels of *in vitro* potency against VEGF receptors. This potency can range from low (e.g.,

sorafenib) to intermediate (e.g., sunitinib) to high (e.g., cabozantinib and lenvatinib). On the other hand, selective inhibitors demonstrate an increased selectivity for VEGF receptors and display intermediate (e.g., pazopanib) or high (e.g., axitinib, tivozanib) *in vitro* inhibitory activity specifically against VEGF receptors.

In 2015, nivolumab an anti-programmed cell death protein 1 (PD-1) inhibitor was approved for VEGF refractory RCC initiating the rise of immunotherapy in treatment options. The combination of immunotherapy and targeted therapy can achieve higher response rates and better outcomes via additive or synergistic mechanisms. Therefore, various combinations of immunotherapy and targeted therapies have been studied in mRCC. In recent years, antibody-based immunotherapies targeting immune checkpoint receptors PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have demonstrated clinical efficacy in mRCC patients. This led to the approval of nivolumab + ipilimumab as a 1st line approach for mRCC patients with intermediate or poor risk disease.

1st line systemic treatment (untreated aRCC)

In the 1st line treatment of RCC, several options are available depending on the patient's risk profile and individual characteristics. These treatment approaches aim to effectively target and manage the disease while considering factors such as efficacy, tolerability, and patient preferences. Clinical advice to the EAG indicated that when initiating 1st line therapy, the emphasis is on selecting the treatment that offers the best potential for long-term survival. After that the focus shifts more towards palliative measures aimed at managing symptoms and improving HRQoL.

The use of 1st-line PD-1 inhibitor therapy, in combination with VEGF receptor-targeted therapy, has shown improved outcomes compared to TKI monotherapy for patients with clear cell aRCC. This approach harnesses the immune system to fight cancer cells while simultaneously inhibiting the pathways that promote tumour growth and spread. The CLEAR trial[45] evaluated the combination of pembrolizumab + lenvatinib and found that it provided an OS advantage compared to sunitinib alone. The pembrolizumab + lenvatinib combination also showed higher response rates and longer PFS. Pembrolizumab + lenvatinib, along with other TKI + PD-1 inhibitor combinations such as avelumab + axitinib, pembrolizumab + axitinib, or cabozantinib + nivolumab, are licensed as 1st-line treatments for clear cell aRCC, regardless of the patient's risk groups. Pembrolizumab + lenvatinib has recently been recommended by NICE (TA858[38]) in patients who are not eligible for treatment with nivolumab + ipilimumab, while avelumab + axitinib is available via the Cancer Drugs Fund (CDF) (TA645[46]), pembrolizumab + axitinib is not recommended by NICE (TA650[47]), and

cabozantinib + nivolumab is under review by NICE in this appraisal. There is no preferred TKI + PD-1 inhibitor combination in existing guidelines. Although clinical advice to the EAG suggests that pembrolizumab + lenvatinib is likely to be preferred over avelumab + axitinib in intermediate/poor risk patients due to a perceived better efficacy. Clinical advice also indicated that cabozantinib + nivolumab is likely to be considered similar to pembrolizumab + lenvatinib rather than a direct comparator to nivolumab + ipilimumab. One clinical expert considered that the cabozantinib + nivolumab combination may be particularly beneficial for patients with bone metastases due to the cabozantinib component of the treatment.

Nivolumab + ipilimumab is a recommended 1st-line treatment for patients with intermediate- and poor-risk disease (TA780[48]). Clinical advice to the EAG noted that choosing between nivolumab + ipilimumab and pembrolizumab + lenvatinib is challenging in the absence of head-to-head trials. Although nivolumab + ipilimumab is considered to be more toxic, it has more mature survival data available, indicating potential long-term benefits in terms of OS related to its mechanism of action as a combination of immune checkpoint inhibitors. NICE recommendations only allow the use of pembrolizumab + lenvatinib in patients who are not able to take nivolumab + ipilimumab.

For patients who undergo risk stratification and are not eligible for IO therapy, single-agent TKIs such as sunitinib (TA169[49]), pazopanib (TA215[50]), tivozanib (TA512[51]) are alternative treatments, in addition to cabozantinib for those with intermediate- and poor-risk disease (TA542[52]). TKIs work by specifically targetin g the signalling pathways involved in RCC development. While checkpoint inhibitors are generally preferred unless there are strong contraindications, clinical feedback to the EAG indicated the use of 1st line single-agent TKIs is still seen in 30-40% of patients currently. This was considered to be higher than optimal. Evidence from the most recent RWE (UK RWE, 2022[53]) shows 60% of patients were treated with a 1st line single agent TKI in the period 2018 to 2022 (sunitinib 25%, tivozanib 8%, pazopanib 18%, cabozantinib 9%). Although nivolumab + ipilimumab (23.4%) and avelumab + axitinib (12.7%) only became available via CDF from 2019 and 2020 respectively and pembrolizumab + lenvatinib received its recommendation outside of the study period, which may perhaps reflect the high usage of 1st line single agent TKIs in the study period. Of note, ESMO guidelines, consider sunitinib or pazopanib are potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease due to a lack of clear superiority for PD-1-based combinations over sunitinib in this subgroup of patients.

2nd and subsequent lines of systemic treatment (previously treated aRCC)

The advent of ICI combinations as the standard 1st line therapy for mRCC has raised questions about the best 2nd line treatment strategy in this new treatment landscape. Currently, limited data are available regarding the optimal 2nd line treatment option for patients who have progressed on a 1st line ICI-based combination therapy. International guidelines, such as those from the ESMO,[43] acknowledge the lack of robust prospective data specifically focusing on 2nd line treatment after 1st line PD-1 inhibitor-based combination therapy.

Treatment options for 2nd line therapy could include a TKI, a PD-1 inhibitor or a mammalian target of rapamycin (mTOR) mTOR inhibitor. Immune checkpoint inhibitors cannot be given more than once in the systemic treatment pathway and therefore nivolumab is not an option. It is also reasonable to consider using a TKI that was not utilised in the 1st line combination as a potential 2nd line treatment option, as there are reasonable probabilities of achieving further clinical benefit with this approach.

In patients who were initially treated with the combination of immunotherapy and VEGF receptor-targeted therapy (e.g. avelumab + axitinib, pembrolizumab + lenvatinib), treatment options in the 2nd line include axitinib,[54] cabozantinib,[55] lenvatinib + everolimus,[56] and everolimus (TA432[57]) depending on the 1st line treatment combination received:

- avelumab + axitinib (TA645[46]) → cabozantinib (TA463[55]), lenvatinib + everolimus (TA432[56]), or everolimus (TA432[57]).
- pembrolizumab + lenvatinib (TA858[38]) → axitinib (TA333[54]), cabozantinib (TA463[55]), or everolimus (TA432[57]).

While the majority of patients receive cabozantinib, in certain cases lenvatinib + everolimus may be considered as an alternative as it as it can only be used after one prior TKI. This option may be preferred in an effort to maximise the available lines of treatment for patients. Clinical advice indicated that lenvatinib + everolimus is preferred over everolimus monotherapy as it allows for a lower dose of everolimus and improved tolerability. Axitinib is not commonly used as a 2nd line treatment and is often reserved for later lines of therapy. Otherwise, 1st line options of sunitinib (still on label as 2nd line treatment) or pazopanib (off label as 2nd line treatment), or tivozanib (off-label as 2nd line treatment) may also be considered. Clinical feedback to the EAG anticipated that following cabozantinib + nivolumab, lenvatinib + everolimus is likely to be preferred as it provides a different approach to the previous regimen.

In patients who were initially treated with the combination of nivolumab + ipilimumab, the treatment options after disease progression include cabozantinib, sunitinib (still on label as 2nd line treatment), pazopanib (off label as 2nd line treatment), or tivozanib (off-label as 2nd line treatment). Clinical advice to the EAG indicated that cabozantinib is typically chosen as the next treatment option (although the EAG note that it is off-label following nivolumab + ipilimumab), as administering another round of checkpoint inhibitor therapy is generally considered futile and is also not allowed in the UK.

In patients who were initially treated with VEGF receptor-directed TKI monotherapy, the recommended treatment options after disease progression include nivolumab (TA417[58]) or cabozantinib (TA463[55]), both of which demonstrated OS benefit in the 2nd-line setting. Other options that can be considered include axitinib (TA333[54]), and lenvatinib + everolimus (TA498[56]).

While approved for 2nd line and 3rd line treatment, clinical advice to the EAG indicated that everolimus and axitinib are typically reserved for 4th line treatment. Although given the toxicity of everolimus only a small proportion of patients would be eligible to receive it due to toxicity.

In England recommendations for subsequent treatments are provided in the Cancer Drugs Fund (CDF) list:[37] These broadly reflect the above. The CDF list only includes drug indications which became available from 2016 onwards when the BlueTeq® high-cost drug management system started to be routinely implemented. Sunitinib, pazopanib and axitinib were therefore not included. Information provided on recommended subsequent therapies, follow-up and treatment breaks has also become more detailed over time. The CDF recommendations demonstrate that 1st line TKIs are recommended and available in the 2nd line setting in the NHS, with two of these being used off-label, as shown in Figure 6.

In clinical practice, expert advice suggested that it is realistic to expect that most patients with RCC would receive up to three lines of treatment. Approximately 10-20% of patients may reach the 4th line of treatment. However, it is uncommon for patients to go beyond the 4th line, and very few would require a 5th line of treatment. This is in line with the UK RWE dataset identified for this pilot.[53] The introduction of new therapies, such as belzutifan, may change the treatment landscape and potentially replace everolimus as a last-line treatment option.

2.4.2.3. Best supportive care

For individuals who cannot tolerate or do not wish to receive active treatment, best supportive care (BSC) is provided. BSC focuses on monitoring disease progression, symptom control, and palliative care without active treatment.[50]

The treatment pathway overview is summarised in Figure 6 and possible treatment sequences are summarised in Figure 7.

Table 1: Current treatment options per NICE recommendations for untreated aRCC

Intervention	Suni	Pazo	Cabo	Tivo	Nivo+ipi	Ave+axi	Pem+lenv
NICE appraisal	TA169[49]	TA215[50]	TA542[52]	TA512[51]	TA780 (CDF review of TA581)) [48]	TA645 (CDF)[46]	TA858[38]
Class	TKI	TKI	TKI	TKI	PD-1 inhibitor + CTLA-4 inhibitor	PD-1 inhibitor + TKI	PD-1/ PD-L1 inhibitor + TKI
Recommendation	1L (ECOG PS 0 or 1)	1L (no prior cytokine therapy; ECOG PS 0 or 1)	1L	1L	1L	1L via CDF	1L (if not suitable for nivo+ipi)
IMDC risk category	All risk	All risk	Int or poor risk per IMDC criteria	Int or poor risk per IMDC criteria	Int or poor risk per IMDC criteria	All risk	Int or poor risk per IMDC criteria

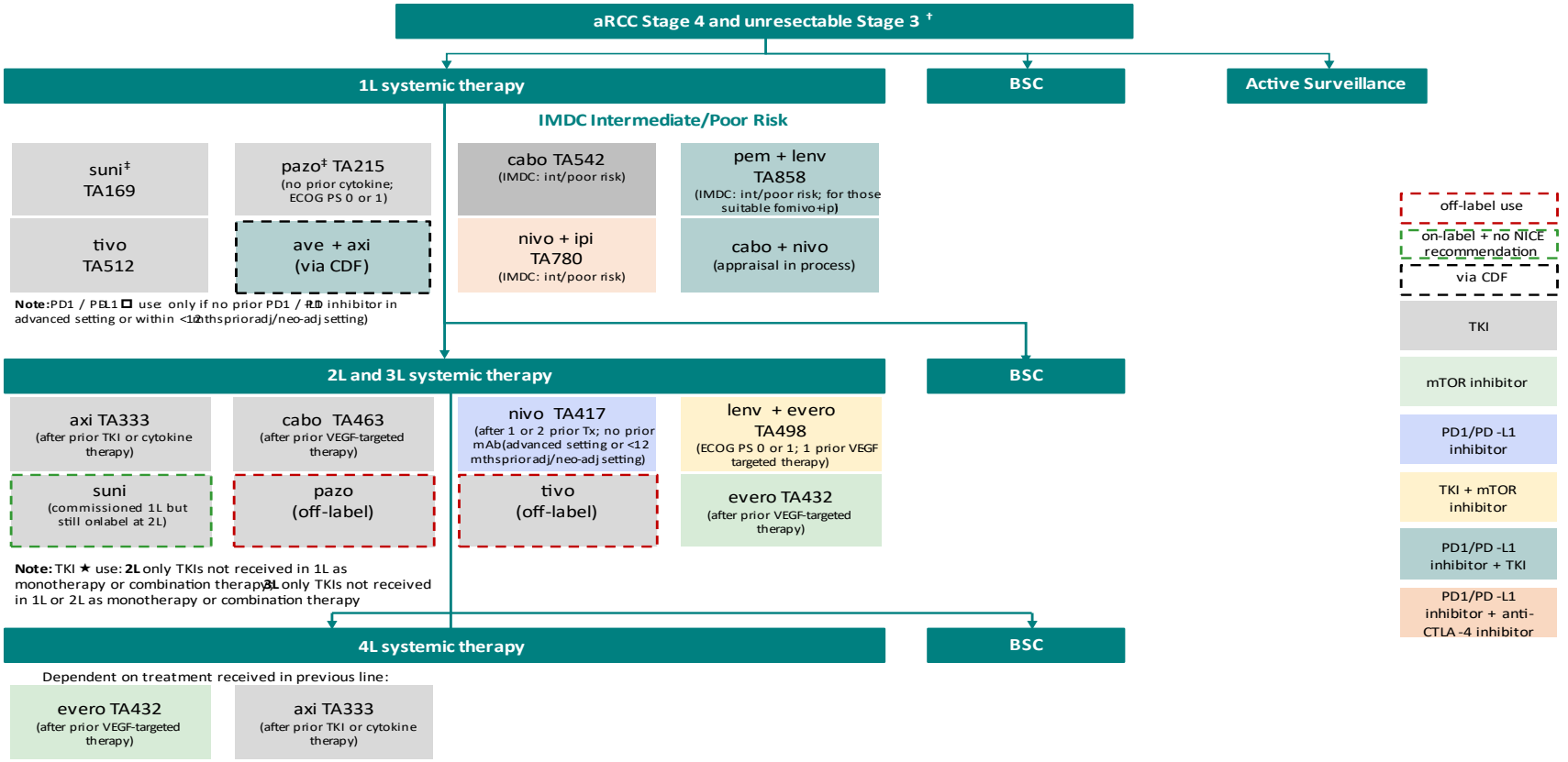
Abbreviations: 1L, 1st line; aRCC, advanced renal cell carcinoma; ave, avelumab; axi, axitinib; cabo, cabozantinib; CDF, Cancer Drugs Fund; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IMDC, International Metastatic renal cell carcinoma Database Consortium; ipi, ipilimumab; lenv, lenvatinib; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; pazo, pazopanib; PD1, programmed death 1; PD-L1, progress death cell ligan 1; pem, pembrolizumab; suni, sunitinib; TA, technology appraisal; tivo, tivozanib; TKI, tyrosine kinase inhibitor

Table 2: Current treatment options per NICE recommendations for untreated aRCC

Intervention	Evero	Axi	Nivo	Cabo	Lenv+evero
NICE appraisal	TA219 → TA432[57]	TA333[54]	TA417[58]	TA463[55]	TA498[56]
Class	mTOR inhibitor	TKI	PD-1	TKI	TKI + mTOR inhibitor
Line of treatment recommended	2L (after prior VEGF-targeted therapy)	2L (after 1L TKI or a cytokine [not recommended by NICE])	2L (after 1 or 2 prior treatments; no prior mAb (advanced setting or <12 mths prior adj/neo-adj setting)	2L (after prior VEGF-targeted therapy)	2L (after 1 prior VEGF targeted therapy and ECOG PS 0 or 1)
Sequencing notes	Clinical advice to the EAG notes that evero would primarily be used at 4L	Clinical advice indicates axi would not be used after tivo as they have a similar MoA			

Abbreviations: 2L, 2nd line; axi, axitinib; adj, adjuvant; cabo, cabozantinib; ECOG, Eastern Cooperative Oncology Group performance status; evero, everolimus, lenv, lenvatinib; mAb, monoclonal antibody; MoA, mechanism of action; mths, months; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; PD-1, programmed death 1; PS, performance status; TA, technology appraisal, tivo, tivozanib; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor receptor

Figure 6: Treatment pathway for advanced stage RCC: overview



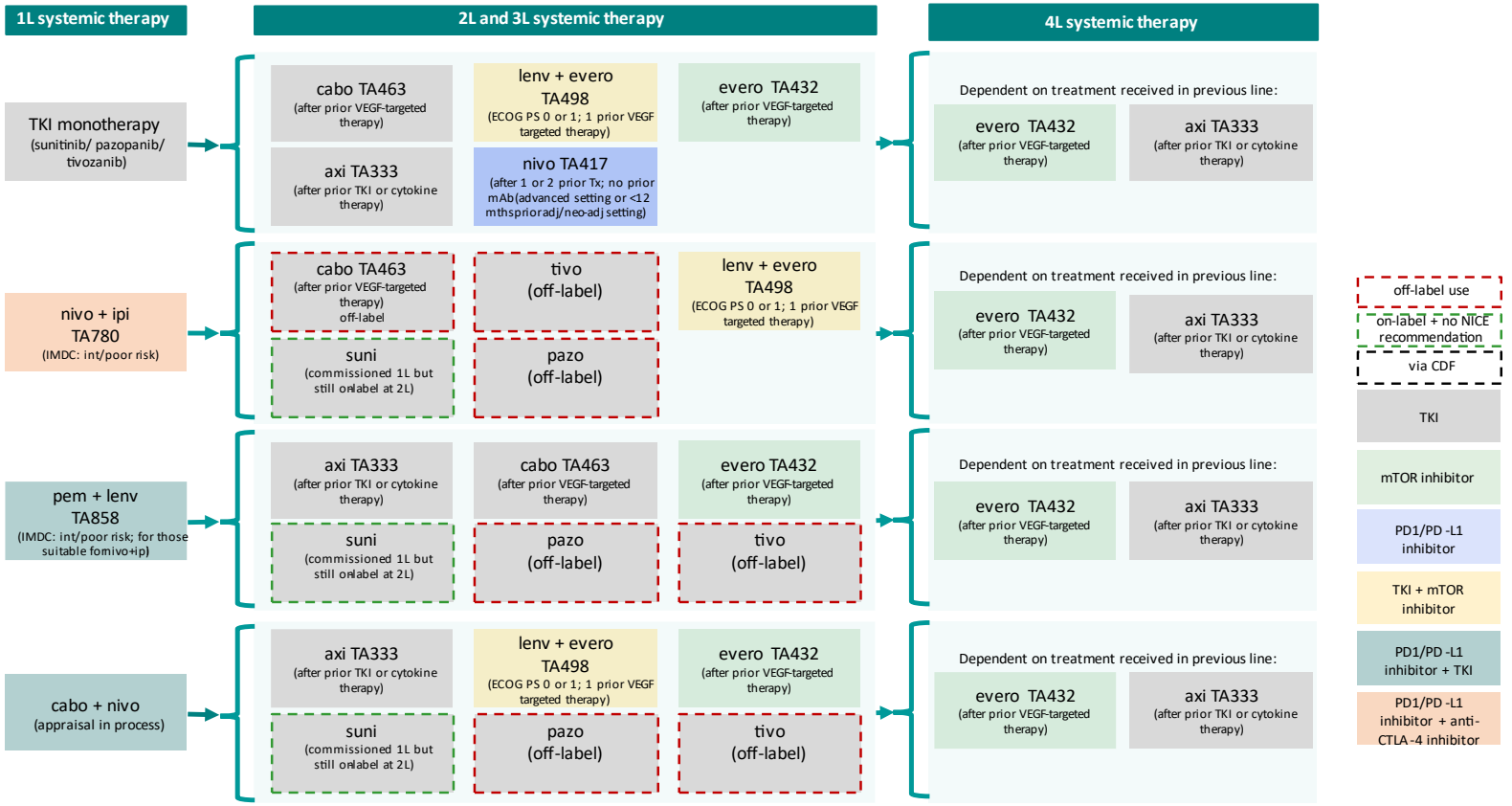
Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; adj adjuvant; aRCC, advanced renal cell carcinoma; ave, avelumab; axi, axitinib; BSC, best supportive care; cabo, cabozantinib; CDF, Cancer Drugs Fund; ESMO, European Society of Medical Oncology; evero, everolimus; IMDC, International Metastatic renal cell carcinoma Database Consortium; int, intermediate; ipi, ipilimumab; lenv, lenvatinib; mTOR, mammalian target of rapamycin; nivo, nivolumab; pazo, pazopanib; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1; pem, pembrolizumab; suni, sunitinib; TA, technology appraisal; tivo, tivozanib; TKI, tyrosine kinase inhibitor; Tx, treatment; VEGF, vascular endothelial growth factor

Notes:

†Cancer has spread into surrounding tissues outside Gerota's fascia or into adrenal gland. Cancer has spread to another part of the body. May or may not spread to lymph nodes

‡Also considered potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease (ESMO guideline recommendations; 2021)

Figure 7: Treatment pathway for advanced stage RCC: possible treatment sequences



Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; adj adjuvant; aRCC, advanced renal cell carcinoma; ave, avelumab; axi, axitinib; BSC, best supportive care; cabo, cabozantinib; CDF, Cancer Drugs Fund; ESMO, European Society of Medical Oncology; evero, everolimus; IMDC, International Metastatic renal cell carcinoma Database Consortium; int, intermediate; ipi, ipilimumab; lenv, lenvatinib; mTOR, mammalian target of rapamycin; nivo, nivolumab; pazo, pazopanib; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1; pem, pembrolizumab; suni, sunitinib; TA, technology appraisal; tivo, tivozanib; TKI, tyrosine kinase inhibitor; Tx, treatment; VEGF, vascular endothelial growth factor

Notes:

†Cancer has spread into surrounding tissues outside Gerota's fascia or into adrenal gland. Cancer has spread to another part of the body. May or may not spread to lymph

nodes
‡Also considered potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease (ESMO guideline recommendations; 2021)

2.5. Decision problem

As noted in Section 1, this pilot is designed to address a broader decision problem than is considered within a standard STA. The platform model to be developed encompasses all stages of the treatment pathway for RCC, including all treatments within the treatment pathway for 1st and subsequent line systemic treatment (Section 2.4). Within the pilot and summarised in this report, the EAG appraised the clinical and cost effectiveness of one new treatment: cabozantinib + nivolumab for untreated advanced or metastatic RCC. A summary of the decision problem for the appraisal of this treatment is provided in Table 3.

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed
Population	People with untreated advanced or metastatic RCC	Per the scope, all evidence identified was for adults
Intervention	Cabo+nivo (submission led by Ipsen)	Per the scope
Comparator(s)	• Pazo • Tivo • Suni • Cabo (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivo+ipi (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Pem+lenv (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Active surveillance	In line with the scope except that active surveillance has not been included as it is considered to happen prior to the decision node at which this model starts. Clinical advice received is that clinical decision-making first involves deciding whether a person would benefit from any kind of systemic therapy and then, once the decision to initiate therapy has been taken, a choice is made between available treatment options
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Duration of response • Time on treatment/time to next treatment (TTND) • Adverse effects of treatment • Health-related quality of life (HRQoL)	Per the scope dependent upon data availability; limited data are available for time on treatment and time to next treatment within published literature

	Final scope issued by NICE	Decision problem addressed
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator or subsequent treatment technologies will be taken into account.	Per the scope
Subgroups	If the evidence allows the following subgroup will be considered: Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria Prior treatment	Per the scope. Data are not available within CheckMate 9ER to explore the impact of prior adjuvant treatment on outcomes
Special considerations including issues related to equity or equality	None	None

Abbreviations: IMDC, International Metastatic RCC Database Consortium; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RCC, renal cell carcinoma

2.6. Description of the technology being evaluated

Cabozantinib is a multiple receptor TKI and nivolumab is a PD-1 inhibitor. The combination was granted approval for the 1st line treatment of advanced RCC on the basis of the CheckMate 9ER Phase 3 trial[59], first by the European Medicines Agency (EMA) on 26th March 2021[60] and then Medicines and Healthcare products Regulatory Agency (MHRA) on 13th May 2021.[61] The marketing authorisation holder for cabozantinib is Ipsen Pharma. The marketing authorisation holder for nivolumab is Bristol-Myers Squibb Pharma EEIG.

Cabozantinib is administered orally at a dose of 40 mg once daily.[62] Nivolumab is given intravenously at a dose of either 240 mg every two weeks or 480mg every four weeks: the former was used in CheckMate 9ER while, based upon initial expert consultation, the latter is more likely to be used in clinical practice. In line with the trial, the Summary of Product Characteristics (SmPC)[62] specifies that cabozantinib *"should be continued until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression."*

Table 4. Technology being evaluated

UK approved name and brand name	**Cabo+nivo**
Mechanism of action	Receptor tyrosine kinases (RTKs) are receptors for many growth factors and proteins implicated in the development and progression of cancer, including [63-65]: • Vascular endothelial growth factor (VEGF) which promotes the growth of new blood vessels • Hepatocyte growth factor that regulates several physiological processes including proliferation, scattering, morphogenesis, and survival of cells, and • Growth factor growth arrest specific 6 (GAS6) which is involved in several cellular functions including growth, migration, aggregation, and differentiation Cabo is a tyrosine kinase inhibitor (TKI) that inhibits multiple RTKs involved in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer [14]. Cabo is a potent inhibitor of multiple RTKs, such as c-MET and VEGF, known to play important roles in tumour cell proliferation and/or tumour neovascularisation in RCC [66,67]. There is an interaction between angiogenesis and immunosuppression in tumour development. VEGF primarily inhibits the innate immune system by upregulating PD-L1 and CTLA-4 expression, thereby maintaining an immunosuppressive environment. In addition, antiangiogenic activity leads to normalisation of the tumour vasculature and exhibits a positive effect on immune-cell infiltration into tumours [68].

UK approved name and brand name	**Cabo+nivo**
	Nivo is a fully human, monoclonal immunoglobulin antibody (IgG4) that acts as a checkpoint inhibitor of PD-1 and blocks its interaction with its ligands. Tumours use PD-L1 expression as defence or escape mechanisms against the host's anti-tumour T cell response; inhibiting PD-L1 restores the function of these anti-tumour T cells which have become ineffective or suppressed [68]. Therefore, the efficacy of PD-L1 inhibition relies on a pre-existing immune response [68]. The combination of cabo+nivo therefore potentiates immune-mediated tumour destruction in parallel to targeted inhibition of tumour growth and progression.
Marketing authorisation/ CE mark status	Cabo+nivo received MHRA approval on 13/05/2021.[69]
Indications and any restriction(s) as described in the SmPC	In accordance with the current marketing authorisation, cabo+nivo is indicated for the treatment of previously untreated adult patients with aRCC or mRCC. Cabometyx® (cabo) monotherapy is licensed for the following indications[69]: • Treating aRCC in treatment-naïve adults with intermediate or poor-risk • Treating aRCC in adults following prior VEGF-targeted therapy • Treating hepatocellular carcinoma in adults who have previously been treated with sora • Treating adults with locally advanced or metastatic DTC, refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy. Opdivo® (nivo) monotherapy is licensed for the following indications[70]: • Treating aRCC after prior therapy in adults • Treating advanced (unresectable or metastatic) melanoma in adults • Adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease after complete resection • Treating locally advanced or metastatic NSCLC after prior chemotherapy in adults • Treating adult patients with relapsed or refractory classical Hodgkin's lymphoma after autologous stem cell transplantation and treatment with brentuximab vedotin • Treating recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy • Treating locally advanced, unresectable, or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy
Method of administration and dosage	Cabo is available as 20 mg, 40 mg, and 60 mg film-coated tablets. The recommended dose for cabo is 40 mg once daily in combination with nivo 240 mg every two weeks or 480 mg every 4 weeks. The treatment should continue until disease progression or unacceptable toxicity. Nivo treatment should continue until disease progression or

UK approved name and brand name	Cabo+nivo
	unacceptable toxicity or up to a maximum duration of 2 years in patients without disease progression[69,70]. For cabo, temporary treatment interruption and/or dose reduction is recommended for management of adverse drug reactions. In monotherapy, dose is reduced to 40 mg daily, and further to 20 mg daily. Whereas, in combination with nivo, it is recommended to reduce the dose to 20 mg of cabo once daily, and then to 20 mg every other day. For nivo, dose reduction is not recommended, and in case of AEs or liver enzymes elevation, either withhold dose or discontinue treatment [69,70].
Additional tests or investigations	No additional tests or investigations are needed to identify patients eligible for cabo+nivo over those needed to identify advanced or mRCC.
List price and average cost of a course treatment	List price: £5,143.00 per 30 x 40 mg tablet pack of cabo[71] £1,097.00 per 100 mg vial; £439.00 per 40 mg vial of nivo[72]
Patient access scheme (if applicable)	A confidential simple patient access scheme is available for cabo. The pack price under this scheme is [redacted] (a [redacted]% discount to the list price). There is a confidential patient access scheme in place for nivo, approved by the DHSC.

Abbreviations: AEs, adverse events; aRCC, advanced RCC; DHSC, Department of Health and Social Care; DTC, differentiated thyroid cancer; cabo, cabozantinib; DHSC, department of health and social care; MHRA, Medicines and Healthcare Products Regulatory Agency; mRCC, metastatic renal cell carcinoma; nivo, nivolumab; NSCLC, non-small-cell lung cancer; PD-1 programmed death 1; PD-L1, programmed death-ligand 1; SmPC, summary of product characteristics; sora, sorafenib; VEGF, vascular endothelial growth factor receptor

Notes: information taken from company submission

2.7. Equality considerations

No equality issues were identified within this appraisal.

3. METHODS FOR REVIEWING CLINICAL EFFECTIVENESS

3.1. Assessment group methods for reviewing clinical evidence

The EAG conducted a systematic literature review (SLR) to identify published evidence and real-world data sets relevant to the decision problem. The methods used were consistent with the NICE preferred methods and with best practice guidance for the conduct of SLRs.[73,74] This section provides:

- A description of the methods used to identify published RCT evidence;
- A description of the methods used to identify real-world data;
- A summary of the methods used to gather clinical input; and
- Information on how data from the company submission was considered

3.1.1. Identification of systematic literature reviews and randomised controlled trials

3.1.1.1. Search strategies and screening process

Systematic searches were conducted to identify 1) clinical effectiveness SLRs and meta-analyses, and 2) randomised controlled trials (RCTs) published since the most recent relevant systematic reviews. The database searches were complemented by supplemental searching, such as citation chasing and hand-searches of grey literature sources. All data from published HTA reports included in the reviews were publicly available; i.e. redacted data from published NICE HTA reports were not included.

Search strategies were developed by an information specialist and quality assured by another information specialist. The search strategies used a combination of indexed keywords (e.g., Medical Subject Headings [MeSH]) and free-text terms appearing in the titles and/or abstracts of database records and were adapted according to the configuration of each database. No limits on publication status (published, unpublished, in-press, and in-progress) were applied. The strategy used for SLR and RCT evidence is described in the following sections. The searches from NICE TA858[38] were used as a starting point for development of search terms for this appraisal. Full search strategies are supplied in Appendix A.

Articles for the SLR and RCT searches were independently assessed for inclusion by two reviewers using the pre-specified inclusion/exclusion criteria. Discrepancies were resolved by

discussion, with involvement of a third reviewer, where necessary. All duplicate papers were double checked and excluded.

Search for RCTs within published SLRs

Searches for relevant SLRs were undertaken in MEDLINE, Embase, Cochrane Database of Systematic Reviews (CDSR) and The International Network of Agencies for Health Technology Assessment (INAHTA) up to 19th December 2022. Relevant NICE technology appraisals were identified by handsearching the NICE website and were screened for further relevant studies.

The search used a combination of terms for RCC with relevant intervention terms. There were no restrictions on cancer stage or line of treatment for this search. The intervention terms were avelumab, axitinib, cabozantinib, everolimus, ipilimumab, lenvatinib, nivolumab, pazopanib, pembrolizumab, sunitinib, and tivozanib, plus relevant brand names and other alternative names.

In MEDLINE and Embase, the EAG used the systematic review, meta-analysis and HTA filter from The Canadian Agency for Drugs and Technologies in Health (CADTH)[75] to identify relevant records. All searches were limited from 2018 onwards; however, as the searches resulted in a high volume of hits (n=1,273 after de-duplication), a decision was taken to limit screening to records published from 2020 onwards (thereby excluding 371 retrieved records published pre-2020). No language filters were used. Conference abstracts were included.

The most recent, highest-quality and most comprehensive SLRs were then sought to identify RCTs relevant for this appraisal. The SLRs identified were qualitatively assessed against the following criteria:

- Is a full paper available (rather than an abstract)?
- Which line(s) of treatment were included?
- How many treatments specified within the decision problem were included within the networks?
- Were the trials included in the most recent NICE TAs for the relevant line of treatment included (TA858, TA645, TA463)?
- For SLRs looking at 1st line treatments: were data presented by risk subgroup?
- Does the methods description indicate that this is a high quality SLR?

Based upon these criteria, four SLRs were identified and screened for RCTs: Heo 2022, Liao 2022, Riaz 2021 and NICE TA858.[38,76-78] The publication date of these SLRs was then used to inform the date from which to run the top-up RCT searches described in the next section.

Heo et al. presented a SLR and network meta-analysis (NMA) of OS and PFS for 1st and 2nd line therapies in participants with advanced RCC based upon 26 RCTs (1st line: 19; 2nd line: 9) with 13,893 participants. The networks presented included a number of treatments that are not available in the NHS, and the search excluded three treatments of interest to our decision problem: cabozantinib + nivolumab, pembrolizumab + lenvatinib in 1st, and everolimus + lenvatinib for people who have been previously treated. The authors searched for trials published between 2000 and June 2020 which would be expected to capture all trials for treatments included in the decision problem for this appraisal given when development of the relevant treatments began. The review was conducted using best practice methods.

Liao et al. presented a SLR and NMA for advanced RCC treatments in the 2nd line setting. Nine RCTs with 4,911 participants were included. The study considered all systemic treatments used in a 2nd line setting and therefore identified evidence for everolimus + lenvatinib, which was missing from the Heo et al. study. Searches were conducted from inception to 20th July 2021. The study reporting was less comprehensive than Heo et al.; however, the study was included due to the broader range of treatments covered and more recent search date.

Riaz et al. presented a living, interactive SLR and NMA of 1st line treatments for advanced RCC. No limits on included treatments were imposed and outcomes were presented by risk score. Evidence was identified for all of the 1st line RCC treatments of interest to the decision problem, except for pembrolizumab + lenvatinib. A comprehensive search was conducted from inception by an experienced medical librarian in consultation with the principal investigator (I.B.R.). A “living” auto search with monthly updates was subsequently created with the last date of evidence included being 22nd October 2020. Study selection and extraction were both semi-automated.

TA858 was the most recent NICE TA in RCC. This appraisal considered treatments in the 1st line setting, and searches were run in October and November 2021. All the 1st line treatments of interest were included with the exceptions of avelumab + axitinib and cabozantinib + nivolumab. Reporting was split by risk group. Screening and extraction were performed by two reviewers.

Full search strategies were provided in the appendix of the report for TA858 and were used to inform the development of the searches conducted within this appraisal.

Top-up search for additional RCTs

A top-up search to identify RCTs published since the latest SLR search dates was conducted. The search was conducted in MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials) and trial registers (WHO International Clinical Trials Registry Platform and Clinicaltrials.gov). The search identified trials published from 2021 onwards, which allowed a reasonable overlap in time to capture RCTs published since the most recent search dates of the reviews for each line of treatment: Liao 2022 and TA858.[38,77]

RCTs were identified using the same intervention terms as used in the search for SLRs. For this search terms focusing on people with advanced, metastatic or otherwise later stage RCC were used. The Cochrane RCT filter was used to identify relevant trials in MEDLINE and Embase. No language limits were applied. Conference abstracts were included.

Scopus was searched for subsequent data cuts of trials included in the identified SLRs, including conference abstracts. Further citation searches were conducted (forward and backward citation searching) in Scopus for all additional RCTs identified that were not included in the latest SLRs. Relevant NICE technology appraisal reports were reviewed to identify any additional unredacted data that had not been subsequently published. The list of published abstracts from the American Society of Clinical Oncology Genitourinary Cancers Symposium, held in San Francisco on the 16 - 18 Feb 2023 (ASCO GU 2023) and the American Society of Clinical Oncology Annual meeting, held in Chicago on the 2-6 June 2023, were hand searched, to identify new trials or new data cuts of already identified trials.

Finally, HRQoL and patient-reported outcomes for the 30 included RCT studies were identified by reviewing the economic searches for the development of the cost-effectiveness model (see Section 4.1.1). Twenty-nine potentially relevant reports were identified by searching for RCT trial numbers in the economic studies Endnote database, which were then sifted down to 23 studies (covering 16 of the 30 RCTs) during full-text review.

To identify ongoing RCTs, the EAG searched Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). The advanced search functionality was used for both platforms, using a combination of intervention terms, population terms, and keywords to identify

RCTs (“random” or “randomized” or “randomised” or “randomisation” or “randomization” or “RCT”). No date or recruitment status limits were applied. The RCT update search of Cochrane CENTRAL (described above) also retrieved registry records.

Contact with study authors

Where data were missing in the published clinical effectiveness studies, the EAG wrote to the authors. This was only done where data for an entire key outcome, Kaplan-Meier data for a key outcome or subgroup data (baseline characteristics or outcomes) were missing. A deadline for response to the initial contact of four weeks was imposed. Additional time was allowed where the author indicated they were able to supply the data requested and where it did not impact on the broader timelines for this appraisal. No responses were received via this route which could be included as agreement was required from the companies funding the relevant trials. Additional data was received for CheckMate 214 from BMS within their response to the preliminary assessment report.

3.1.1.2. Inclusion and exclusion criteria

In the first round of screening, SLRs that included RCTs of pharmacological treatments for advanced RCC published since 2020 were included. Reviews focusing on the efficacy of radiotherapy or surgical interventions were excluded. The highest-quality and broadest systematic reviews were then used to identify relevant RCTs, from which line of treatment and comparators were extracted and compared to the full platform model decision problem to identify any gaps.

In top-up searches, RCTs for people with advanced RCC of systemic treatments funded within the NHS (pazopanib, tivozanib, sunitinib, cabozantinib, nivolumab + ipilimumab, lenvatinib + pembrolizumab, axitinib, lenvatinib + everolimus, everolimus, cabozantinib + nivolumab, nivolumab, avelumab + axitinib, best supportive care) were included where they reported at least one outcome from OS, PFS, TTNT, TTD, response rates, adverse effects of treatment, and HRQoL. As a protocol clarification, the EAG also included studies with placebo as a comparator and only included studies with relevant comparisons of drugs prescribed at the licensed doses. In addition, as a protocol deviation, the EAG included studies with sorafenib as a comparator. This is because past TAs have acknowledged the importance of sorafenib as a linking treatment in evidence networks and the EAG also anticipated needing to use sorafenib as a linking treatment.

Further details on these inclusion/exclusion criteria used for SLRs and RCTs are presented in Table 5.

Table 5: Inclusion and exclusion criteria: SLRs and RCTs

	Include	Exclude
Population	Studies of participants with advanced (unresectable Stage 3 or Stage 4) RCC at any treatment line	Studies of participants with early stage (not advanced) RCC
Intervention	Round 1 (systematic reviews): any pharmacological treatment for advanced RCC used in the systemic setting Round 2 (RCTs and extensions of RCTs): cabo+nivo, pazo, tivo, suni, cabo, nivo+ipi, pem+lenv, axi, lenv+evero, evero, nivo, ave+axi*, Sora and placebo were included as linking treatments for use in the NMA	Any other treatments not listed under inclusion Treatments used in the adjuvant setting
Comparator	• Any of the other interventions listed above (i.e. head-to-head studies) • Dose comparison studies • Usual care / physicians' choice / BSC / placebo	Non-pharmacological treatments only
Outcomes	Studies reporting at least one outcome from: • OS • PFS • TTNT • Time on treatment • Response rates • Duration of response • AEs of treatment† • HRQoL	Studies not reporting an included outcome
Study design	Round 1: systematic reviews of RCTs published since 2020 Round 2: RCTs. The most recent conference abstract for each intervention and outcome will be included unless a full journal article is available	Round 1: systematic reviews that did not contain RCTs, systematic reviews of treatment effect modifiers. Round 2: non-randomised trials, observational studies, case reports, editorials and commentaries

Abbreviations: AE, adverse events; BSC, best supportive care; HRQoL, health-related quality of life; NMA, network meta-analysis; OS, overall survival, PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomised controlled trials; TEAEs, treatment-emergent adverse events; TTNT, time to next treatment

Notes: * As belzutifan was included within the NICE draft scope it was included within the search terms for the searches conducted, these studies will, however, not be included during screening † Grade 3+ TEAEs and the total number of treatment-emergent adverse events leading to discontinuation will be extracted. Additional lower grade AEs of interest may be extracted following clinical advice

3.1.1.3. Data extraction and quality assessment strategy

All relevant published evidence for a given trial is extracted in one single entry in the data extraction matrix. Included clinical effectiveness studies (identified via SLRs and top-up searches) were extracted by one reviewer into a bespoke database and checked by a second reviewer. The data extraction grid is provided in Appendix D. Discrepancies were resolved by discussion, with the involvement of a third reviewer where necessary. For time to event outcomes, both summary hazard ratios and figures for Kaplan Meier curves from the last data cut were extracted. Digitisation of curves using standard methods (the Guyot algorithm[79]) was conducted, assuming censoring linearly across time intervals.

Quality assessments of individual studies were assessed by one reviewer in Microsoft Excel and checked by a second reviewer. Any disagreements were resolved through discussion, with arbitration by a third reviewer if consensus could not be reached. RCTs were assessed using standardised criteria for critically appraising the quality of clinical effectiveness evidence as recommended by NICE for submissions to its HTA programme.[80] The assessment included the consideration of domains that could pose a variable risk of bias for individual outcomes at the outcome level (performance and detection bias, attrition bias, and reporting bias), and identifying any other sources of bias resulting from a design or methodological feature of the study. The latter included bias considerations specific to trial designs that include an element of treatment switching (i.e., crossover trials assigning sequential treatments as well as trials allowing crossover following disease progression) as such trials are prone to carryover bias in the period following the switch due to residual treatment effect from the previous period.

A determination of overall domain bias was made based on the worst-rated of the sub-domains – for example, overall selection bias would be determined by the worst-rated of the randomisation, allocation concealment and baseline imbalance domains. A determination of overall study bias was additionally assessed by considering the key domains for parallel RCTs (selection and attrition bias) and crossover RCTs (selection, attrition and other bias); the overall judgment represented the worst-rated of these domains. Performance and detection biases were omitted from key domains for overall bias considerations as primary outcomes in cancer trials are predominantly hard, objective outcomes; reporting bias was similarly omitted as a key domain as the primary outcomes that inform sample size calculations are rarely omitted from reported results. Finally, biases related to conflict of interest were also omitted as a key domain

since these conflicts are usually present in cancer trials due to manufacturer sponsorship, but influences are carefully monitored and managed in such trials.

It is important to note that the approach to quality assessment in this report is different to that taken in TA858; with the latter being informed by the Centre for Review and Dissemination (CRD) Guidance for Undertaking Reviews in Healthcare. The EAG's approach, following NICE guidance, specifically evaluated the *adequacy* of methods to minimise bias, rather than evaluating whether such methods were reportedly followed (e.g., NICE guidance calls for the assessment of 'Was the allocation adequately concealed?', while in TA858 the question under consideration was 'Was the allocation of treatment concealed?').

3.1.2. Identification of real-world evidence

3.1.2.1. Searches for real-world evidence

In line with the recommendations in the NICE RWE framework,[81] a systematic search process was followed to identify real-world (observational) evidence to characterise the treatment pathway, the natural history of the disease and the characteristics of people with RCC treated in clinical practice. A four-pronged search strategy was used:

1. MEDLINE and Embase: Search results for observational studies in the UK about RCC were uploaded into Endnote, followed by assessment of abstracts to identify any registry/RWE data sources used. The search combined the Scottish Intercollegiate Guidelines Network (SIGN) observational studies filter[82] and the NICE UK filter.[83] Search strategies are provided in Appendix A. Results (n = 2,683) were exported into Endnote and screened by one reviewer using the pre-specified inclusion criteria (Section 3.1.2.3).
2. Health Data Research UK Innovation Gateway: Search terms included 'renal cell cancer', 'renal cell carcinoma', 'kidney cancer' or 'kidney carcinoma'. Results were sifted on screen by one review using the inclusion criteria.
3. Web search (Google and Bing): Individual searches within each database were conducted using terms for RCC and RWE. RCC search terms were: 'renal cell cancer', 'renal cell carcinoma', 'kidney cancer', and 'kidney carcinoma. RWE search terms were 'registry', 'real-world data', and 'real-world evidence'. The first 50 results of each search were sifted on screen by one reviewer using the inclusion criteria.
4. Reviewers flagged potential evidence sources—that met the inclusion—during screening of the main clinical and economic search results.

Further to the above-described search process, RWE sources were also identified from company and stakeholder submissions during the research process. Table 25 describes the potential sources of RWE found and from where they were identified.

3.1.2.2. Screening process

Articles identified from the RWE searches were assessed in a targeted manner by one reviewer using the pre-specified inclusion/exclusion criteria (see Section 3.1.2.3). The potential uses for this evidence are listed below. In each case information was considered for both the whole patient population and according to IMDC risk score subgroups:

- Understand current treatment pathways (sequences) being used.
- Assess the generalisability of trial data based on demographic and disease-related characteristics (particularly prognostic variables).
- Improve long-term extrapolations (particularly for historical therapies).
- Inform baseline risk (either as scenario analysis or base case).
- Understand the difference between trial-based assessment of progression and intermediate disease-related outcomes recording in practice.
- Inform doses used in practice for treatments where dose adjustments can be applied & understand the proportion of planned doses that are missed.
- Look at how HRQoL changes over time
- Inform healthcare resource utilisation (HCRU) and costs per health state
- Fill in data gaps for later lines for any comparators which have not been studied in trials (this is not expected to be required).
- Explore the impact of sequencing on effectiveness (this is considered unlikely to be possible).

3.1.2.3. Inclusion and exclusion criteria

The inclusion/exclusion criteria used for identification of RWE are presented in Table 6.

Table 6: Inclusion and exclusion criteria: RWE

PICOS item	Include	Exclude
Population	Studies of participants with advanced (unresectable Stage 3 or Stage 4) RCC	Studies of participants with early stage (not advanced) RCC
Intervention	Any pharmacological treatment for advanced RCC used in the systemic setting	Any pharmacological treatment for advanced RCC not used in the systemic setting
Outcomes	Studies reporting at least one outcome from: • OS • Prognostic variables • PFS • Prognostic variables • Time to progression • TTNT • Time to discontinuation • HRQoL • Current treatment pathways (sequences) being used) • Risk scores • Health costs	Studies not reporting an included outcome
Study design	Real-world evidence	
Other	Geography: UK Time: collection of data within the last 10 years with a focus on datasets including more recent data (2018 onwards)	Geography: Other than UK Time: collection of data > 10 years

Abbreviations: HRQoL, health-related quality of life; OS, overall survival, PFS, progression-free survival; RCC, renal cell carcinoma; RWE, real-world evidence

3.1.2.4. Data extraction and quality assessment strategy

Data extraction of identified RWE was at trial level. Included observational studies were extracted by one reviewer into tables set-up in a word document and checked by a second reviewer. Discrepancies were resolved by discussion, with the involvement of a third reviewer where necessary.

For critical appraisal, ROBINS-I was used to appraise the quality of non-randomised comparative cohort studies. For RWE identified from external datasets, such as patient registries, NICE's Data Suitability Assessment Tool (DataSAT) was completed to provide structured information on data suitability including provenance, quality and relevance.[81] These criteria were considered when conducting quality appraisal.

3.1.2.5. Consultation with clinical experts

As part of its appraisal, the EAG recruited and consulted with three clinical experts in RCC.

- Professor James Larkin, Consultant Medical Oncologist, Royal Marsden Foundation NHS Trust
- Dr Amarnath Challapalli, Consultant Clinical Oncologist, Bristol Cancer Institute, University Hospitals Bristol NHS Foundation Trust
- Dr Teele Kuusk, Urology Consultant, Barts Health NHS Trust

These experts were selected to represent a range of expertise across medical and clinical oncology and urology. The clinical experts were recruited in accordance with the NICE conflict of interest policy.

The following conflicts of interest were declared by the clinical experts:

- Within the last 12 months, Dr James Larkin received honorariums from BMS, Eisai, Merck, Novartis and Pfizer, consultancy fees by BMS, Eisai and Merck, speaker fees from Eisai, Eusa Pharma, Merck, Novartis and Pfizer and institutional research support from BMS, Novartis and Pfizer.
- Within the last 12 months, Dr Amarnath Challapalli received speaker fees and honoraria from Ipsen, BMS, Eisai, Eusa Pharma, Novartis and Pfizer.
- Dr Teele Kuusk declared no conflict of interest for the past 12 months.

To ascertain views on topics such as disease characteristics, typical treatment pathways, disease and treatment outcomes, and treatment effect modifiers (see Appendix M for further details), all three clinical experts took part in a video consultation and provided answers to follow-up questions. Dr Larkin had earlier taken part in another video consultation (prior to the scoping workshop). Expert views were used to provide background information on the condition and on current treatments in UK clinical practice, to guide the methods of this appraisal and to aid interpretation of the appraisal findings.

In addition to this consultation, a broader group of experts (total of 9) were recruited to participate in an expert elicitation exercise to inform long-term OS estimates. This procedure is described in Section 5.2.

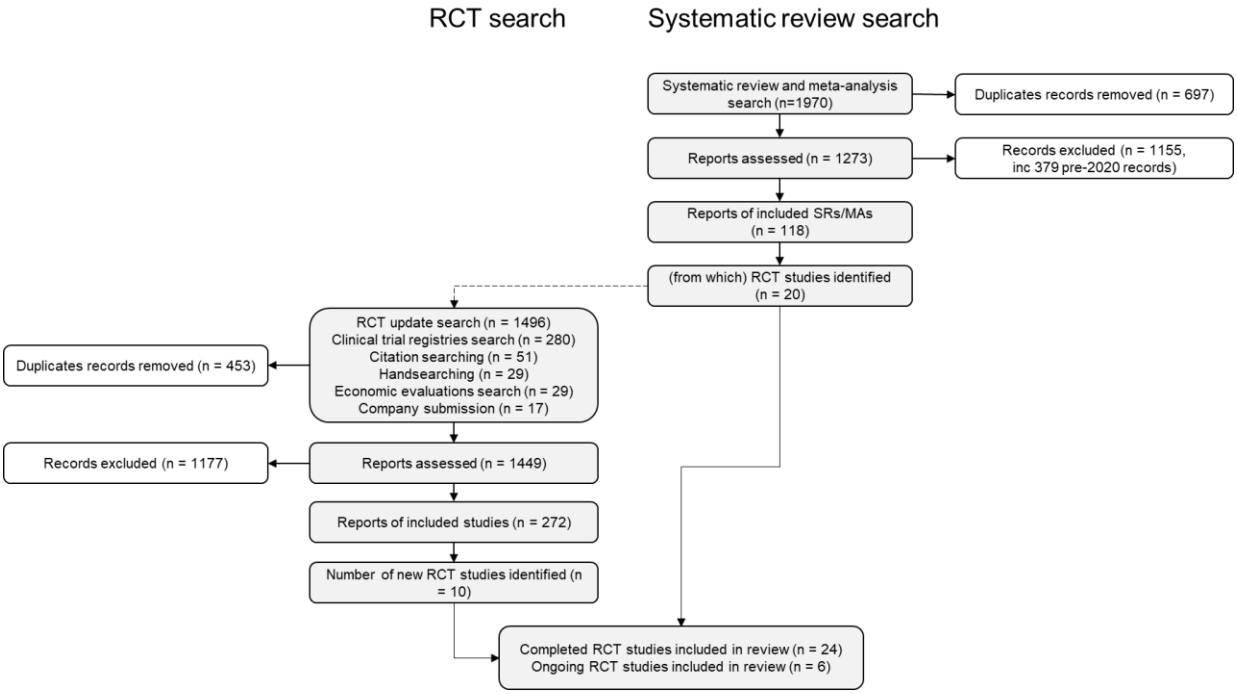
3.1.3. Handling of the company submission

The company submission (CS) was appraised and new information was used to inform the broader project. Specifically, the company's definition of the decision problem and the SLRs and NMAs it conducted were reviewed and compared against the methods used in the EAG's assessment, and references identified by the company were searched to ensure these were identified in the EAG's own searches. New data presented by the company that were not in published reports (for example, new data cuts and information about trial methods contained in the trial clinical study report [CSR]) were extracted and included in our appraisal and analyses. Most prominently, the CS included a new data cut from CheckMate-9ER with data up to a median of 44-months. The company provided Excel files for the relevant time to event endpoints, specifying the number of events and censors per endpoint for PFS, OS, TTD and TTP that were used in the EAG's NMAs and economic model. An appraisal of the company's definition of the decision problem, the methods used in their SLR and analyses, and the latest results from CheckMate 9ER is presented in Section 3.4. A comparison of the company NMA versus the EAG NMA can be found in Section 3.7.7.2.

3.2. Results of the searches for systematic literature reviews and randomised controlled trials

Figure 8 provides an overview of the clinical review searches for SLRs and RCTs. PRISMA diagrams for the individual SLR and RCT searches can be found in Appendix B. In total, 118 SLRs and meta-analyses were identified, and 30 RCTs—20 identified from the SLRs, and a further ten from the RCT top up search and other supplementary search techniques.

Figure 8: Overview of clinical effectiveness searches



Abbreviations: RCT, randomised control trials; SR, systematic reviews; MA, meta-analyses

3.3. Critique of trials identified in the review

3.3.1. Included studies

In total, 30 trials were identified for inclusion in the review. Of these, six are ongoing and are addressed below in Section 3.8. The remaining 24 trials are described below and summarised in Table 7.

Table 7: Clinical evidence included

Study name	Lead reference	Population	Clear cell type (%)	Risk score (IMDC or MSKCC)	Trt line	Comparison
ASPEN (NCT01108445)	Armstrong 2016, Lancet Oncol[84]	Advanced and Metastatic (N=108)	0	Mixed	1L*	suni vs evero
AXIS (NCT00678392)	Rini 2011, Lancet[85]	Advanced and Metastatic (N=723)	100	Mixed	2L	axi vs sora
BERAT (EUDRACT 2011-005939-78)	Grunwald 2022, Oncol Res Treat[86]	Metastatic (N=22)	NR	NR	2L	TKI (axi & suni) vs evero
BIONIKK (NCT02960906)	Vano 2022, Lancet Oncol[87]	Metastatic (N=202)	100	Mixed	1L+	nivo vs nivo+ipi, nivo+ipi vs VEGFR-TKI (suni+pazo)
CABOSUN (NCT01835158)	Choueiri 2018, Eur J Cancer[88]	Metastatic (N=157)	100	Intermediate and poor	1L	cabo vs suni
CheckMate 025 (NCT01668784)	Motzer 2015, NEJM[89]	Advanced and Metastatic (N=821)	100	Mixed	2L and 3L	nivo vs evero
CheckMate 214 (NCT02231749)	Motzer 2018, NEJM[90]	Advanced and Metastatic (N=1096)	100	Mixed	1L	nivo+ipi vs suni
CheckMate 9ER (NCT03141177)	Choueiri 2021a, NEJM[59]	Advanced and Metastatic (N=651)	100	Mixed	1L	cabo+nivo vs suni
CLEAR (NCT02811861)	Motzer 2021b, NEJM[45]	Advanced and Metastatic (N=1069)	100	Mixed	1L	pem+lenv vs lenv+evero vs suni
COMPARZ (NCT00720941)	Motzer 2013, NEJM[91]	Metastatic (N=1110)	100	Mixed	1L	pazo vs suni
CROSS-J-RCC (NCT01481870)	Tomita 2020, Clin Genitourin Cancer[92]	Metastatic (N=120)	100	Favourable and intermediate	1L	suni vs sora
ESPN (NCT01185366)	Tannir 2016, Eur Urol[93]	Metastatic (N=72)	16.7	Mixed	1L*	evero vs suni
Hutson et al, 2017 (NCT00920816)	Hutson 2013, Lancet Oncol[94]	Metastatic (N=288)	100	Favourable and intermediate	1L*	axi vs sora
JAVELIN RENAL 101 (NCT02684006)	Motzer 2019, NEJM[95]	Advanced and Metastatic (N=886)	100	Mixed	1L	ave+axi vs suni

Study name	Lead reference	Population	Clear cell type (%)	Risk score (IMDC or MSKCC)	Trt line	Comparison
METEOR (NCT01865747)	Choueiri 2015, NEJM[96]	Advanced and Metastatic (N=658)	100	Mixed	2L and 3L	cabo vs evero
NCT01136733 (NCT01136733)	Motzer 2015, Lancet Oncol[97]	Advanced and Metastatic (N=153 (101 relevant))	100	Mixed	2L	lenv+evero vs evero
RECORD-1 (NCT00410124))	Motzer 2008 Lancet[98]	Metastatic (N=410)	100	Mixed	2L and 3L	evero vs placebo
RECORD-3 (NCT00903175)	Motzer 2014 J Clin Oncol[99]	Metastatic (N=471)	85	Mixed	1L*	suni vs evero
SWITCH (NCT00732914)	Eichelberg 2015 Eur Urology[100]	Advanced and Metastatic (N=365)	87	Favourable and intermediate	1L	suni vs sora
SWITCH II (NCT01613846)	Retz 2019 Eur J Cancer[101]	Advanced and Metastatic (N=377)	87	Favourable and intermediate	1L	pazo vs sora
SWOG 1500 (NCT02761057)	Pal 2021 Lancet[102]	Advanced and Metastatic (N=152 (94 relevant))	0	Mixed	1L¤	cabo vs suni
TIVO-1 (NCT01030783)	Motzer 2013 J Clin Oncol[103]	Metastatic (N=517)	100	Favourable and intermediate	1L and 2L	tivo vs sora
TIVO-3 (NCT02627963)	Rini 2020 Lancet Oncol[104]	Metastatic (N=350)	100	Mixed	3L and 4L	tivo vs sora
VEG105192 (NCT00334282)	Sternberg 2010 J Clin Oncol[105]	Advanced and Metastatic (N=435)	100	Favourable and intermediate	1L and 2L¥	pazo vs placebo

Abbreviations: RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor; trt, treatment; VEGFR, vascular endothelial growth factor receptors; vs, versus

Notes:

* These trials are not included in the 1st line networks as they do not contain two treatments (or one treatment and a linking treatment) which can be used at 1st line in England and Wales

+ This trial is not currently included in the 1st line network because it includes a non-standard design

¥ This trial is not included in the 1st line network as no other trials compared to placebo and therefore inclusion did not add any value to the network

¤ This trial is not included in the 1st line network as the definition of PFS is not consistent with other trials and given a different histological profile

3.3.2. Description and critique of the design of the studies

Of the 24 included RCTs, the earliest participants were recruited in 2006, with the most recent data cuts in published records drawing from December 2019. Trials included as few as three and as many as 200 centres, with at least 14 trials including UK centres; and had sample sizes across arms comparing relevant treatments of between 22 and 1,110 participants.

Based on an initial consideration of relevant treatments mapped against lines, 18 studies reporting treatments tested at relevant lines were prioritised for inclusion in the review and 8 studies were de-prioritised. Thus, for example, a trial reporting a test at 1st line of a treatment reimbursed only at 2nd line would have been deprioritised. In one situation (NCT01136733), we deprioritised a trial arm in a three-arm trial but retained the relevant comparison.

3.3.2.1. Design of the studies

An overview of study design characteristics for the included trials is shown in Table 8. Of the 24 included trials, 18 were parallel trials and six were crossover trials. The six crossover trials sought to test two-drug sequences characterised by treatment with the first drug to progression; for example, in SWITCH,[100] patients were randomised to sunitinib followed by sorafenib after progression, or sorafenib followed by sunitinib after progression. All 18 parallel trials tested individual treatments to progression or death, with post-progression treatment generally not directly specified, though in six studies[84,98,103,105-107] receipt of the comparator treatment after progression was permitted. In two of these studies (RECORD-1 and VEG105192), this was a crossover from placebo to the comparator treatment.

Though some RCTs included independent masked review (e.g. of progression status), 20 trials were described by study authors as open-label; the remaining trials were distributed as one double-blind, two single-blind, and one triple-blind. Though three trials did not provide sufficient information, 21 trials used stratified randomisation, generally based on risk category and, where relevant, prior treatment.

Only one trial did not report any industry funding (SWOG 1500).

Table 8: Study design characteristics of included trials

Trial name	Line	Comparison	Design (Blinding)	Study sponsor	Continent: Country	Number of centres (number UK centres)	Enrolment period	Final follow-up	Date of last datacut
Prioritised									
1L									
CABOSUN	1L	cabo vs suni	Parallel (Single blind)	Industry and non-industry	North America: USA	77 (0)	Not stated	Median 34.5 months	September 2016
CheckMate 214*	1L	nivo+ipi vs suni	Parallel (Open label)	Industry	Mixed: USA, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Czechia, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, RO Korea, Mexico, Netherlands, Poland, Spain, Sweden, Taiwan, Turkey, UK	175 (6)	Oct 2014 - Feb 2016	67.7 months	February 2021
CheckMate 9ER	1L	cabo+nivo vs suni	Parallel (Single blind)	Industry	Mixed: USA, Europe, Rest of World	125 (3)	Not stated	44 months	May 2022
CLEAR	1L	pem+lenv vs lenv+evero vs suni	Parallel (Open label)	Industry	Mixed: USA, Australia, Austria, Belgium, Canada, Czechia, France, Germany, Greece, Ireland, Israel, Italy, Japan, RO Korea, Netherlands, Poland, Russian Federation, Spain, Switzerland, UK	200 (8)	Oct 2016 - July 2019	49.8 months	August 2020
COMPARZ	1L	pazo vs suni	Parallel (Open label)	Industry	Mixed: North America, Europe, Australia, Asia	Not stated (Not stated)	Aug 2008 - Sept 2011	34.1 months	May 2012
CROSS-J-RCC	1L	suni vs sora	Crossover (Open label)	Industry and non-industry	Asia: Japan	39 (0)	Feb 2010 - July 2012	NR; KM >48 months	June 2015
JAVELIN RENAL 101	1L	ave+axi vs suni	Parallel (Open label)	Industry	Mixed: USA, Canada, Western Europe, Rest of the World	144 (7 investigators, but NR how many centres)	Mar 2016 - Dec 2017	34.1 months	April 2020
SWITCH	1L	suni vs sora	Crossover (Open label)	Industry and	Europe: Germany, Austria, Netherlands	72 (0)	Feb 2009-Dec 2011	15 months	January 2014

Trial name	Line	Comparison	Design (Blinding)	Study sponsor	Continent: Country	Number of centres (number UK centres)	Enrolment period	Final follow-up	Date of last datacut
				non-industry					
SWITCH II	1L	pazo vs sora	Crossover (Open label)	Industry and non-industry	Europe: Germany, Austria, Netherlands	67 (0)	Jun 2012-Sep 2016	NR; KM >45 months	November 2016
TIVO-1*	1L & 2L	tivo vs sora	Parallel (Open label)	Industry	Mixed: USA, Argentina, Bulgaria, Canada, Chile, Czechia, France, Hungary, India, Italy, Poland, Romania, Russian Federation, Serbia, Ukraine, UK	76 (3)	Feb 2010 - Aug 2010	30 months	December 2011
2L +									
AXIS	2L	axi vs sora	Parallel (Open label)	Industry	Mixed: USA, Australia, Austria, Brazil, Canada, China, France, Germany, Greece, India, Ireland, Italy, Japan, RO Korea, Poland, Russian Federation, Singapore, Slovakia, Spain, Sweden, Taiwan, UK	175 (11)	15/09/08 - 23/07/10	37 months	November 2011
BERAT*	2L	TKI (axi/suni) vs evero	Crossover (Open label)	Industry	Europe: Germany	5 (0)	Nov 2012 - Aug 2016	NR' KM curve up to 800 days	January 2020
CheckMate 025*	2L+	nivo vs evero	Parallel (Open label)	Industry	Mixed: USA, Argentina, Australia, Austria, Belgium, Brazil, Canada, Czechia, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Norway, Poland, Romania, Russian Federation, Spain, Sweden, UK	146 (5)	Oct 2012 - Mar 2014	72 months	NR
METEOR	2L+	cabo vs evero	Parallel (Open label)	Industry	Mixed: Multiple	173 (11)	Aug 2013 - Nov 2014	18.8 months	December 2015
NCT01136733	2L+	lenv+evero vs evero	Parallel (Open label)	Industry	Mixed: Czech Republic, Poland, Spain, UK, USA	37 (11)	March 2012-June 2013	approx. 24 months median at	December 2014

Trial name	Line	Comparison	Design (Blinding)	Study sponsor	Continent: Country	Number of centres (number UK centres)	Enrolment period	Final follow-up	Date of last datacut
								follow-up	
RECORD-1*	2L+	evero vs placebo	Parallel (Double blind)	Industry	Mixed: Australia, Canada, Europe, Japan, USA	86 (NR)	Nov 2006-Nov 2007	21 months	November 2008
TIVO-3	3L+	tivo vs sora	Parallel (Open label)	Industry	Mixed: USA, Belgium, Canada, Czechia, Denmark, France, Germany, Hungary, Italy, Poland, Spain, UK	120 (17)	May 2016 - Aug 2017	NR; KM up to 48 months	May 2021
Deprioritised									
ASPEN	1L	suni vs evero	Parallel (Open label)*	Industry and non-industry	Mixed: USA, Canada, UK	17 (6)	23/09/2010 - 28/10/2013	29 months	May 2016
BIONIKK	1L	nivo vs nivo+ipi, nivo+ipi vs VEGFR-TKI (suni/pazo)	Parallel (Open label)	Industry	Europe: France	15 (0)	28/06/2017 - 18/07/2019	Median 42.1 months (40.5 - 45.2)	NR
ESPN*	1L	evero vs suni	Crossover (Open label)	Industry and non-industry	North America: USA	3 (0)	Not stated	23.6 months	May 2014
Hutson et al, 2017	1L	axi vs sora	Parallel (Open label)	Industry	Mixed: USA, Mexico, Asia, Eastern Europe	126 (0)	Jun 2010 - Apr 2011	4.5 years	December 2014
RECORD-3*	1L	suni vs evero	Crossover (Open label)	Industry	Mixed: USA, Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Hong Kong, Italy, South Korea, Mexico, Netherlands, Peru, Spain, Taiwan, Thailand, Turkey, United Kingdom	83 (3)	Oct 2009-Jun 2011	Median 3.7 years	May 2015
SWOG 1500	1L*	cabo vs suni	Parallel (Open label)	Non-industry	North America: USA, Canada	65 (0)	April 2016-Dec 2019	NR; KM to 40 months	October 2020

Trial name	Line	Comparison	Design (Blinding)	Study sponsor	Continent: Country	Number of centres (number UK centres)	Enrolment period	Final follow-up	Date of last datacut
SUNNIFORECAST	1L	nivo+ipi vs SoC	Parallel (Open label)	Industry	Europe: Belgium, Czech Republic, France, Germany, Netherlands, Spain, United Kingdom	30 (2)	Nov 2017-ongoing	NR	NR
VEG105192*	1L and 2L	pazo vs placebo	Parallel (Triple blind)	Industry and non-industry	Mixed: Argentina, Australia, Austria, Brazil, Chile, China, Czech Republic, Estonia, Greece, Hong Kong, India, Ireland, Italy, RO Korea, Latvia, Lithuania, Mexico, New Zealand, Pakistan, Poland, Russian Federation, Slovakia, Tunisia, Ukraine, UK	80 (5)	Apr 2006-Apr 2007	Unclear	March 2010

Abbreviations: NR, not reported; SD, standard deviation; UK, United Kingdom; USA, United States of America; vs, versus

*Crossover to the comparator permitted following progression

3.3.2.2. Population

Inclusion/ exclusion criteria

Included trials included participants aged 18 years or older with histologically confirmed RCC, measurable via RECIST guidelines, and with participants having adequate performance status (generally defined as ECOG performance status of 0 or 1, or as Karnofsky Performance Score of 70% or above). All trials required participants to have advanced or metastatic RCC, though the exact form of wording varied including within different reports of the same trial. Exclusion criteria related principally to other health parameters, such as controlled hypertension and adequate organ function; in addition, most trials reported explicit exclusion criteria with respect to brain and central nervous system metastases.

Additional criteria related principally to prior lines of treatment and risk group. These are discussed under baseline characteristics.

Baseline characteristics

An overview of the sample characteristics in the prioritised and deprioritised trials is shown in Table 9.

Histology. Of the 24 trials, 17 included patients with clear cell RCC only, or RCC with a clear cell component. Studies with a whole or majority (>85%) clear cell component were prioritised for inclusion. Three trials that were prioritised and two that were de-prioritised included participants with both clear cell and non-clear cell RCC.[86,93,99-101] The remaining three trials specifically targeted participants with predominantly non-clear-cell RCC histology.[84,108]

Risk distribution. Risk distribution was measured by a combination of IMDC and MSKCC risk scores. For convenience, both sets of risk scoring methods are described as producing risk score classes as ‘favourable’, ‘intermediate’ or ‘poor’. Two prioritised trials[86,92] did not enrol any participants assessed as having poor risk, and a further three prioritised[100,101,103] and two de-prioritised trials[94,105] enrolled a very low number of participants assessed as being at poor risk (i.e. ≤5% of the trial sample). One prioritised trial[88] only enrolled participants assessed as being at intermediate or poor risk. Proportions of participants assessed as being at favourable risk ranged in trials from 0 to 52%, while for intermediate risk, participants proportions ranged from 37% to 81%. Proportions of participants assessed as being at poor risk ranged from 0% to 40%.

Prior lines of systemic therapy. Of 24 trials, 17 RCTs included participants for whom the study drug was classed as their 1st line of systemic therapy. Of these 17 trials, 14 were only in participants receiving 1st line treatment. The remaining three trials enrolled patients to receive 1st line and 2nd line treatments; for these trials, the proportion of patients receiving their first systemic treatment ranged from 93% to 53%. Ten trials in the 1st line setting were prioritised for inclusion.

Correspondingly, 10 trials enrolled participants receiving 2nd line or later therapy. Distinguishing between participants receiving 2nd line and 3rd line systemic treatments was complicated by the fact that trials inconsistently included participants on the basis of prior lines of treatment belonging to a specific class. However, data presented in included studies indicated that beyond three trials enrolling a mix of 1st line and 2nd line patients, an additional two trials enrolled only participants for the 2nd line of treatment. Of the remaining five trials, four enrolled participants across 2nd line and 3rd line, with ranges of 2nd line treatment between 20% and 72%; and one trial enrolled only participants at the 3rd and 4th lines of therapy, with 60% of participants at 3rd line. Seven trials in the 2nd line-plus setting were prioritised for inclusion.

Prior systemic TKI or immunotherapy. Data on the proportions of participants with prior systemic TKI were inconsistently reported. All of the 11 trials that reported data on prior TKI use were prioritised for inclusion, and included five trials[96-98,104,107] that enrolled only participants with prior TKI, five trials[88,91,106,109,110] that enrolled participants only without prior TKIs, and one trial[85] that enrolled a blend of participants with and without prior TKI. Data on the proportions of participants with prior immunotherapies were also inconsistently reported. All of the 12 trials reporting data on this point were prioritised for inclusion, and included six trials with no participants who had previously received prior immunotherapies.

Prior surgery. Data on prior nephrectomy were reported for 22 trials, of which 17 were prioritised for inclusion. One prioritised trial[103] enrolled only participants with prior nephrectomy. In two trials[86,93] (one prioritised and one deprioritised), a minority of participants had previously undergone nephrectomy. In all other trials, the vast majority of participants (more than two thirds) had undergone nephrectomy prior to the trial.

Table 9: Population characteristics of included trials

Trial name	N (UK pts)	Key inclusion and exclusion criteria						Baseline characteristics					
		Age	Hist	Risk	Prior trt	ECOG	Other	Median age (range) years	Histology (% clear cell; % sarco features)	≥ 2 met sites	% bone mets	% risk status: Fav; Int; Poor	% prior nephrectomy
Prioritised													
1L													
CABOSUN	157 (NR)	≥18	CC	I/P	None	0-2	Pts with known brain mets: adequately treated and stable for 3 months	63.0 (31, 87)	100 / NR	72.6	36.3	0; 81; 19	74.5
CheckMate 214	1096 (NR)	≥18	CC	-	None	KPS≥70	Exclusion: CNS mets or auto immune disease & glucocorticoid or immunosuppressant use	62 (21 - 85)	100 / 13	78	21.1	23; 61; 16	81.2
CheckMate 9ER	651 (21)	≥18	CC	-	None	KPS≥70	One previous adjuvant or neoadjuvant therapy Exclusion: active CNS, active autoimmune disease	Cabo+nivo 62 (29-90). Suni 61 (28-86)	100 / 11.9	71.7	23.0	23; 57; 20	69.9
CLEAR	1069 (NR)	≥18	CC	-	None	KPS≥70	Exclusion: unstable CNS mets, active autoimmune disease in the past 2 years	Pem+lenv 64 (34–88), lenv+evero 62 (32–86), suni 61 (29–82)	100 / 6.8	68.8	25.1	32; 55; 10	74.6
COMPARZ	1110 (NR)	≥18	CC	-	None	KPS≥70	Exclusion: brain mets, poorly controlled hypertension	Pazo 61 (18-88), suni 62 (23-86)	100 / NR	38.3	17.6	27; 59; 11	83.2
CROSS-J-RCC	120 (0)	18-80	-	F/I	None	0-2	Exclusion: unstable brain mets (not stable 2 months before screening)	67 (41-79); suni first 67 (41-79), sora first 66 (44-79)	100 / NR	92.5	28.3	21.7; 78.3; 0	88.3
JAVELIN RENAL 101	886 (NR)	≥18	CC	-	None	0 or 1	Exclusion: active CNS mets, autoimmune disease, and current or previous use of	Ave+axi 62.0 (29.0-83.0). suni 61.0 (27.0 -88.0)	100 / 12	58.2	23.3	22; 65; 11	81.7

Trial name	N (UK pts)	Key inclusion and exclusion criteria						Baseline characteristics					
		Age	Hist	Risk	Prior trt	ECOG	Other	Median age (range) years	Histology (% clear cell; % sarco features)	≥ 2 met sites	% bone mets	% risk status: Fav; Int; Poor	% prior nephrectomy
							glucocorticoid or immunosuppressants 7 days before randomization						
SWITCH	365 (0)	18-85	-	F/I	None	0 or 1	Unsuitable for cytokine therapy Exclusion: symptomatic met brain tumours	65 (39-84)	87 / NR	64	15	42; 55; 0.5	92
SWITCH II	377 (0)	18-85	-	F/I	None	KPS≥70	Unsuitable for cytokine therapy Exclusion: uncontrolled brain mets	68 (26-86)	87 / NR	NR	20	49; 48; 2	99
TIVO-1	517 (4)	≥18	CC	-	0 or 1	0 or 1	Prior nephrectomy Exclusion: prior VEGF Unstable brain mets ≥ 3 months following prior treatment	59 (23 - 85)	100 / NR	68.3	21.9	30; 65; 5	100
2nd line +													
AXIS	723 (NR)	≥18	CC	-	1*	0 or 1	Life expectancy of ≥12 weeks Exclusion: CNS mets	NR for whole sample	100 / NR	NR	NR	20; 64; 10	91
BERAT	22 (0)	NR	-	F/I	NR	0 or 1	CNS mets were permitted if local treatment was completed ≥3 months, and steroids were discontinued	55.3	NR / NR	90	10	NR; NR; 0	20
CheckMate 025	821 (26)	≥18	CC	-	1-2	KPS≥70	Exclusion: CNS mets Condition treated with glucocorticoids (equivalent to >10 mg of prednisone daily)	62 (18–88)	100 / NR	83	18	36; 49; 15	88

Trial name	N (UK pts)	Key inclusion and exclusion criteria						Baseline characteristics					
		Age	Hist	Risk	Prior trt	ECOG	Other	Median age (range) years	Histology (% clear cell; % sarco features)	≥ 2 met sites	% bone mets	% risk status: Fav; Int; Poor	% prior nephrectomy
METEOR	658 (26)	≥18	CC	-	≥1 TKI	KPS≥70	Disease progression during or within six months of the most recent VEGFR/TKI treatment, and within 6 months before randomisation Pts with known brain mets that were adequately treated and stable were eligible	Cabo 63 (32-86), evero 62 (31-84)	100 / NR	81.5	22	46; 42; 13	85
NCT01136733	101 (50)	≥18	CC	-	1 TKI	0 or 1	Within 9 months of stopping previous treatment Exclusion: brain mets	61, 37-79	100 / NR	79	07	23; 37; 40	88
RECORD-1	410 (NR)	≥18	CC	-	≥1	KPS≥70	Progressed on or within 6 months of stopping treatment with suni or sora, or both drugs Previous therapy with bev, IL2, or IFNα permitted Exclusion: untreated CNS mets	61, 27-85	100 / NR	91	35	29; 56; 14	97
TIVO-3	350 (NR)	≥18	CC	-	2 or 3¥	0 or 1	Life expectancy ≥3 months Exclusion: CNS mets (other than lesions that were radiographically stable without any steroid treatment for at ≥3 months)	63 (30, 90)	100 / NR	89.1	NR	21; 61; 18	NR

Trial name	N (UK pts)	Key inclusion and exclusion criteria						Baseline characteristics					
		Age	Hist	Risk	Prior trt	ECOG	Other	Median age (range) years	Histology (% clear cell; % sarco features)	≥ 2 met sites	% bone mets	% risk status: Fav; Int; Poor	% prior nephrectomy
Deprioritised trials													
ASPEN	108 (NR)	≥18	nCC	-	None	KPS≥60	Life expectancy ≥3 months Exclusion: active untreated CNS mets	63 (23, 100)	0 / 14.8	NR	25	27; 60; 14	79.6
BIONIKK	202 (0)	≥18	NR	-	None	0-2	Exclusion: uncontrolled or symptomatic brain mets	Medians across groups ranged from 59 to 66	100 / 26.6	74.4	20.6	30; 50; 20	NR
ESPN	72 (0)	≥18	Mix¤	-	None	0 or 1	Exclusion: untreated brain metastases	Evero 58 (23–73), suni 60 (28–76)	16.7 / 26	82.4	26	10; 74; 16	47.1
Hutson et al, 2017	288 (0)	≥18	CC	-	None	0 or 1	Life expectancy 12 weeks Exclusion: brain mets or CNS involvement	Axi 58·0 (23–83), sora 58·0 (20–77)	100 / NR	NR	27.8	51; 43; 3	86.8
RECORD-3	471 (NR)	≥18	Mix	-	None	KPS≥70	Exclusion: CNS mets	62 (20-89)	85 / NR	68	23	29; 56; 15	67
SWOG 1500	90 (0)	≥18	nCC	-	0 o 1	Zubrod PS 0 - 1	Patients with known brain mets who had received adequate treatment were eligible Exclusion: prior treatment with excluding VEGF-directed or MET-directed drugs	65 (58-75)	Papillary RCC 0 / NR	NR	14.4	26; 61; 14	73.3
SUNNIFO RECAST	237 (NR)	≥18	nCC	-	None	KPS≥70	Exclusion: ccRCC component >50% Active brain mets requiring systemic corticosteroids	NR for whole sample	148 papillary, 83 non-papillary, 0 clear cell; sarcomatoi	NR	NR	NR; NR; NR	NR

Trial name	N (UK pts)	Key inclusion and exclusion criteria						Baseline characteristics					
		Age	Hist	Risk	Prior trt	ECOG	Other	Median age (range) years	Histology (% clear cell; % sarco features)	≥ 2 met sites	% bone mets	% risk status: Fav; Int; Poor	% prior nephrectomy
									d features NR				
VEG105192	435 (NR)	≥18	CC	-	0 or 1 +	0 or 1	Exclusion: CNS mets	NR for whole sample	100 / NR	83.2	27.4	39; 54; 3	88.5

Abbreviations: ave, avelumab; axi, axitinib; bev, bevacizumab; cabo, cabozantinib; CC, clear cell; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; evero, everolimus; fav, favourable; IFNα, interferon alpha; IL-2, interleukin 2; int, intermediate; KPS, Karnofsky Performance Status; lenv, lenvatinib; MET, mesenchymal-epithelial transition; mets, metastasis; NA not applicable; nCC, non clear cell; nivo, nivolumab; NR not reported; pazo, pazopanib; pem, pembrolizumab; PS, performance status; Pts, patients; RCC, renal cell carcinoma; sora, sorafenib; suni, sunitinib; TKI, tyrosine kinase inhibitors; trt, treatment; UK, United Kingdom; VEGF, vascular endothelial growth factor

* RECIST-defined progressive disease as assessed by investigators after one previous systemic 1L regimen with a suni-based, bevacizumab + interferon-alfa-based, temsirolimus-based, or cytokine-based regimen, 2 weeks or more since end of previous systemic treatment (4 weeks or more for bevacizumab + interferon-alfa),

¥ one of which included a VEGFR TKI other than tivo or sora

¤ Advanced papillary, chromophobe, collecting duct carcinoma, Xp11.2 translocation, unclassified RCC, or ccRCC with >20% sarcomatoid features in their primary tumours

+ progressed on one prior cytokine-based systemic therapy (amended to include treatment-naive patients living in countries where there were barriers to the access of established therapies or where cytokines were not recognized as standard treatment for RCC)

3.3.2.3. Interventions and comparators

An overview of the intervention characteristics used in the included trials is shown in Table 10. Interventions and comparators were distributed unevenly across the included trials. Our commentary focuses here only on relevant arms in included trials. There was evidence from at least one trial for all relevant active interventions. No trials used 'current care', investigator's choice or best supportive care as a comparator, but placebo was used as a comparator in two trials,[98,105] one of which was prioritised for inclusion. Sunitinib was the most commonly represented treatment. An overview of interventions is as follows:

- Sunitinib: 14 trials (10 prioritised)
- Single-agent everolimus: 8 trials (5 prioritised)
- Sorafenib (used as a linking treatment): 7 trials (6 prioritised)
- Pazopanib: 4 trials (2 prioritised)
- Single-agent axitinib: 3 trials (2 prioritised)
- Single-agent cabozantinib: 4 trials (3 prioritised).
- Single-agent nivolumab: 2 trials (1 prioritised)
- Nivolumab + ipilimumab: 2 trials (1 prioritised)
- Single-agent tivozanib: 2 trials (2 prioritised)
- Lenvatinib + everolimus: 2 trials (2 prioritised)
- Avelumab + axitinib: 1 trial (1 prioritised)
- Cabozantinib + nivolumab: 1 trial (1 prioritised)
- Pembrolizumab + lenvatinib: 1 trial (1 prioritised)

Table 10: Intervention characteristics of included trials

Trial name	% Prior TKI; % prior IO (systemic)	Comparison	Treatment details (include dose, delivery etc)	RDI	Treatment stopping rules	Any subsequent systemic tx (% of ITT)
Prioritised						
1L						
CABOSUN	NA	Cabo vs suni	Cabo (orally): 60mg OD. Suni (orally): 50mg OD for 4 wks then 2-wk break per cycle.	NR	N/A	Int 60.8 Control 61.5
CheckMate 214	NA	Nivo+ipi vs suni	Nivo (IV): 3 mg/ kg bodyweight over 60-minute period/ 3 wks for four doses and then at a dose of 3 mg/ kg bodyweight every 2 wks. Ipi (IV): 1 mg/ kg bodyweight over a period of 30 minutes/ 3 wks for four doses. Suni (orally): 50 mg OD for 4 wks, 2 wks off per cycle. Nivo or ipi dose reductions not allowed. Dose delays for adverse events were permitted in both groups.	Nivo induction: 79*; Nivo maintenance: [redacted] Ipi: 79*	Treated beyond progression: Nivo+ipi n=157 (29%), Suni n=129 (24%)	Int 53.5 Control 66.5
CheckMate 9ER	NA	Cabo+nivo vs suni	Nivo (IV): 240 mg every 2 wks and cabo(orally) 40 mg OD. Suni (orally): 50 mg OD for 4 wks then 2-wk break in 6-wk cycle.	Nivo: [redacted] Cabo: [redacted] Suni: NR	Nivo stopped after 2 years (from the first dose)	Int 25.1 Control 40.5
CLEAR	NA	Pem+lenv vs lenv+evero vs suni	Pem+lenv: for 21-day cycle, lenv (orally) 20 mg OD and pem (IV) 200 mg on day 1 of cycle. Suni (orally): 50 mg OD (4 wks on/2 wks off). Dose reduction and interruptions: investigators decide the probability of the event being related to 1 or both drugs. lenv dose reduction to 14, 10, and 8	Median Pem+lenv Len: 69.6% Median number of pem infusions per patient 22 (range, 1 to 39). Suni 83.2%	Maximum 35 treatments for pem All patients could continue treatment beyond progression if they received clinical benefit and tolerated the study-drug treatment	Int pem+lenv = 32.96 Control 57.7

Trial name	% Prior TKI; % prior IO (systemic)	Comparison	Treatment details (include dose, delivery etc)	RDI	Treatment stopping rules	Any subsequent systemic tx (% of ITT)
			mg/day). Dose reductions below 8 mg/day must be discussed with sponsor.			
COMPARZ	NA	Pazo vs suni	Pazo was administered orally at a once-daily dose of 800 mg, with continuous dosing. Suni was administered orally in 6-week cycles at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment. Dose reductions for pazo (to 600 mg and then to 400 mg) and suni (to 37.5 mg and then to 25 mg) were permitted due to adverse events.	NR	N/A	Int NR Control NR
CROSS-J-RCC	NA	Suni vs sora	Suni (orally): 50 mg OD (4 wks on/2 wks off). Suni dose reductions to 37.5mg then 25 mg/day schedule 4/2. Dose reduction below 25 mg/day discussed with the sponsor.	Median RDI - suni 65.8% (range 7.1%-100%), sora 61.2% (range 10.7%-100%)	N/A	Int NR Control NR
JAVELIN RENAL 101	NA	Ave+axi vs suni	Ave+axi: ave (IV) 10mg/kg every 2 wks and axi (orally) 5 mg BID. Suni (orally): 50 mg OD (4 wks on/2 wks off).	Ave 91.5%; Axi 89.4%; Sun 83.9% (all median)	N/A	Int 46.2 Control 60.6
SWITCH	NA	Suni vs sora	Suni (orally): 50 mg OD, 4 wks on 2 wks off; dose reductions permitted	NR	N/A	Int 57% crossed over Control 42% crossed over
SWITCH II	NA	Pazo vs sora	Pazo (orally) 800mg OD, dose reductions permitted	NR	N/A	Int 64.0 Control 58.5
TIVO-1	NA	Tivo vs sora	Tivo (orally) 1.5mg OD for 3 wks followed by 1 wk off per cycle. Specific guidelines for hypertension, otherwise AEs ≥ grade 3 were managed by a dose reduction to 1.0 mg per day.	Tivo 94%; sora 80%	N/A	Int 18.1 Control 64.2
2L+						
AXIS	TKI 54%; IO Cytokines 35%; Bev 8%	Axi vs sora	Axi (orally): 5 mg BID with continuous dosing, if tolerated (no adverse reactions above grade 2 for at least 2 weeks) dose increased to 7 mg twice daily unless the patient's blood pressure was higher than	Median 99% for axi and 92% for sora	Patients were treated until progression of disease (RECIST version 1·017),	Int 54.4 Control 56.6

Trial name	% Prior TKI; % prior IO (systemic)	Comparison	Treatment details (include dose, delivery etc)	RDI	Treatment stopping rules	Any subsequent systemic tx (% of ITT)
			150/90 mm Hg or the patient was receiving anti hypertensive medication. If tolerated, increased to a maximum of 10 mg twice daily. Dose could be reduced to 3 mg twice daily and then further to 2 mg twice daily.		occurrence of unacceptable toxic effects, death, or withdrawal of patient consent	
BERAT	TKI NR; IO NR	TKI (axi/suni) vs evero	Axi: 5mg BID starting dose Suni: 50 mg OD, 4-2 regimen. Evero: 10mg OD	NR	Trial stopped due to poor accrual	Int TKI 60% Control evero 80%
CheckMate 025	TKI 100%; IO NR	Nivo vs evero	Nivo (IV): 3 mg/ kg of body weight as a 60-minute every 2 wks. Evero (orally):10 mg OD. Dose modifications were not permitted for nivo but were permitted for evero.	NR	Continuation after initial disease progression was allowed if the investigator noted that there was a clinical benefit and the study drug had an acceptable side-effect profile	Int 67.3 Control 72.0
METEOR	TKI 100%; IO >7%	Cabo vs evero	Cabo (orally): OD at 60 mg. Evero (orally): OD at 10 mg.	Cabo: NS; Evero 84%	Patients were allowed to continue study treatment beyond radiographic progression at the discretion of the investigator.	Int 50 Control 55
NCT01136733	TKI 100%; IO 3%	Lenv+evero vs evero	Lenv+evero: lenv (18 mg/day) as one 10 mg capsule and two 4 mg capsules + eve (5 mg/day) as one 5 mg tablet. Single-agent evero (10 mg/day) two 5 mg tablets	NR	N/A	Int 27.5 Control 36
RECORD-1	TKI 100%; IO 65%	Evero vs placebo	Evero (orally): 10 mg/d + BSC. Matching placebo plus BSC	NR	N/A	Int NR Control 79.9
TIVO-3	TKI 100%; IO/TKI tivo	Tivo vs sora	Tivo (orally): 1·5 mg OD in 4-wk cycles comprising 21 days on treatment followed by 7 days off treatment. Dose reduction to	NR	N/A	Int 64.6 Control 58.5

Trial name	% Prior TKI; % prior IO (systemic)	Comparison	Treatment details (include dose, delivery etc)	RDI	Treatment stopping rules	Any subsequent systemic tx (% of ITT)
	27%, sora 25%		1.0 mg OD allowed for patients with treatment-related AEs ≥ Grade 3. Dose interruptions allowed for persistent AEs.			
De-prioritised						
ASPEN	TKI NA; IO NA	Suni vs evero	Suni (orally): 50 mg OD on days 1-28 of each 42-day cycle. Dose reductions permitted or recommended for Grade 3 toxic effects and required for Grade 4 toxic effects: reduction to 37·5 mg or 25 mg; holds such as alternative dosing treatment cycles of 2 weeks on treatment and 1 week off treatment, depending on the timing and severity of toxic effects. Evero (orally): 10 mg OD on days 1-42 for each 42 day cycle. Dose reductions permitted or recommended for Grade 3 toxic effects and required for Grade 4 toxic effects: reduction to 5 mg once daily and then to 5 mg every other day.	NR	N/A	Int 71 Control 58
BIONIKK	TKI NR; IO NR	Nivo vs nivo+ipi, nivo+ipi vs VEGFR-TKI (suni/pazo)	Nivo+ipi (IV): nivo 3 mg/kg plus ipi 1 mg/kg every 3 wks for 4 doses then IV nivo 240 mg every 2 wks. Nivo (IV): 240 mg every 2 wks. Suni (orally) 50 OD for 4 wks every 6 wks Pazo (orally) 800 mg OD continuously.	NR	NR	Nivo: 62 Nivo+Ipi: 57.4 TKI: 50
ESPN	TKI NA; IO NA	Evero vs suni	Evero 10 mg/d orally 4 wk on and 2 wk off; suni 50 mg/d orally 4 wk on and 2 wk off	NR	N/A	Int NR Control NR
Hutson et al, 2017	TKI 0; IO 0	Axi vs sora	AXI (orally): 5 mg BID with food, in 4-wk cycles. Doses can be increased first to 7 mg BID, and subsequently to 10 mg BID for patients who had not had any grade 2+ TRAEs for at least 2 wks and had blood pressure ≤150/90 mm Hg. Those with AEs or lab abnormalities could have dose reduced to 3 mg BID, and then 2 mg BID. PD patients who had clinical benefit could continue on treatment	Axi 125%, Sora 98%	NR	Int 15.1 Control 19.8

Trial name	% Prior TKI; % prior IO (systemic)	Comparison	Treatment details (include dose, delivery etc)	RDI	Treatment stopping rules	Any subsequent systemic tx (% of ITT)
RECORD-3	TKI 0; IO 0	Suni vs evero	Evero: 10 mg/day Suni: 50 mg/ day (4 wks on, 2 wks off)	Evero 98%, suni 87%	N/A	Int 55 Control 51
SWOG 1500	NA	Cabo vs suni	Cabo(orally): 60 mg OD, dose reductions permitted, Suni (orally) 50 mg 4 wks on, 2 wks off, dose reductions permitted	NR	N/A	Int NR Control NR
SUNNIFORECAST	TKI 0; IO 0	Nivo+ipi vs SoC	Nivo+ipi: nivo (IV) 3 mg/kg + ipi (IV) 1 mg/kg every 3 wks for 4 doses followed by nivo fixed dose 240 mg IV every 2 wks or fixed dose 480 mg IV every 4 wks	NR	N/A	Int NR Control NR
VEG105192	TKI 0; IO 0	Pazo vs placebo	Pazo (Orally): 800 mg OD Administered 1 hour before or 2 hours after meals. Dose modification guidelines for AEs were prespecified (details not reported).	NR	N/A	Int 30.3 Control 65.5

Abbreviations: AEs, adverse events; ave, avelumab; axi, axitinib; BID, twice daily; BSC, best supportive care; cabo, cabozantinib; evero, everolimus; Int, intermediate; IO, immuno-oncology; ipi, ipilimumab; ITT, intention to treat; IV, intravenous; lenv, lenvatinib; N/A, not applicable; nivo, nivolumab; NR, not reported; OD, once daily; pazo, pazopanib; PD, progressed disease; pem, pembrolizumab; RDI, relative dosing intensity; RECIST, Response Evaluation Criteria in Solid Tumors; SoC, standard of care; sora, sorafenib; suni, sunitinib; tivo, tivozanib; TKI, tyrosine kinase inhibitor; Tx, treatment; UK, United Kingdom; VEGR, vascular endothelial growth factor receptor; vs, versus; wks, weeks

Notes: dosing is only included for treatments which are part of the UK treatment pathway

*79% reported to receive all 4 doses of nivo and ipi within the induction phase

3.3.2.4. Outcomes

The outcomes reported in the 24 trials are summarised in Table 11. The account of outcomes is derived from publicly available trial reports.

Overall survival

OS was measured in all included trials. Details of follow-up duration were reported for 17 trials, and in a range of ways. Where trials reported the time to final follow-up (n=8), this was below two years in one case and up to seven years in one case; five trials had final follow-ups of between two and four years. An additional trial reported minimum follow-up of 13 months. The remaining eight trials reported median or average follow-up period. Four trials reported median or average follow-up of less than two years, one a median follow-up of two years and a final three trials a median follow-up of between three and six years. Because most analysis protocols were event-driven and included interim analyses, OS data were of variable maturity between trials, highlighting the need for extrapolation.

Adjustment for crossover and treatment-switching was inconsistently addressed in included trials. In trials with a crossover design, OS was not adjusted as the goal of the analysis was to capture the crossover between two different drugs. Treatment-switching adjustments to OS were reported in relatively few trials. Where subsequent treatments were reported, these were inconsistently aligned with UK practice, often making use of treatments (e.g. sorafenib) that are not part of UK treatment pathways. Information on subsequent treatments forming sequences that would be 'disallowed' in UK practice (e.g. immuno-oncology therapies followed by immuno-oncology therapies) was only inconsistently presented across trials.

Progression-free survival

PFS on first treatment was also included in all 24 trials. 23 of 24 trials used a standard definition for PFS of time to the first of RECIST-assessed progression or death. One trial (SWOG 1500) used a non-standard definition which included clinical progression and symptomatic deterioration (investigator assessed). Where PFS censoring rules were mentioned in trial protocols the trials specified FDA analysis rules where patients are censored on receipt of subsequent treatment if this is prior to progression. It is noted that that EAG in TA858 performed sensitivity analysis looking at the use of EMA rules which count receipt of subsequent treatment as an event. These are analyses are redacted and the amount of difference this made to the appraisal is unclear. 10 trials assessed PFS via blinded independent central review (BICR), 2

used an independent review committee with no or unclear blinding and the remaining 12 were investigator-assessed. All of the combination therapy trials were assessed via independent central review except CheckMate 214.

Because an important element of PFS is monitoring of disease status, the tumour scan frequency used in the trials were extracted. In the 20 trials reporting tumour scan frequency, seven used a based frequency of eight weeks, and six used a base frequency of every 12 weeks or three months (with one including an interim scan after six weeks on treatment). Two trials scanned every eight weeks in the first year of study treatment with every 12 weeks thereafter. Two trials scanned 12 weeks after randomisation, then took scans every six weeks for a period of time (up to 13–14 months post-randomisation) and then every 12 weeks thereafter. Two trials scanned at Weeks 6 and 12, and then every eight weeks. One trial scanned every six weeks until Week 12 and then every eight weeks until progression. Three trials described additional scan frequency related to bone and brain metastases where relevant.

Additional time-to-event outcomes

Four trials reported TTP outcomes in publicly available trial reports, including one reporting time to deterioration on treatment as a composite outcome. Three trials also reported time to next treatment outcomes. Six trials reported time to discontinuation.

Duration of response and response rate

Duration of response was reported in 13 trials. Response rate was reported in 24 trials.

Adverse events

The incidence and prevalence of AEs were reported in some form for all 24 trials. This generally included reporting of most common adverse events, though discontinuation due to AEs was also reported for nearly all trials in some form.

Health-related quality of life

HRQoL outcomes were identified for 16 trials. Utility data identified are presented in the later sections relevant to the economic analysis (Section 4.3.7.1).

Table 11: Outcomes reported by RCTs included in the review

Trial name	OS	PFS	TTP	TTNT	TTD	Duration of response	Response rate	Adverse events	HRQoL
ASPEN	X	X					X	X	X
AXIS	X	X				X	X	X	X
BERAT	X	X					X	X	X
BIONIKK	X	X		X		X	X	X	
CABOSUN	X	X			X		X	X	
CheckMate 025	X	X	X			X	X	X	X
CheckMate 214	X	X		X	X	X	X	X	X
CheckMate 9ER	X	X		X	X	X	X	X	X
CLEAR	X	X				X	X	X	X
COMPARZ	X	X					X	X	X
CROSS-J-RCC	X	X			X	X	X	X	
ESPN	X	X					X	X	
Hutson et al, 2017	X	X	X*			X	X	X	X
JAVELIN RENAL 101	X	X				X	X	X	¥
METEOR	X	X					X	X	X
NCT01136733	X	X				X	X	X	
RECORD-1	X	X					X	X	X
RECORD-3	X	X				X	X	X	X
SWITCH	X	X	X		X		X	X	
SWITCH II	X	X	X		X		X	X	X
SWOG 1500	X	X					X	X	
TIVO-1	X	X					X	X	X
TIVO-3	X	X				X	X	X	
VEG105192	X	X				X	X	X	X
TOTAL	24	24	4	3	6	13	24	24	16

Abbreviations: HRQoL, health-related quality of life; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; TTD, time to discontinuation; TTNT, time to next treatment; TTP, time to progression.
Notes: *Time to treatment failure ¥ utility data reported within the economics section of TA645 but not clinical outcomes reported by arm

3.3.2.5. Critical appraisal of the included studies

The full quality assessments of RCTs included in this appraisal are presented in Table 12. A summary of bias issues across the trials is provided in the following section. None of the included trials were appraised as being at a low overall risk of bias. Of the seventeen prioritised trials, five were appraised as being at a high risk of bias and twelve were appraised as being at an unclear risk of bias.

Table 12: Summary of domain-level risk of bias judgments, main issues per study and overall study-level risk of bias

Trial name	Overall line	Selection bias	Performance and detection biases	Attrition bias	Reporting bias	Conflict of interest	Other bias	Overall study-level risk of bias	Main issues
Prioritised									
AXIS	2L	Low	High	Unclear	Low	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, potential conflict from industry funding
BERAT	2L	Unclear	High	High	Unclear	High	High	**High**	Unclear reporting of randomisation and allocation concealment, small sample with potential baseline imbalances, open-label trial with some highly subjective outcomes, very high differential attrition with no methods to account for missing data, the paper reported on more outcomes than were listed in the trial registry, potential conflict from industry funding, risk of carryover effect as no washout period is specified
CABOSUN	1L	High	Unclear	Unclear	Low	High	Low	**High**	Dynamic allocation of treatment, open-label trial with some subjective outcomes, very high but non-differential attrition with inadequate methods to account for missing data, potential conflict from industry funding
CheckMate 025	2L and 3L	Low	High	Unclear	Low	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, some imbalances in attrition by reason with inadequate methods to account for missing data, potential conflict from industry funding
CheckMate 214	1L	Low	High	Unclear	Low	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, some imbalances in attrition by reason with methods to account for missing data unclear, potential conflict from industry funding

Trial name	Overall line	Selection bias	Performance and detection biases	Attrition bias	Reporting bias	Conflict of interest	Other bias	Overall study-level risk of bias	Main issues
CheckMate 9ER	1L	Low	High	Unclear	Low	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, potential conflict from industry funding
CLEAR	1L	Low	High	Unclear	Unclear	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, very high differential attrition, linked to study endpoints, with methods to account for missing data unclear, some outcomes reported in the trial registry is not reported in the papers (ongoing trial), potential conflict from industry funding
COMPARZ	1L	Low	High	Unclear	Low	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, very high but non-differential attrition with inadequate methods to account for missing data, potential conflict from industry funding
CROSS-J-RCC	1L	Unclear	Unclear	Unclear	Unclear	Unclear	High	**High**	Unclear reporting of randomisation, open-label trial with some subjective outcomes, very high differential attrition with methods to account for missing data unclear, paper reported more outcomes than is listed in the trial registry, unclear conflict as the trial was not industry-funded but some authors received industry funding, risk of carryover effect as no washout period is specified
JAVELIN RENAL 101	1L	Low	High	Unclear	Unclear	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, some imbalances in attrition by reason with inadequate methods to account for missing data, some outcomes reported in the trial registry are not reported in the paper (reported in TA645 but redacted), potential conflict from industry funding

Trial name	Overall line	Selection bias	Performance and detection biases	Attrition bias	Reporting bias	Conflict of interest	Other bias	Overall study-level risk of bias	Main issues
METEOR	2L and 3L	Low	Unclear	Unclear	Low	High	Low	**Unclear**	Open-label trial with some subjective outcomes, very high differential attrition, but linked to study endpoints, with inadequate methods to account for missing data, potential conflict from industry funding
NCT01136733	2L	High	Unclear	High	Low	High	Low	**High**	Dynamic allocation of treatment, small sample with potential baseline imbalances, open-label trial with some subjective outcomes, very high differential attrition, linked to study endpoints as well as other reasons, with inadequate methods to account for missing data, potential conflict from industry funding
RECORD-1	2L and 3L	Low	Low	Unclear	Unclear	High	Low	**Unclear**	Very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, some outcomes reported in the trial registry are not reported in the paper, potential conflict from industry funding
SWITCH	1L	Unclear	Unclear	Unclear	Unclear	High	Unclear	**Unclear**	Unclear reporting of randomisation, open-label trial with some subjective outcomes, some imbalances in attrition by reason with methods to account for missing data unclear, paper reported more outcomes than is listed in the trial registry, potential conflict from industry funding, unclear risk of carryover effect as washout period may be insufficient
SWITCH II	1L	Unclear	Unclear	Unclear	Unclear	High	High	**High**	Unclear reporting of randomisation and allocation concealment, open-label trial with some subjective outcomes, very high but non-differential attrition with methods to account for missing data unclear, paper reported outcomes not listed in the trial registry and did not report other outcomes listed in the trial registry, potential conflict from industry funding, risk of carryover effect as no washout period is specified

Trial name	Overall line	Selection bias	Performance and detection biases	Attrition bias	Reporting bias	Conflict of interest	Other bias	Overall study-level risk of bias	Main issues
TIVO-1	1L and 2L	Low	High	Unclear	Unclear	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, some outcomes reported in the trial registry are not reported in the papers, potential conflict from industry funding
TIVO-3	3L and 4L	Low	Unclear	Unclear	Low	High	Low	**Unclear**	Open-label trial with some subjective outcomes, very high differential attrition, but linked to study endpoints, with inadequate methods to account for missing data, potential conflict from industry funding
De-prioritised									
VEG105192	1L and 2L	Low	Low	Unclear	Unclear	High	Low	**Unclear**	Very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, some outcomes reported in the trial registry are not reported in the paper, potential conflict from industry funding
ASPEN	1L	Unclear	High	Unclear	Low	High	Low	**Unclear**	Unclear reporting of randomisation, open-label trial with some highly subjective outcomes, some imbalances in attrition by reason with methods to account for missing data unclear, potential conflict from industry funding
BIONIKK	1L	High	Unclear	Unclear	Low	High	Low	**High**	Small sample with baseline imbalances, open-label trial with some subjective outcomes, some imbalances in attrition by reason with methods to account for missing data unclear, potential conflict from industry funding
ESPN	1L	Unclear	Unclear	Unclear	Low	High	Low	**Unclear**	Unclear reporting of randomisation and allocation concealment, small sample with potential baseline imbalances, open-label trial with some subjective outcomes, very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, potential conflict from industry funding

Trial name	Overall line	Selection bias	Performance and detection biases	Attrition bias	Reporting bias	Conflict of interest	Other bias	Overall study-level risk of bias	Main issues
Hutson 2017	1L	Unclear	High	Unclear	Low	High	Low	**Unclear**	Unclear reporting of randomisation, open-label trial with some highly subjective outcomes, some imbalances in attrition by reason with methods to account for missing data unclear, potential conflict from industry funding
RECORD-3	1L	Low	High	Unclear	Low	High	Low	**Unclear**	Open-label trial with some highly subjective outcomes, very high but non-differential attrition with inadequate methods to account for missing data, potential conflict from industry funding
SWOG 1500	1L	High	Unclear	Unclear	Low	Unclear	Low	**High**	Dynamic allocation of treatment, small sample with potential baseline imbalances, open-label trial with some subjective outcomes, very high differential attrition, but linked to study endpoints, with methods to account for missing data unclear, unclear conflict as the trial was not industry-funded but some authors received industry funding

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line

Selection bias

Overall, thirteen of the included trials were assessed as having a low risk of selection bias. Only one of these (AXIS) reported fully on an adequate method of random sequence generation, while the remaining 12 described randomisation using interactive voice or web response systems (IxRS). As this has been accepted as evidence of random sequence generation in previous company submissions and NICE TAs, the EAG pragmatically accepted these trials as having adequate methods of sequence generation. However, the EAG views the use of IxRS to be a feature of allocation concealment and considers sequence generation to have been poorly reported in the 12 trials. In the absence of precedent, the EAG would have judged these trials as having an unclear risk of bias relating to sequence generation. Seven of the included trials had an unclear risk of selection bias, driven in large part by unclear descriptions of the methods used to generate the random sequence. Three of these trials additionally did not report adequate allocation concealment in sufficient detail; two trials included small sample sizes and reported some baseline imbalances between randomised groups.

Four trials had a high overall risk of selection bias. This was driven largely by an inadequate randomisation method namely dynamic allocation - a primarily deterministic, non-random approach to balance prognostic factors at baseline[111] in three trials (CABOSUN, NCT01136733 and SWOG 1500). Two of these trials (NCT01136733 and SWOG 1500) had additional potential sources of bias as they included small sample sizes and reported potential baseline imbalances despite the dynamic allocation processes. A fourth trial (BIONIKK), despite describing adequate methods of random sequence generation and allocation concealment in sufficient detail, showed imbalances in most baseline characteristics of participants due to very small sample sizes.

Performance and detection bias

Only two trials were judged as having a low overall risk of performance and detection bias, as they described blinding all groups to treatment assignment. As such, none of the outcomes assessed in these trials were considered to be at risk of these biases. Ten trials were judged to be at unclear risk overall as patients and investigators were not blinded and since both groups were involved in the assessment of outcomes that are, to some extent, subjective. Twelve trials were considered to be at high risk overall as patients and investigators were not blinded and since both groups were involved in the assessment of subjective outcomes.

A lack of blinding in the 22 trials was not considered to have a major impact on OS as this is a hard, objective outcome. In eight trials where the assessors of radiological outcomes based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria were blinded, but other groups were not, outcomes such as PFS, response rate, duration of response, and time to treatment failure were similarly judged as having no major impact due to the blinded and predominantly objective nature of the outcome assessment. Given the largely objective nature of these outcomes, an overall lack of blinding was still considered to be very unlikely to impact on bias. Conversely, a lack of blinding was considered to pose some risk of bias for outcomes such as adverse events, which are patient-reported and, to some extent, investigator-determined; a lack of blinding was judged very likely to result in bias for patient-reported quality of life outcomes.

Attrition bias

Attrition bias was not a major concern with safety outcomes, since most RCTs analysed these in all participants who had received at least one dose of a study treatment. The only exceptions were the BERAT trial, where adverse events were not reported following crossover, and the SWOG 1500 trial, where one patient in each arm received no protocol therapy and were excluded from the safety assessment.

For effectiveness outcomes, 22 and two trials were at unclear and high risk of attrition bias, respectively. Only three trials (CABOSUN, RECORD-3 and SWITCH II) did not report unexpected imbalances in drop-outs between groups. Very high non-differential overall attrition was observed in all three , though reasons for attrition and numbers per reason were similar. However, due to inadequate reporting of appropriate intention-to-treat (ITT) analytical approaches or the reporting of inadequate approaches to account for missing data in the presence of this attrition, all three trials were judged as having unclear risk of attrition bias. Nine additional trials (AXIS, CheckMate 9ER, CLEAR, ESPN, METEOR, NCT01136733, RECORD-1, SWOG1500 and TIVO-1) reported very high, differential dropouts between groups, but these were predominantly linked to study endpoints and were not judged to be unexplained imbalances. However, due to inadequate reporting of appropriate ITT approaches or the reporting of inadequate approaches to account for missing data unrelated to study endpoints, all were judged as having an unclear risk of attrition bias. Eleven trials (ASPEN, BERAT, BIONIKK, CheckMate 025, CheckMate 214, COMPARZ, Hutson 2017, JAVELIN RENAL 101,SWITCH, TIVO-3 and VEG105192) reported high or very high attrition by specific reason not related to study endpoints; with such high attrition it is not possible to rule out that some

drop-outs were related to the true value of the outcomes. This was not mitigated by the description of adequate ITT approaches for ten of the trials and, as a result, these trials were judged also as having an unclear risk of attrition bias. The eleventh trial (BERAT) did not report any ITT approach to dealing with missing data and was judged as having a high risk of attrition bias. Finally, one trial (CROSS-J-RCC) reported very high differential attrition between groups and did not provide reasons for dropouts or discontinuations in the second line. This was not mitigated by the description of adequate ITT approaches and the trial was judged as having an unclear risk of attrition bias.

All trials but one reported using ITT analysis approaches: BERAT did not account for missing data following crossover. For the remaining trials, the appropriateness of the ITT approach either could not be fully assessed due to insufficient detail about how missing data were handled or was found to be lacking. In the case of the latter, protocols or statistical analysis plans seem to indicate last observation carried forward (LOCF) and other single imputation approaches to missing dates. As per Cochrane guidance, these approaches are not considered to be appropriate methods of imputation that address bias, as they are 'unlikely to remove the bias that occurs when missingness in the outcome depends on its true value, unless there is no change in the outcome after the last time it was measured'.[112]

Reporting bias

Fifteen trials did not have evidence of reporting bias, as all outcomes listed in trial registries or published protocols were reported on. Two exceptions were the BIONIKK trial, where certain laboratory outcomes listed were not yet reported on, but intentions to do so separately were reported; and for the CABOSUN and TIVO-3 trials, where adverse events were not listed but reported – this was considered a reasonable inclusion and not a source of potential bias.

Nine trials had unclear risk of reporting bias as the publications reported either more or less outcomes than those listed in the trial registry or protocol. In terms of specific outcomes of interest, it was noted that the CLEAR trial is ongoing and may still be measuring the relevant outcomes, though a recent American Society of Clinical Oncology conference abstract[109] provided no additional data on these outcomes. JAVELIN RENAL 101 did not report EQ-5D and FKSI results in the publications, but did provide these data in NICE TA645; however, these are redacted and not available to the EAG. Furthermore, TIVO-1 listed duration of response in its trial registry but did not report this outcome in the publications.

Conflicts of interest

Only two studies were considered to be at unclear risk for conflict of interest: both were not sponsored by pharmaceutical companies, though authors did list the receipt of various funds from pharmaceutical companies.

Authors of all remaining trials reported receiving fees, grants and other monies from pharmaceutical companies, including the company that sponsored the trial; in several cases some authors also declared being employees or holding stock in the sponsoring company. These trials were considered to have a high risk of bias related to conflict of interest.

Other biases

No specific other biases were identified for the parallel trials. Three crossover trials (BERAT, CROSS-J-RCC and SWITCH-II) were identified as having high risk of bias due to carryover effects as no washout period was specified; therefore, post-crossover results should be interpreted with caution. Another crossover trial (SWITCH) did specify a washout period, but it was not clear whether this was of sufficient duration to eliminate all carryover effects. This trial was judged to have unclear bias for this domain. The two remaining crossover trials (ESPN and RECORD-3) were considered to be at low risk of bias due to carryover effects as the washout periods specified were longer than the clearance of the included treatments.

Overall bias

The overall bias of the included trials, assessed by considering the worst-rated of the key domains (parallel RCTs: selection and attrition bias; crossover RCTs: selection, attrition and other bias) as the overall judgment, indicated that none of the trials were at low overall risk of bias. According to this approach, seventeen trials were judged to be at unclear overall risk of bias; all were at unclear risk for the attrition bias domain while four were additionally at unclear risk of selection bias. Eleven trials were judged to be at high overall risk of bias, primarily due to a high risk of attrition bias. Overall attrition in the various arms of trials judged to be at high risk of attrition bias (BERAT and NCT01136733,) ranged from 20% to 94%. Five of the trials at high overall risk of bias did not have a high risk of bias for the attrition domain; instead, overall bias for these trials was driven by a high risk of selection bias, due to dynamic allocation (CABOSUN and SWOG 1500) or considerable baseline imbalances (BIONIKK), or a high risk of bias due to carryover effects in two crossover trials (CROSS-J-RCC and SWITCH II). Two trials had more than one key domain at high risk of bias, with BERAT at high risk of both attrition bias and bias

relating to carryover effect following crossover and NCT01136733 at high risk of both selection and attrition biases.

CheckMate 9ER, the key trial of interest, was judged to have an unclear overall risk of bias because of an unclear risk of attrition bias. Very high, differential overall attrition (44% in the cabozantinib + nivolumab (CABO/NIV) arm and 71% in the sunitinib (SUN) arm) was reported; however, this related to study endpoints with considerable dropouts due to discontinuation (43% CABO/NIV and 69% SUN) and disease progression (27% CABO/NIV and 46% SUN). The reporting of single imputation approaches was not considered an ideal method to deal with missing data unrelated to study outcomes.. Random sequence generation was poorly reported, but pragmatically accepted as presenting low risk of bias due to the use of IxRS for randomisation.

Consequently, results from the NMA are based on underlying evidence with various methodological shortcomings. Most notable of these is very high attrition with inadequate or unclear approaches to handling missing data and demonstrating that missingness is the outcome is not related to its true value. It is highly unlikely that such high attrition would not effectively subvert randomisation as missingness is likely to depend on the true value of the outcome.

3.3.3. Clinical effectiveness results from trials identified in the review

3.3.3.1. Overall survival

1st line

Overall risk

Nine prioritised trials evaluated OS in an overall risk population in the 1st line setting. All trials included a comparison with sunitinib (7 trials) and/or sorafenib (four trials). Two trials compared sunitinib and sorafenib and found no clear difference in OS between the two treatments. Pazopanib was evaluated in two trials, otherwise all interventions (avelumab + axitinib; tivozanib, cabozantinib + nivolumab, pembrolizumab + lenvatinib, and nivolumab + ipilimumab) were evaluated in only one trial. There was no clear difference between pazopanib and either sunitinib or sorafenib. Median OS was highly variable for sunitinib, ranging between 27.4 – 54.3 months. Median OS was between 29.3 – 30 months for sorafenib and was 28.3 for pazopanib.

Cabozantinib + nivolumab and nivolumab + ipilimumab were associated with the largest benefits for OS compared with sunitinib (CheckMate 9ER and CheckMate 214). These were followed by pembrolizumab + lenvatinib in the CLEAR trial, though 95% confidence intervals around the effect reached the line of null effect. It was noted, however, that median PFS in the sunitinib arm of CLEAR was significantly greater than in either CheckMate 9ER or CheckMate 214 (54.3 months compared to 35.5 and 38.4 months). The EAG did not identify a clear reason for the difference between trials. Median OS had not been reached in the latest data cut for avelumab + axitinib, though initial findings suggest that this performed well in comparison to sunitinib. There was no benefit for tivozanib over sorafenib.

Favourable risk

Seven trials reported OS at 1st line for the favourable risk group. All trials involved a comparison with sunitinib (7 trials) and/or sorafenib (2 trials). Median OS was not reached or not reported for most trials, though where available median OS ranged from 43.6 to 68.4 months for sunitinib. The other treatments (nivolumab + ipilimumab, pembrolizumab + lenvatinib, avelumab + axitinib,

cabozantinib + nivolumab, and pazopanib) were each evaluated in only one trial. All relative effects were associated with extremely wide 95% confidence intervals, largely due to the small sample size and the lack of available data at the time of calculation. As a consequence of this and unexplained variation between trials, no treatment was clearly associated with a clinical benefit for OS over its comparator.

Intermediate/poor risk

Eight trials reported OS at 1st line in an intermediate/poor risk population. All trials involved a comparison with sunitinib (8 trials). Sorafenib was only compared with sunitinib (2 trials). All other treatments (nivolumab + ipilimumab, pembrolizumab + lenvatinib, avelumab + axitinib, pazopanib, cabozantinib, and cabozantinib + nivolumab) were each evaluated by only one trial. Median OS ranged between 21.2 – 37.8 months for sunitinib (NR for sorafenib). A clinical benefit was seen for both nivolumab + ipilimumab and cabozantinib + nivolumab in comparison with sunitinib. A benefit was also seen for pembrolizumab + lenvatinib and avelumab + axitinib in comparison with sunitinib, though in both cases the 95% confidence intervals approached the line of null effect. A benefit was seen for cabozantinib in CABOSUN, though this was the trial with the smallest number of participants (n=158) and 95% confidence intervals spanned widely both sides of the line of null effect and median OS was considerably shorter than was reported for other interventions. Median OS for nivolumab + ipilimumab, cabozantinib + nivolumab, pembrolizumab + lenvatinib, and avelumab + axitinib all exceeded 40 months.

2nd line-plus

Seven trials reported OS in the 2nd line setting, all in an overall risk population. Everolimus was evaluated in five trials, sorafenib and axitinib were each evaluated in two trials, and all other treatments (nivolumab, cabozantinib, everolimus + lenvatinib, tivozanib and placebo) were each evaluated in one trial. Median OS following everolimus was fairly consistent across trials, ranging from 15.3 to 16.5 months. Cabozantinib, nivolumab, and everolimus + lenvatinib all outperformed everolimus alone. There was no clear difference between everolimus, sorafenib, axitinib, and tivozanib.

Table 13: OS in prioritised included trials

Trial name	First author	Intervention name	Control name	Risk group	Follow-up time category	N (int)	N (control)	Median OS (95%CI)	HR (95%CI)
1L									
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	Overall	5yr+	550	546	Int: 55.7 (NR); Control: 38.4 (NR)	0.72 (0.62, 0.85)
CLEAR	Motzer (2023)	Pem+lenv	Suni	Overall	4-5yr	355	357	Int: 53.7 (48.7, NE); Control: 54.3 (40.9, NE)	0.79 (0.63, 0.99)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	Overall	4-5yr	60	64	Int: 38.4 (NR); Control: 30.9 (NR)	0.934 (0.588, 1.485)
SWITCH	Eichelberg (2015)	Sora	Suni	Overall	1-2yr	182	183	Int: 30 (NR); Control: 27.4 (NR)	0.99 (0.73, 1.33)
SWITCH II	Retz (2019)	Sora	Pazo	Overall	3-4yr	189	188	Int: NR; Control: NR	1.22 (0.91, 1.65)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	Overall	2-3yr	442	444	Int: NE (42.2, NE); Control: 37.8 (31.4, NE)	0.79 (0.64, 0.97)
COMPARZ	Motzer (2014)	Pazo	Suni	Overall	2-3yr	557	553	Int: 28.3 (26.0, 35.5); Control: 29.1 (25.4, 33.1)	0.92 (0.79, 1.06)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	Overall	3-4yr	323	328	Int: 49.48 (40.31, NE); Control: 35.52 (29.24, 42.25)	0.7 (0.56, 0.87)
TIVO-1	Motzer (2013)	Tivo	Sora	Overall	2-3yr	260	257	Int: 29.3 (NR); Control: 28.8 (NR)	1.245 (0.95, 1.62)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	Fav	5yr+	125	124	Int: 74.1 (NR); Control: 68.4 (NR)	0.94 (0.65, 1.37)
CLEAR	Motzer (2023)	Pem+lenv	Suni	Fav	4-5yr	110	124	Int: Not reached (NR); Control: 59.9 (58.8, NE)	0.94 (0.58, 1.52)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	Fav	4-5yr	12	14	Int: NR; Control: NR	0.35 (0.1, 1.2)
SWITCH	Eichelberg (2015)	Sora	Suni	Fav	1-2yr	71	82	Int: NR; Control: NR	1.24 (0.61, 2.56)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	Fav	2-3yr	94	96	Int: NE (NE, NE); Control: NE (39.8, NE)	0.66 (0.36, 1.22)

COMPARZ	Motzer (2014)	Pazo	Suni	Fav	2-3yr	151	152	Int: 42.5 (37.9, NE); Control: 43.6 (37.1, 47.4)	0.88 (0.63, 1.21)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	Fav	3-4yr	74	72	Int: NE (40.67, NE); Control: 47.61 (43.63, NE)	1.07 (0.63, 1.79)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	Int/poor	5yr+	425	422	Int: 47 (NR); Control: 26.6 (NR)	0.68 (0.58, 0.81)
CLEAR	Motzer (2023)	Pem+lenv	Suni	Int/poor	4-5yr	243	229	Int: 47.9 (40.5, NE); Control: 34.3 (26.3, 54.3)	0.74 (0.57, 0.96)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	Int/poor	4-5yr	45	49	Int: NR; Control: NR	1.2 (0.7, 1.95)
SWITCH	Eichelberg (2015)	Sora	Suni	Int/poor	1-2yr	108	94	Int: NR; Control: NR	0.83 (0.53, 1.31)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	Int/poor	2-3yr	343	347	Int: 42.2 (33.1, NE); Control: 37.8 (29.6, NE)	0.79 (0.64, 0.98)
COMPARZ	Motzer (2014)	Pazo	Suni	Int/poor	2-3yr	389	380	Int: NR; Control: NR	0.891 (0.75, 1.06)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	Int/poor	3-4yr	249	256	Int: 49.5 (34.9, NE); Control: 29.2 (23.7, 36.0)	0.65 (0.51, 0.83)
CABOSUN	Choueiri (2018)	Cabo	Suni	Int/poor	2-3yr	79	78	Int: 26.6 (14.6, NE); Control: 21.2 (16.3, 27.4)	0.8 (0.53, 1.21)
2L+									
AXIS	Motzer (2013)	Axi	Sora	Overall	3-4yr	361	362	Int: 20.1 (16.7, 23.4); Control: 19.2 (17.5, 22.3)	0.969 (0.8, 1.174)
BERAT	Grunwald (2022)	Evero	Axi	Overall	1-2yr	5	5	Int: 15.29 (6.0, NE); Control: 18.64 (5.9, 32.5)	1.12 (0.27, 4.61)
CheckMate 025	Escudier (2022)	Nivo	Evero	Overall	5yr+	410	411	Int: NR; Control: NR	0.74 (0.63, 0.86)
METEOR	Choueiri (2016)	Cabo	Evero	Overall	1-2yr	330	328	Int: 21.4 (18.7, NE); Control: 16.5 (14.7, 18.8)	0.66 (0.53, 0.83)
NCT01136733	Motzer (2015)	Lenv+evero	Evero	Overall	2-3yr	51	50	Int: 25.5 (16.4, NE); Control: 15.4 (11.8, 19.6)	0.51 (0.3, 0.88)
RECORD-1	Motzer (2010)	Evero	PBO	Overall	1-2yr	277	139	Int: 14.8 (NR); Control: 14.4 (NR)	0.87 (0.65, 1.15)

TIVO-3	Rini (2022)	Tivo	Sora	Overall	1-2yr	175	175	Int: NR; Control: NR	0.89 (0.7, 1.14)

Abbreviations: axi, axitinib; cabo, cabozantinib; CI; confidence interval; evero, everolimus; HR, hazard ratio; int, intermediate; ipi, ipilimumab; lenv, lenvatinib; NE, not estimable; nivo, nivolumab; NR, not reported; OS, overall survival; pazo, pazopanib; PBO, placebo; pem, pembrolizumab; sora, sorafenib; suni, sunitinib; tivo, tivozanib

3.3.3.2. Progression-free survival

1st line

Overall risk

Nine trials reported PFS for the overall risk population in the 1st line setting. All trials involved a comparison either with sunitinib or sorafenib. Sunitinib outperformed sorafenib: median PFS ranged across trials as 5.6 – 9.1 months for sorafenib and 8.4 – 10.2 months for sunitinib. Pazopanib was evaluated in two trials, while all other treatments were evaluated in one trial only. Pazopanib outperformed sorafenib but was no different to sunitinib. In order of best performing treatments first, the treatments that performed better than sunitinib were pembrolizumab + lenvatinib, cabozantinib + nivolumab, avelumab + axitinib, and nivolumab + ipilimumab.

Favourable risk

In the favourable risk group, eight trials reported PFS in the 1st line setting. All trials involved a comparison either with sunitinib or sorafenib. Sunitinib outperformed sorafenib: no trials reported median PFS for sorafenib, while two trials reported median PFS for sunitinib as 13.8 – 13.9 months. All other treatments were evaluated in one trial only. Sunitinib outperformed nivolumab + ipilimumab. In order of best performing treatment first, pembrolizumab + lenvatinib, tivozanib, avelumab + axitinib, and cabozantinib + nivolumab outperformed sunitinib. However, in the case of avelumab + axitinib and cabozantinib + nivolumab, 95% confidence intervals crossed the line of null effect, suggesting some meaningful uncertainty in the findings. There was no difference between pazopanib and sunitinib.

Intermediate/poor risk

In the intermediate/poor risk group, nine trials evaluated PFS in the 1st line setting. All trials involved a comparison either with sunitinib or sorafenib. There was no clear difference in PFS between sunitinib and sorafenib. All other treatments were evaluated in one trial only. There was no difference between pazopanib and sunitinib. In order of best performing treatments first, the treatments that performed better than sunitinib or sorafenib were pembrolizumab + lenvatinib, cabozantinib, cabozantinib + nivolumab,

avelumab + axitinib, nivolumab + ipilimumab, and tivozanib. For tivozanib, 95% confidence intervals crossed the line of null effect and there was therefore meaningful uncertainty in this result.

It was noted that while cabozantinib + nivolumab performed similarly to cabozantinib alone in comparison with sunitinib in the intermediate/poor risk group, median PFS was longer for cabozantinib + nivolumab than for cabozantinib alone. There were differences between trials that could reduce the comparability of effects between trials; CABOSUN was noted to be a smaller trial set in the USA only, and with a slightly higher rate of participants with bone metastases. However, given the magnitude of difference in the median PFS between cabozantinib and cabozantinib + nivolumab, the EAG considered it plausible that the addition of nivolumab was associated with an increased benefit over sunitinib than cabozantinib alone. Further evidence may be needed to resolve the extent of this benefit.

2nd line-plus

In the 2nd line setting, eight trials evaluated PFS, all in an overall risk population. The treatments evaluated were everolimus (five trials), cabozantinib (1 trial), everolimus + lenvatinib (1 trial), sorafenib (3 trials) tivozanib (2 trials), nivolumab (1 trial), axitinib (1 trial) and placebo (1 trial). All trials included a comparison with either placebo, everolimus or sorafenib. Median PFS was 1.9 months for placebo, between 3.7 to 5.5 months for everolimus, and was 3.9 to 5.7 for sorafenib. The longest PFS was reported for everolimus + lenvatinib at 14.6 months, though there was considerable uncertainty in this (95% Cis 5.9, 20.1). Cabozantinib, everolimus + lenvatinib and nivolumab each out-performed everolimus alone, though the effect of nivolumab was uncertain due to imprecision. Axitinib was shown to outperform sorafenib, as did tivozanib though with some uncertainty.

Table 14: PFS in prioritised included trials

Trial name	Author (year)	Int. name	Cont. name	Risk group	BICR / IA	PFS assessment method	Follow-up time cat.	N (int)	N (control)	Median PFS (95%CI)	HR (95%CI)
1L											
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	Overall	IA	RECIST, FDA rule	5yr+	550	546	Int: NR; Control: NR	0.86 (0.73, 1.01)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	Overall	BICR	RECIST, FDA rule	3-4yr	323	328	Int: 16.6 (12.8, 19.5); Control: 8.4 (7.0, 9.7)	0.59 (0.49, 0.71)
CLEAR	Motzer (2023)	Pem+lenv	Suni	Overall	ICR (no blinding)	RECIST, FDA rule	4-5yr	355	357	Int: 23.9 (20.8, 27.7); Control: 9.2 (6.0, 11.0)	0.47 (0.38, 0.57)
COMPARZ	Motzer (2013)	Pazo	Suni	Overall	BICR	RECIST, FDA rule	1-2yr	557	553	Int: 8.4 (8.3, 10.9); Control: 9.5 (8.3, 11.1)	1.05 (0.9, 1.22)
COMPARZ	Motzer (2013)	Pazo	Suni	Overall	IA	RECIST, FDA rule	1-2yr	557	553	Int: 10.5 (8.3, 11.1); Control: 10.2 (8.3, 11.1)	1 (0.86, 1.15)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	Overall	IA	RECIST, censoring rules unclear	4-5yr	60	64	Int: 8.7 (5.5, 21.1); Control: 7 (6.1, 12.2)	0.67 (0.42, 1.08)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	Overall	BICR	RECIST, FDA rule	2-3yr	442	444	Int: 13.9 (11.1, 16.6); Control: 8.5 (8.2, 9.7)	0.67 (0.57, 0.79)
SWITCH	Eichelberg (2015)	Sora	Suni	Overall	IA	RECIST, FDA rule	<1yr	182	183	Int: 5.9 (NR); Control: 8.5 (NR)	1.19 (0.93, 1.53)
SWITCH II	Retz (2019)	Sora	Pazo	Overall	IA	RECIST, censoring rules unclear	3-4yr	189	188	Int: 5.6 (4.7, 6.3); Control: 9.3 (7.4, 10.6)	1.51 (1.19, 1.92)

Trial name	Author (year)	Int. name	Cont. name	Risk group	BICR / IA	PFS assessment method	Follow-up time cat.	N (int)	N (control)	Median PFS (95%CI)	HR (95%CI)
TIVO-1	Motzer (2013)	Tivo	Sora	Overall	BICR	RECIST, FDA rule	NR	181	181	Int: 12.7 (NR); Control: 9.1 (NR)	0.76 (0.58, 0.99)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	Fav	IA	RECIST, FDA rule	RECIST, FDA rule	125	124	Int: NR; Control: NR	1.6 (1.13, 2.26)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	Fav	BICR	RECIST, FDA rule	3-4yr	74	72	Int: 21.42 (13.08, 24.71); Control: 13.86 (9.56, 16.66)	0.72 (0.49, 1.05)
CLEAR	Motzer (2023)	Pem+lenv	Suni	Fav	ICR (no blinding)	RECIST, FDA rule	4-5yr	110	124	Int: NR; Control: NR	0.5 (0.35, 0.71)
COMPARZ	Motzer (2013)	Pazo	Suni	Fav	BICR	RECIST, FDA rule	1-2yr	151	152	Int: NR; Control: NR	1.01 (0.74, 1.37)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	Fav	IA	RECIST, censoring rules unclear	4-5yr	12	14	Int: NR; Control: NR	0.245 (0.082, 0.734)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	Fav	BICR	RECIST, FDA rule	2-3yr	94	96	Int: 20.7 (16.6, 26.3); Control: 13.8 (11.1, 23.5)	0.71 (0.49, 1.016)
SWITCH	Eichelberg (2015)	Sora	Suni	Fav	IA	RECIST, FDA rule	<1yr	71	82	Int: NR; Control: NR	1.3 (0.81, 2.09)
TIVO-1	Motzer (2013)	Tivo	Sora	Fav	BICR	RECIST, FDA rule	NR	70	87	Int: NR; Control: NR	0.59 (0.378, 0.921)
CABOSUN	Choueiri (2018)	Cabo	Suni	Int/poor	BICR	RECIST, FDA rule	2-3yr	79	78	Int: 8.6 (6.8, 14.0); Control: 5.3 (3.0, 8.2)	0.48 (0.31, 0.74)

Trial name	Author (year)	Int. name	Cont. name	Risk group	BICR / IA	PFS assessment method	Follow-up time cat.	N (int)	N (control)	Median PFS (95%CI)	HR (95%CI)
CABOSUN	Choueiri (2018)	Cabo	Suni	Int/poor	IA	RECIST, FDA rule	2-3yr	79	78	Int: 8.3 (6.5, 12.4); Control: 5.4 (3.4, 8.2)	0.56 (0.37, 0.83)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	Int/poor	BICR	RECIST, FDA rule	5yr+	425	422	Int: NR; Control: NR	0.73 (0.61, 0.87)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	Int/poor	BICR	RECIST, FDA rule	RECIST, FDA rule	249	256	Int: 15.61 (11.17, 19.15); Control: 7.05 (5.68, 8.90)	0.56 (0.46, 0.69)
CLEAR	Motzer (2023)	Pem+lenv	Suni	Int/poor	ICR (no blinding)	RECIST, FDA rule	4-5yr	243	229	Int: NR; Control: NR	0.43 (0.34, 0.55)
COMPARZ	Motzer (2013)	Pazo	Suni	Int/poor	BICR	RECIST, FDA rule	1-2yr	322	328	Int: NR; Control: NR	0.98 (0.80, 1.19)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	Int/poor	IA	RECIST, censoring rules unclear	4-5yr	45	49	Int: NR; Control: NR	1 (0.62, 1.63)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	Int/poor	BICR	RECIST, FDA rule	2-3yr	343	347	Int: 12.9 (11.1, 16.6); Control: 8.4 (7.9, 10.1)	0.66 (0.55, 0.787)
SWITCH	Eichelberg (2015)	Sora	Suni	Int/poor	IA	RECIST, FDA rule	<1yr	108	94	Int: NR; Control: NR	1.14 (0.77, 1.67)
TIVO-1	Motzer (2013)	Tivo	Sora	Int/poor	BICR	RECIST, FDA rule	NR	190	170	Int: NR; Control: NR	0.821 (0.635, 1.062)
2L+											
AXIS	Motzer (2013)	Axi	Sora	Overall	BICR	RECIST, censoring rules unclear	3-4yr	361	362	Int: 8.3 (6.7, 9.2); Control: 5.7 (4.7, 6.5)	0.66 (0.55, 0.78)

Trial name	Author (year)	Int. name	Cont. name	Risk group	BICR / IA	PFS assessment method	Follow-up time cat.	N (int)	N (control)	Median PFS (95%CI)	HR (95%CI)
BERAT	Grunwald (2022)	Evero	Axi	Overall	IA	RECIST, censoring rules unclear	1-2yr	5	5	Int: 3.7 (2.6, 8.4); Control: 2.2 (1.9, NC)	1 (0.26, 3.85)
CheckMate 025	Escudier (2022)	Nivo	Evero	Overall	IA	RECIST, FDA rule	5yr+	410	411	Int: NR; Control: NR	0.84 (0.72, 0.99)
METEOR	Choueiri (2016)	Cabo	Evero	Overall	BICR	RECIST, FDA rule	<1yr	330	328	Int: 7.4 (6.6, 9.1); Control: 3.9 (3.7, 5.1)	0.51 (0.41, 0.62)
METEOR	Choueiri (2016)	Cabo	Evero	Overall	IA	RECIST, FDA rule	<1yr	330	328	Int: 7.4 (6.6, 9.1); Control: 5.1 (3.9, 5.5)	0.54 (0.44, 0.65)
NCT01136733	Motzer (2015)	Lenv +evero	Evero	Overall	IA	RECIST, censoring rules unclear	1-2yr	51	50	Int: 14.6 (5.9, 20.1); Control: 5.5 (3.5, 7.1)	0.4 (0.24, 0.68)
RECORD-1	Motzer (2010)	Evero	PBO	Overall	BICR	RECIST, FDA rule	1-2yr	277	139	Int: 4.9 (4.0, 5.5); Control: 1.9 (1.8, 1.9)	0.33 (0.25, 0.43)
RECORD-1	Motzer (2010)	Evero	PBO	Overall	IA	RECIST, FDA rule	1-2yr	277	139	Int: 5.5 (4.6, 5.8); Control: 1.9 (1.8, 2.2)	0.32 (0.25, 0.41)
TIVO-3	Atkins (2022)	Tivo	Sora	Overall	IA	RECIST, FDA rule	1-2yr	175	175	Int: NR; Control: NR	0.624 (0.49, 0.79)
TIVO-3	Rini (2020)	Tivo	Sora	Overall	BICR	RECIST, FDA rule	1-2yr	175	175	Int: 5.6 (5.29, 7.33); Control: 3.9 (3.71, 5.55)	0.73 (0.56, 0.94)

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; CI; confidence interval; evero, everolimus; FDA, Food and Drug Administration; HR, hazard ratio; int, intermediate; ipi, ipilimumab; lenv, lenvatinib; NE, not estimable; nivo, nivolumab; NR, not reported; OS, overall survival; pazo, pazopanib; PBO, placebo; pem, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours sora, sorafenib; suni, sunitinib; tivo, tivozanib

3.3.3.3. Response rates

1st line

Overall risk

Nine trials reported response rates in an overall risk population at 1st line. All trials involved either a comparison with sunitinib (9 trials) and/or sorafenib (3 trials). All other treatments (pazopanib, avelumab + axitinib, cabozantinib + nivolumab, pembrolizumab + lenvatinib, and nivolumab + ipilimumab) were evaluated in one trial only.

Response rates for sunitinib ranged between 23.3% and 36.8%. There was a trend for response rates to increase slightly with longer follow-up, with some exceptions. Response rates for sorafenib across trials ranged from 15.6% to 30.2%, with no pattern related to follow-up duration. Two trials compared sunitinib and sorafenib and did not find any clear difference in response rate.

Large effects were reported for (in order of best performing treatments first) pembrolizumab + lenvatinib, cabozantinib + nivolumab, and avelumab + axitinib, all in comparison with sunitinib. A moderate benefit was also reported for nivolumab + ipilimumab in comparison with sunitinib.

Favourable risk

Four trials reported response rate in a favourable risk population in the 1st line. All trials involved a comparison with sunitinib. Response rates for sunitinib ranged between 45.8% to 52%, with no trend over time. In order of the best performing treatments first, large effects were seen for avelumab + axitinib and cabozantinib + nivolumab, and a moderate effect for pembrolizumab + lenvatinib. A lower rate of response was shown following nivolumab + ipilimumab in comparison with sunitinib.

Intermediate/poor risk

Five trials reported response rates in an intermediate/poor risk population in the 1st line. All trials involved a comparison with either sunitinib (5 trials) or sorafenib (1 trial). All other treatments (cabozantinib, cabozantinib and nivolumab, avelumab + axitinib, nivolumab + ipilimumab, and tivozanib) were evaluated in only one trial.

Response rates for sorafenib were variable across trials, and ranged between 9.0% and 28.8%, with no trend over time. Response rates for sorafenib were reported using both BICR and IA in the TIVO-1 trial, with a difference in response depending on the method used: 23.3% using BICR and 30.7% using IA. A difference in response rate between IA and BICR assessment was also shown for the CABOSUN trial (cabozantinib vs. sunitinib). In general, in other population groups, there was a trend across trials for response rates to be slightly higher when assessed using IA than BICR, though the difference was not universal and not always as large.

A very large effect was reported for pembrolizumab + lenvatinib in comparison with sunitinib, and while the 95% confidence intervals around the effect were large, the lower bounds were still greater than any other reported effect. Large effects were also reported for cabozantinib + nivolumab, avelumab + axitinib, cabozantinib and nivolumab + ipilimumab.

2nd line-plus

Seven trials reported response rates in the 2nd line-plus, all in an overall risk population. Treatments evaluated were everolimus (five trials), sorafenib (two trials), axitinib (2 trials), cabozantinib (1 trial), everolimus + lenvatinib (1 trial), tivozanib (1 trial), nivolumab (1 trial) and placebo (1 trial). Response rates for everolimus and axitinib were fairly consistent across trials: response rates for everolimus were low and ranged between 0% and 6%.

The largest effect was reported for everolimus + lenvatinib in comparison with everolimus alone (a response rate of 43.1% vs 6.0%). Large effects were also reported for cabozantinib and nivolumab. Moderate effects were seen for tivozanib and axitinib.

Table 15: Response rates in prioritised included trials

Trial name	Author (date)	Intervention	Control	Follow-up time category	Risk group	Assessor (IA or BICR)	N (int)	N (control)	Prop (int)	Prop (control)	OR (95%CI)
1L											
SWITCH	Eichelberg (2015)	Sora	Suni	<1yr	Overall	IA	182	183	30.22%	27.87%	1.12 (0.71, 1.76)
COMPARZ	Motzer (2013)	Pazo	Suni	1-2yr	Overall	BICR	557	553	30.70%	24.77%	1.35 (1.03, 1.75)
COMPARZ	Motzer (2013)	Pazo	Suni	1-2yr	Overall	IA	557	553	33.39%	28.93%	1.23 (0.95, 1.59)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	2-3yr	Overall	IA	442	444	59.30%	31.80%	3.13 (2.37, 4.12)
SWITCH II	Retz (2019)	Sora	Pazo	3-4yr	Overall	IA	189	188	28.57%	46.28%	0.46 (0.30, 0.71)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	3-4yr	Overall	BICR	323	328	56.04%	28.05%	3.27 (2.36, 4.53)
CLEAR	Motzer (2023)	Pem+lenv	Suni	4-5yr	Overall	BICR	355	357	71.30%	36.70%	4.28 (3.12, 5.86)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	4-5yr	Overall	Unclear	60	64	23.33%	15.63%	1.64 (0.67, 4.05)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	5yr+	Overall	BICR	550	546	39%	32.00%	1.36 (1.06, 1.74)
CLEAR	Grunwald (2021)	Pem+lenv	Suni	2-3yr	Fav	BICR	74	72	68.20%	50.80%	1.97 (1.01, 3.86)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	2-3yr	Fav	IA	94	96	75.50%	45.80%	3.65 (1.97, 6.77)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	3-4yr	Fav	BICR	74	72	67.57%	45.83%	[redacted]
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	5yr+	Fav	BICR	125	124	30.00%	52.00%	0.41 (0.24, 0.69)
CLEAR	Grunwald (2021)	Pem+lenv	Suni	2-3yr	Int/poor	BICR	188	188	72.40%	28.80%	6.51 (4.15, 10.20)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	2-3yr	Int/poor	IA	343	347	55.10%	28.00%	3.16 (2.30, 4.34)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	3-4yr	Int/poor	BICR	249	256	52.61%	23.05%	[redacted]

Trial name	Author (date)	Intervention	Control	Follow-up time category	Risk group	Assessor (IA or BICR)	N (int)	N (control)	Prop (int)	Prop (control)	OR (95%CI)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	5yr+	Int/poor	BICR	425	422	42.00%	27.00%	1.97 (1.47, 2.62)
CABOSUN	Choueiri (2018)	Cabo	Suni	2-3yr	Overall/int/poor	BICR	79	78	20.25%	8.97%	2.58 (1.00, 6.67)
CABOSUN	Choueiri (2018)	Cabo	Suni	2-3yr	Overall/int/poor	IA	79	78	32.91%	11.54%	3.76 (1.63, 8.70)
TIVO-1*	Motzer (2013)	Tivo	Sora	NR	Overall	BICR	260	257	33.10%	23.30%	1.62 (1.10, 2.39)
TIVO-1*	Motzer (2013)	Tivo	Sora	NR	Overall	IA	260	257	35.40%	30.70%	1.23 (0.85, 1.78)
2L+											
METEOR	Choueiri (2016)	Cabo	Evero	<1yr	Overall	BICR	330	328	17.27%	3.35%	6.02 (3.09, 11.71)
METEOR	Choueiri (2016)	Cabo	Evero	<1yr	Overall	IA	330	328	23.64%	4.27%	6.94 (3.84, 12.56)
AXIS	Rini (2011)	Axi	Sora	1-2yr	Overall	BICR	361	362	19.39%	9.39%	2.32 (1.50, 3.60)
NCT01136733	Motzer (2015)	Lenv+evero	Evero	1-2yr	Overall	IA	51	50	43.14%	6.00%	11.89 (3.26, 43.26)
RECORD-1	Motzer (2010)	Evero	Placebo	1-2yr	Overall	BICR	277	139	1.81%	0.00%	5.63 (0.31, 102.6)
TIVO-3	Verzoni (2021)	Tivo	Sora	1-2yr	Overall	IA	175	175	23.43%	11.43%	2.37 (1.32, 4.25)
AXIS	Motzer (2013)	Axi	Sora	3-4yr	Overall	IA	361	362	22.71%	12.43%	2.07 (1.39, 3.08)
CheckMate 025	Motzer (2020)	Nivo	Evero	5yr+	Overall	IA	410	411	22.93%	4.14%	6.89 (4.03, 11.80)
BERAT	Grunwald (2022)	Evero	Axi	NR ('short')	Overall	IA	5	5	0.00%	20.00%	0.27 (0.01, 8.46)

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; BICR, blinded independent central review; CI; confidence interval; evero, everolimus; IA, investigator-assessed; ipi, ipilimumab; lenv, lenvatinib; NE, not estimable; nivo, nivolumab; NR, not reported; OR, odds ratio; pazo, pazopanib; PBO, placebo; pem, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours sora, sorafenib; suni, sunitinib; tivo, tivozanib

* 1L and 2L

3.3.3.4. Duration of response

In total, 9 trials reported the duration of response with treatment, five[106,109,110,113] in the 1st line setting and four[85,97,107,114] in the 2nd line-plus setting.

1st line

In the 1st line population, the comparator in all trials was sunitinib. The median duration of response for sunitinib ranged between 14.5 – 32.0 months for patients at overall risk (5 studies[106,109,110,113]) and was 20.8 months and 9.8 months in those with favourable and poor risk, respectively (1 trial[113]). Duration of response with sunitinib was particularly long for the CheckMate-214 trial compared to the other trials, which did not appear to be explained by the follow-up duration, treatment dose or participant characteristics.

Duration of response was available for avelumab + axitinib in the overall, favourable and intermediate/poor risk groups (1 trial[113]), and cabozantinib + nivolumab (1 trial[110]), pembrolizumab + lenvatinib (1 trial[109]) and NIVO/IPI (1 trial[106]) in the overall risk group. In the overall risk population, and in descending order, median duration of response was not reached for nivolumab + ipilimumab (with a follow-up of over 5 years in CheckMate 214[106]), 26.7 months for pembrolizumab + lenvatinib, 22.08 months for cabozantinib + nivolumab, and 19.4 months for avelumab + axitinib. In the JAVELIN trial,[113] unlike for sunitinib where there was a difference in duration of response between favourable and intermediate/poor risk groups, median duration of response was similar: 22.6 months and 19.3 months for favourable and intermediate/poor risk groups, respectively.

2nd line-plus

In the 2nd line population, all trials reported the duration of response in the overall risk group. Two trials used everolimus[97,107] as the comparator and two trials[85,114] used sorafenib. Median duration of response ranged from 8.5 to 14 months for everolimus and 9 to 10.6 months for sorafenib. A comparison of the two trials using everolimus as a comparator did not satisfactorily resolve the difference in duration of response: while NCT01136733 included a higher proportion of participants at poor risk, it also primarily

included people treated at 2nd line, while more than a quarter of participants in CheckMate 025 (28%) were receiving 3rd line treatment.

Duration of response was available for axitinib (1 trial), lenvatinib + everolimus (1 trial), tivozanib (1 trial) and nivolumab (1 trial). In descending order, median duration of response was 20.3 months for tivozanib, 18.2 months for nivolumab, 13 months for lenvatinib + everolimus, and 11 months for axitinib.

Table 16: Duration of response in prioritised included trials

Trial name	First author	Int. name	Control name	Follow-up time category	N (int)	N (cont)	Risk group	Assessor (IA or BICR)	Intervention median (95%CI)	Control median (95%CI)	HR (95%CI)
1L											
JAVELIN Renal 101	Haanen 2023	Ave+ axi	Suni	2-3yr	260	141	Overall	IA	19.4 (15.2, 22.3)	14.5 (8.8, 17.1)	
CROSS-J-RCC	Tomita (2020)	Suni	Sora	4-5yr	60	64	Overall	Unclear	32.0	14.9	
CheckMate 9ER	Company submission	Cabo +nivo	Suni	3-4yr	181	92	Overall	BICR	22.08 (17.97, 26.02)	16.07 (11.07, 19.35)	
CLEAR	Motzer 2023	Pem+ lenv	Suni	4-5yr	253	131	Overall	BICR	26.7 (22.8, 34.6)	14.7 (9.4, 18.2)	
CheckMate 214	Motzer 2022	Nivo+ipi	Suni	5yr+	550	546	Overall	BICR	Not reached (59.0, NE)	24.8 (19.7, 30.1)	0.49 (0.35, 0.68)
JAVELIN Renal 101	Haanen 2023	Ave+ axi	Suni	2-3yr	71	44	Fav	IA	22.6 (15.2, 31.7)	20.8 (14.5, 24.9)	
JAVELIN Renal 101	Haanen 2023	Ave+ axi	Suni	2-3yr	189	97	Int/poor	IA	19.3 (13.9, 22.1)	9.8 (7.0, 15.3)	
2L+											
AXIS	Rini 2011	Axi	Sora	1-2yr	361	362	Overall	NR	11 (7.4, NE)	10.6 (8.8, 11.5)	
NCT01136733	Motzer 2015	Lenv+ evero	Evero	1-2yr	51	50	Overall	NR	13 (3.7, NE)	8.5 (7.5, 9.4)	

Trial name	First author	Int. name	Control name	Follow-up time category	N (int)	N (cont)	Risk group	Assessor (IA or BICR)	Intervention median (95%CI)	Control median (95%CI)	HR (95%CI)
TIVO-3	Verzoni 2021	Tivo	Sora	1-2yr	175	175	Overall	IA	20.3 (9.8, 29.9)	9 (3.7, 16.6)	
CheckMate 025	Motzer 2020	Nivo	Evero	5yr+	410	411	Overall	NR	18.2 (12.9, 25.8)	14 (8.3, 19.2)	

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; BICR, blinded independent central review; CI; confidence interval; evero, everolimus; HR, hazard ratio; IA, investigator-assessed; ipi, ipilimumab; lenv, lenvatinib; nivo, nivolumab; NR, not reported; pazo, pazopanib; PBO, placebo; pem, pembrolizumab; RECIST, Response Evaluation Criteria in Solid Tumours sora, sorafenib; suni, sunitinib; tivo, tivozanib; yr, year

3.3.3.5. Time to next treatment

The time to next treatment was only available for two trials, CheckMate 9ER and CheckMate 214, with data provided by the manufacturers as part of this appraisal. Data was available in the 1st line setting for an overall risk, favourable risk, and intermediate/poor risk population from CheckMate 9ER and for an intermediate/poor risk population in CheckMate 214. CheckMate 9ER evaluated cabozantinib + nivolumab and CheckMate 214 evaluated nivolumab + ipilimumab, both trials involved a comparison with sunitinib. Median time to next treatment for sunitinib in CheckMate 9ER was [redacted] across all risk groups, whereas this was [redacted] the length of time for sunitinib in the intermediate/poor risk group in Checkmate 214. It is likely this was due to the non-standard definition used, which was the survival time from end of therapy in patients who never received subsequent systemic treatment, or the time from end of therapy until subsequent systemic treatment in patients who received subsequent systematic treatment. Both [redacted] and [redacted] showed a [redacted] time to next treatment than [redacted].

Table 17: Time to next treatment in prioritised included trials

Trial name	First author	Int. name	Con. name	Risk group	Line	Follow-up time category	N (int)	N (con)	Median (int)	95% CI (int)	Median (cont)	95% CI (con)	Prop (int)	Prop (con)
CheckMate 9ER	Company clarification response	Cabo+ nivo	Suni	Overall	1L	3-4yr	263	288						
CheckMate 9ER	Company clarification response	Cabo+ nivo	Suni	Fav	1L	3-4yr	60	57						
CheckMate 9ER	Company clarification response	Cabo+ nivo	Suni	Int / poor	1L	3-4yr	203	231						
CheckMate 214	Stakeholder submission	Nivo+ipi	Suni	Int / poor	1L	5yr+	423	416						

Abbreviations: cabo, cabozantinib; CI; confidence interval; con, control; int, intermediate / intervention; nivo, nivolumab; NE, non-evaluable; NR, not reported; suni, sunitinib; yr, year

3.3.3.6. Time on treatment

Time on treatment was available for eight trials evaluating 1st line treatment in the overall risk group: CLEAR, CROSS-J-RCC, SWITCH, SWITCH II, COMPARZ, CheckMate 9ER, CheckMate 214 and TIVO-1. For CheckMate 9ER, both the duration of treatment and the time to discontinuation was reported, whereas all other studies reported only the duration of treatment. Data are shown in Table 18.

The median duration of treatment was reported for sunitinib in six trials[91,92,100,106,109,110] in the overall risk group, which ranged between 6.7 and 10.1 months and in two trials in the intermediate/poor risk population, which ranged between 6.1 and 7.1 months. Median duration of response in the overall risk population was also available for pazopanib (2 trials[91,101]), cabozantinib + nivolumab (1 trial[110]), nivolumab + ipilimumab (1 trial[106]), pembrolizumab + lenvatinib (1 trial[109]) and tivozanib (1 trial[103]). In descending order, median treatment duration was 21.8 months for cabozantinib + nivolumab, 17 months for pembrolizumab + lenvatinib, 12 months for tivozanib, 7.9 for nivolumab + ipilimumab, 5.7 to 8 months for pazopanib. Treatment duration was often similar between trial arms,

though cabozantinib + nivolumab, pembrolizumab + lenvatinib and tivozanib were each associated with a clear longer treatment duration than their comparator.

Duration of response was only available from one trial in the favourable risk population. This data showed that duration of treatment was longer in both arms (cabozantinib + nivolumab and sunitinib) than in the overall risk population, though the increase for cabozantinib + nivolumab was negligible ([redacted] compared to 21.8 months). Sunitinib was associated with more than 4 months' additional treatment duration in the favourable risk population compared to the overall group.

Duration of treatment was reported in three trials in the intermediate/poor risk group. Treatment duration with sunitinib was similar across all three trials, ranging from 6.1 to 7.1, and was comparable with the overall risk population. Median duration of treatment for cabozantinib and for nivolumab + ipilimumab were no different than their comparator, sunitinib; 8.4 and [redacted], respectively. Treatment duration was substantially longer for cabozantinib + nivolumab than sunitinib, however, at a median of [redacted].

In the 2nd line-plus population, four trials reported duration of treatment, all in an overall risk population: RECORD-1, TIVO-3, AXIS and CheckMate 025. Evidence was available for everolimus (2 trials), nivolumab (1 trial), axitinib (1 trial), tivozanib (1 trial), sorafenib (2 trials), and placebo (1 trial).

In descending order, duration of treatment was a mean of 8.2 months for axitinib, median 6.4 months for tivozanib, a median of 4.6 to a mean of 5.2 months for sorafenib, a median of 4.6 months for everolimus in RECORD-1, and a median of 2.0 months for placebo.

Axitinib and tivozanib each showed a longer treatment duration than their comparator, sorafenib, and everolimus had a longer treatment duration than placebo.

Table 18: Time on treatment in prioritised included trials

Trial name	First author	Year	Int name	Control name	Follow-up time category	N (int)	N (cont)	Risk group	ToT (int)	ToT (control)
1L										
SWITCH	Eichelberg	2015	Sora	Suni	<1yr	177	176	Overall	Mean 8.7 months (SD 8.6)	Mean 10.1 months (SD 10.2)
COMPARZ	Motzer	2013	Pazo	Suni	1-2yr	557	553	Overall	Median 8 (range 0, 38)	Median 7.6 range 0, 38)
SWITCH II	Retz	2019	Sora	Pazo	3-4yr	189	188	Overall	Median 2.1 (range 0.3, 21.4)	Median 5.7 (range 0.3, 43.3)
CheckMate 9ER	Company submission	2023	Cabo+nivo	Suni	3-4yr	323	328	Overall	Median 21.8 (IQR 8.8, 34.0)	Median 8.9 (IQR 2.9, 20.7)
CheckMate 9ER	Company submission	2023	Cabo+nivo	Suni	3-4yr	323	328	Overall	[redacted]	[redacted]
CROSS-J-RCC	Tomita	2020	Suni	Sora	4-5yr	60	64	Overall	Median 6.7 (95%CI NR);	Median 5.9 (95%CI NR);
CheckMate 214	Motzer	2022	Nivo+ipi	Suni	5yr+	550	546	Overall	Median 7.9 (IQR 2.1, 21.8)	Median 7.8 (IQR 3.5, 19.6)
CLEAR	Motzer	2023	Pem+lenv	Suni	NR	355	357	Overall	Median 17 (95%CI 9.4, 25.4)	Median 7.8 (95%CI 3.7, 17.8)
TIVO-1	Motzer	2013	Tivo	Sora	NR	259	257	Overall	Median 12 (95%CI NR);	Median 9.5 (95%CI NR)
CheckMate 9ER	Company submission	2023	Cabo+nivo	Suni	3-4yr	74	71	Fav	[redacted]	[redacted]

Trial name	First author	Year	Int name	Control name	Follow-up time category	N (int)	N (cont)	Risk group	ToT (int)	ToT (control)
CABOSUN	Choueiri	2018	Cabo	Suni	2-3yr	78	72	Int/poor	Median 8.39 (95%CI 5.72, 8.39)	Median 7.09 (95%CI 5.09, 6.68)
CheckMate 9ER	Company submission	2023	Cabo+nivo	Suni	3-4yr	246	249	Int/poor	[redacted]	[redacted]
CheckMate 214	Stakeholder submission	2023	Nivo+ipi	Suni	5yr+	423	416	Int/poor	[redacted]	[redacted]
2L+										
RECORD-1	Motzer	2010	Evero	Placebo	1-2yr	277	139	Overall	Median 4.64 (95%CI NR);, range 0.62, 4.96)	Median 1.97 (95%CI NR); range 0.69, 6.4)
TIVO-3	Rini	2020	Tivo	Sora	1-2yr	175	175	Overall	Median 6.48 (95%CI NR); IQR 3.7, 14.0)	Median 4.64 (95%CI NR); IQR 2.3, 7.7)
AXIS	Motzer	2013	Axi	Sora	3-4yr	361	362	Overall	Mean 8.2 (SD NR, range <0.1, 33.4)	Mean 5.2 (SD NR, range 0.2, 34.1)

Abbreviations: axi, axitinib; cabo, cabozantinib; evero, everolimus; ipi, ipilimumab; IQR, interquartile range; lenv, lenvatinib; nivo, nivolumab; NR, not reported; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib; ToT, time on treatment; yr, year

Note: *Time to discontinuation

3.3.3.7. Adverse events of treatment

Discontinuation due to adverse events

No studies reported separate adverse event rate data in population subgroups, and so all evidence was reported in an overall risk group or, in the case of one trial in the 1st line setting, in an intermediate/poor risk population that was the entire the trial sample.

1st line

In the 1st line setting, nine studies reported the rate of discontinuation due to adverse events in an overall risk population. All trials involved a comparison with sunitinib (7 trials) and/or sorafenib (4 trials). Pazopanib was evaluated in two trials, all other interventions (tivozanib, pembrolizumab + lenvatinib, nivolumab + ipilimumab, cabozantinib + nivolumab, and avelumab + axitinib) were evaluated in only one trial.

The rate of discontinuation due to AEs ranged between 11.5% to 28.4% for sunitinib and 7.0% to 32.3% for sorafenib, with no clear relationship with the length of follow-up. Avelumab + axitinib, cabozantinib + nivolumab, nivolumab + ipilimumab, and pembrolizumab + lenvatinib all had a higher rate of discontinuation due to adverse events than sunitinib. Rates of discontinuation were particularly high for avelumab + axitinib, cabozantinib + nivolumab, pembrolizumab + lenvatinib and nivolumab + ipilimumab, where the rate of discontinuation exceeded 30% of the trial arm. Rates of discontinuation for tivozanib were comparable with sunitinib, while rates of discontinuation for pazopanib were comparable with sunitinib and lower than sorafenib.

One trial reported discontinuation due to adverse events in an intermediate/poor risk population. The rate of discontinuation was similar for cabozantinib and sunitinib.

2nd line-plus

Seven trials reported the rate of discontinuation due to adverse events in the 2nd line-plus setting. Of these, five trials evaluated everolimus, two trials evaluated sorafenib, two trials evaluated axitinib, and the remaining treatments (cabozantinib, everolimus + lenvatinib, tivozanib, and nivolumab) were each evaluated in one trial. Rates of discontinuation due to adverse events ranged between 0% and 16.1% for everolimus, 12.4% to 29.7% for sorafenib, and 0% to 7.5% for axitinib. Rates of discontinuation were generally lower than in the 1st line setting, and relative effects were therefore imprecise. There was a trend for a higher rate of discontinuation following everolimus + lenvatinib than everolimus alone, otherwise rates of discontinuation were similar between everolimus and cabozantinib, nivolumab, and axitinib. With the exception of TIVO-1, where rates of discontinuation appeared higher than other trials, rates of discontinuation were generally less than 15% of the trial arm.

Table 19: Discontinuation due to adverse events in prioritised included trials

Trial name	Author (year)	Int name	Control name	Follow-up time category	N (int)	N (cont)	Risk group	% (int)	% (control)	OR (95%CI)
1L										
SWITCH	Eichelberg (2015)	Sora	Suni	<1yr	182	183	Overall	18.13%	28.42%	0.56 (0.34, 0.92)
CLEAR	Motzer (2021)	Pem+lenv	Suni	1-2yr	355	357	Overall	16.90%	11.48%	1.57 (1.02, 2.40)
COMPARZ	Motzer (2013)	Pazo	Suni	1-2yr	557	553	Overall	24.24%	20.25%	1.26 (0.95, 1.67)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	2-3yr	442	444	Overall	31.22%	15.99%	2.38 (1.73, 3.30)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	2-3yr	323	328	Overall	36.84%	20.43%	2.27 (1.60, 3.23)
SWITCH II	Retz (2019)	Sora	Pazo	3-4yr	189	188	Overall	32.28%	23.40%	1.56 (0.99, 2.46)
SWOG 1500	Pal (2021)	Cabo	Suni	3-4yr	44	46	Overall	22.73%	23.91%	0.94 (0.35, 2.49)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	4-5yr	60	64	Overall	21.67%	18.75%	1.20 (0.50, 2.88)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	5yr+	550	546	Overall	34.18%	19.41%	2.16 (1.64, 2.84)
TIVO-1	Motzer (2013)	Tivo	Sora	NR	260	257	Overall	7.31%	7.00%	1.05 (0.54, 2.04)
CABOSUN	Choueiri (2018)	Cabo	Suni	NR	79	78	Int/poor	20.25%	20.51%	0.98 (0.45, 2.14)
2L+										
METEOR	Choueiri (2016)	Cabo	Evero	1-2yr	330	328	Overall	12.12%	10.37%	1.19 (0.73, 1.94)
NCT01136733	Motzer (2015)	Lenv+evero	Evero	1-2yr	51	50	Overall	17.65%	10.00%	1.93 (0.60, 6.22)

Trial name	Author (year)	Int name	Control name	Follow-up time category	N (int)	N (cont)	Risk group	% (int)	% (control)	OR (95%CI)
RECORD-1	Motzer (2010)	Evero	Placebo	1-2yr	277	139	Overall	13.00%	1.44%	10.23 (2.43, 43.16)
TIVO-3	Zengin (2020)	Tivo	Sora	1-2yr	175	175	Overall	20.57%	29.71%	0.61 (0.38, 1.00)
AXIS	Motzer (2013)	Axi	Sora	3-4yr	361	362	Overall	7.48%	12.43%	0.57 (0.34, 0.94)
CheckMate 025	Motzer (2020)	Nivo	Evero	5yr+	410	411	Overall	13.90%	16.06%	0.84 (0.57, 1.24)
BERAT	Grunwald (2022)	Evero	Axi	NR ('short')	5	5	Overall	0.00%	0.00%	-

Abbreviations axi, axitinib; cabo, cabozantinib; con, control; evero, everolimus; int, intervention; ipi, ipilimumab; IQR, interquartile range; lenv, lenvatinib; nivo, nivolumab; NR, not reported; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib; ToT, time on treatment; yr, year

Note: *Time to discontinuation

Grade 3+ adverse events

1st line

Nine trials reported the rate of Grade 3+ AEs in an overall risk population in the 1st line setting. All trials involved a comparison with sunitinib (7 trials) and/or sorafenib (4 trials). Pazopanib was evaluated in 2 trials, all other treatments (pembrolizumab + lenvatinib, avelumab + axitinib, cabozantinib + nivolumab, nivolumab + ipilimumab, and tivozanib) were each evaluated in one trial. All interventions were associated with high rates of grade 3+ events. Rates ranged between 64.5% to 83.3% for sunitinib, 57.1% to 75.0% for sorafenib, and 62.2% to 74.0% for pazopanib. Rates for all other treatments exceeded 60% of the trial arm and were particularly high (exceeding three quarters of the sample) following cabozantinib + nivolumab, pembrolizumab + lenvatinib, and avelumab + axitinib. The risk of grade 3+ AEs was lower for tivozanib than sorafenib, and for nivolumab + ipilimumab than sunitinib, each evaluated in one trial.

In an intermediate/poor risk population, there was a small increased risk of grade 3+ AEs following cabozantinib in comparison with sunitinib, but the difference was not statistically significant. In general, rates of grade 3+ events were comparable with those reported in the 1st line setting.

2nd line-plus

Four trials reported rates of grade 3+ adverse events in the 2nd line setting, all in an overall risk population. All trials involved a comparison with everolimus, while the other treatments (cabozantinib, everolimus + lenvatinib, nivolumab, and axitinib) were all evaluated in one trial. There was wide variation in the rates of grade 3+ adverse events across trials, with rates for everolimus ranging between 36.8% (in the trial with the longest follow-up) to 58.8%. The highest risk was reported for axitinib, where 80% of participants experienced a Grade 3+ AE. Risk was also high for cabozantinib and everolimus + lenvatinib, where more than 70% of participants experienced a Grade 3+ event. Axitinib, cabozantinib, and everolimus + lenvatinib were each associated with an increased risk of Grade 3+ events relative to everolimus, while nivolumab had a lower risk of events relative to everolimus.

Table 20: Grade 3+ adverse events in prioritised included trials

Trial name	Author (year)	Intervention name	Control name	Follow-up time category	N (int)	N (con)	Risk group	% (int)	% (con)	OR (95% CI)
1L										
SWITCH	Eichelberg (2015)	Sora	Suni	<1yr	182	183	Overall	64.29 %	64.48 %	0.99 (0.65, 1.52)
CLEAR	Motzer (2021)	Pem+lenv	Suni	1-2yr	355	357	Overall	81.69 %	68.35 %	2.07 (1.46, 2.93)
COMPARZ	Motzer (2013)	Pazo	Suni	1-2yr	557	553	Overall	73.97 %	72.69 %	1.07 (0.82, 1.39)
JAVELIN Renal 101	Haanen (2023)	Ave+axi	Suni	2-3yr	442	444	Overall	79.64 %	76.58 %	1.20 (0.87, 1.65)
SWITCH II	Retz (2019)	Sora	Pazo	3-4yr	189	188	Overall	57.14 %	62.23 %	0.81 (0.54, 1.22)

Trial name	Author (year)	Intervention name	Control name	Follow-up time category	N (int)	N (con)	Risk group	% (int)	% (con)	OR (95% CI)
SWOG 1500	Pal (2021)	Cabo	Suni	3-4yr	44	46	Overall	72.73 %	67.39 %	1.29 (0.52, 3.19)
CheckMate 9ER	Company submission (2023)	Cabo+nivo	Suni	3-4yr	323	328	Overall	[redacted]	[redacted]	1.70 (1.16, 2.49)
CROSS-J-RCC	Tomita (2020)	Suni	Sora	4-5yr	60	64	Overall	83.33 %	75.00 %	1.67 (0.69, 4.03)
CheckMate 214	Motzer (2022)	Nivo+ipi	Suni	5yr+	550	546	Overall	67.82 %	76.23 %	0.66 (0.50, 0.86)
TIVO-1	Motzer (2013)	Tivo	Sora	NR	260	257	Overall	61.15 %	69.65 %	0.69 (0.48, 0.99)
CABOSUN	Choueiri (2018)	Cabo	Suni	NR	79	78	Int/poor	67.09 %	60.26 %	1.34 (0.70, 2.58)
2L+										
METEOR	Choueiri (2016)	Cabo	Evero	1-2yr	330	328	Overall	71.21 %	58.84 %	1.73 (1.25, 2.39)
NCT01136733	Motzer (2015)	Lenv+evero	Evero	1-2yr	51	50	Overall	70.59 %	50.00 %	2.40 (1.06, 5.44)
CheckMate 025	Motzer (2020)	Nivo	Evero	5yr+	410	411	Overall	21.40 %	36.80 %	0.47 (0.34, 0.64)
BERAT	Grunwald (2022)	Evero	Axi	NR ('short')	5	5	Overall	40.00 %	80.00 %	0.17 (0.01, 2.82)

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; con, control; evero, everolimus; int, intervention; ipi, ipilimumab; lenv, lenvatinib; nivo, nivolumab; pazo, pazopanib; OR, odds ratio; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib; yr, year

3.3.3.8. Health-related quality of life

1st line

Overall risk

Six trials reported HRQoL in an overall risk population in the 1st line: all six trials reported a disease specific HRQoL (FKSI total [4 trials] and FKSI DRS [2 trials]) and four trials reported generic HRQoL (EQ-5D index [3 trials] and EQ-5D VAS [1 trial]). This section focusses condition specific analysis on the FKSI total as the more comprehensive and frequently reported scale. All trials involved a comparison with sunitinib (four trials) or sorafenib (two trials). One trial was a mix of 1st and 2nd line (TIVO-1).

Baseline FKSI total scores were reported to be between 58.4 – 60.1 (reported in 2 trials; CheckMate 9ER and CheckMate 214) and baseline FKSI DRS scores were 29.2 – 31.3 [CLEAR and TIVO-1]. Baseline EQ-5D scores ranged between 0.73 – 0.83 (CheckMate 9ER, CLEAR, TIVO-1). None of the trials reported meaningful differences in HRQoL between treatment arms according to established MID thresholds.[115-118] Four trials reported mean change in HRQoL in each arm (CLEAR, SWITCH II, CheckMate 214 and TIVO-1), which showed that pembrolizumab + lenvatinib, sunitinib, sorafenib and pazopanib were all associated with meaningful reductions in disease-specific HRQoL over time, whereas there was no change for nivolumab and ipilimumab. There were reductions in generic HRQoL following pembrolizumab + lenvatinib, sunitinib, tivozanib and sorafenib, but these were not greater than the threshold for a minimally important difference.

Favourable risk

Two trials reported HRQoL in a favourable risk population in the 1st line: one trial reported both disease-specific and generic HRQoL (FKSI-DRS and EQ-5D index) and one trial reported only disease-specific HRQoL (FKSI total). Neither trial reported baseline HRQoL. The CLEAR trial reported a bigger reduction in FKSI-DRS scores within the year following treatment with pembrolizumab + lenvatinib than sunitinib, and this approached the threshold for a minimally important difference. Both arms experienced meaningful reductions in both disease-specific and generic HRQoL during this time, which passed or approached the threshold for a minimally

important difference. Arm-specific changes in HRQoL were not reported for C CheckMate 9ER, but there was no meaningful difference in FKSI total scores between cabozantinib + nivolumab and sunitinib.

Intermediate/poor risk

Three trials reported HRQoL in an intermediate/poor risk population in the 1st line: three trials reported disease-specific HRQoL (FKSI total [2 trials] and FKSI-DRS [1 trial]) and two trials reported generic HRQoL (EQ-5D index [1 trial] and EQ-5D VAS [1 trial]). All trials involved a comparison with sunitinib. Treatment with sunitinib was followed by meaningful reductions in HRQoL [2 trials]. Pembrolizumab + lenvatinib was associated with a smaller reduction in disease-specific and generic HRQoL [1 trial], while there was no meaningful change in disease-specific HRQoL following nivolumab and ipilimumab. Cabozantinib + nivolumab showed a meaningful benefit for HRQoL over sunitinib, but baseline scores and the change in HRQoL in each arm was not provided. Numerical benefits were also shown for nivolumab + ipilimumab and pembrolizumab + lenvatinib as compared to sunitinib.

2nd line-plus

Four trials reported HRQoL in the 2nd line-plus, all in an overall risk population: four trials reported disease-specific HRQoL (FKSI total [3 trials] and FKSI-DRS 9 [1 trial]). Three trials involved a comparison with everolimus (vs. cabozantinib, sorafenib and nivolumab) and one trial was a comparison with sorafenib (vs axitinib). HRQoL increased in both arms of the BERAT trial (everolimus vs axitinib), but otherwise HRQoL in the trials remained the same or decreased following treatment. There was a difference in disease-specific HRQoL between nivolumab and everolimus, with higher HRQoL at follow up for those receiving nivolumab, but arm-specific change in HRQoL was not reported, and there was no difference in generic HRQoL between arms. There was no difference in disease-specific HRQoL between cabozantinib and everolimus.

Table 21: HRQoL data in prioritised included trials

Trial name	First author	Int name	Con name	Risk gp	Definition of event and censor variables	Measure	Follow-up time category	N (int)	N (con)	BL (int)	BL (con)	Outcome (int)	Outcome (con)	Mean diff (95%CI)
1L														

Trial name	First author	Int name	Con name	Risk gp	Definition of event and censor variables	Measure	Follow-up time category	N (int)	N (con)	BL (int)	BL (con)	Outcome (int)	Outcome (con)	Mean diff (95%CI)
CLEAR	Motzer (2022)	Pem + lenv	Suni	All	Disease specific HRQoL	FKSI-DRS. Mean change, LS mean difference	<1yr	355	357	31.28 (4.41)	30.89 (4.90)	Mean: -1.75 (SE 0.59)	Mean: -2.19 (SE 0.66)	0.44 (-1.11, 2.00)
COMPARZ	Motzer (2013)	Pazo	Suni	All	Disease specific HRQoL	FKSI total score. Difference in mean change score intervention vs control	1-2yr	377	408	NR	NR	NR	NR	1.41 (NR)
CheckMate 9ER	Cella (2022)	Cabo + Nivo	Suni	All	Disease specific HRQoL	FKSI total, LS mean change score. HR is time to deterioration	1-2yr	323	328	58.74 (10.57)	58.39 (9.92)	NR	NR	2.38 (1.20, 3.56)
SWITCH II	Retz (2019)	Sora	Pazo	All	Disease specific HRQoL	FKSI-10	3-4yr	183	183	NR	NR	Mean: -3.1 (SD NR)	Mean: -3.7 (SD NR)	NR
CheckMate 214	Motzer (2022)	Nivo + Ipi	Suni	All	Disease specific HRQoL	FKSI-19 LS mean change	5yr+	550	546	60.1	59.1	Mean: 0.36 (SD NR)	Mean: -1.51 (SD NR)	1.87 (0.95, 2.79)
CLEAR	Motzer (2022)	Pem + lenv	Suni	All	Generic HRQoL	EQ5D-Index, Mean change, LS mean difference	<1yr	355	357	0.83 (0.19)	0.81 (0.22)	Mean: -4 (SE 0.9)	Mean: -6 (SE 1.1)	2 (0, 5)
CheckMate 9ER	Cella (2022)	Cabo	Suni	All	Generic HRQoL	EQ-5D-3L UK index score, LS mean change score. HR is the time to deterioration	1-2yr	323	328	0.78 (0.25)	0.73 (0.29)	NR	NR	0.04 (0.01, 0.07)
CheckMate 214	Cella (2020)	Nivo + ipi	Suni	All	Generic HRQoL	EQ-5D VAS LS mean using MMRM	5yr+	550	546	NR	NR	NR	NR	2.4 (0.4, 4.5)
TIVO-1	Motzer (2013)	Tivo	Sora	All	Disease specific HRQoL	FKSI-DRS LS mean change from baseline	NR	256	250	29.16 (4.77)	29.35 (5.10)	Mean: -0.94 (SE 0.33)	Mean: -0.93 (SE 0.34)	NR
TIVO-1	Motzer (2013)	Tivo	Sora	All	Generic HRQoL	EQ-5D. This is a LS mean change score from baseline	NR	256	250	0.73 (0.25)	0.73 (0.26)	Mean: -0.05 (SD 0.02)	Mean: -0.06 (SD 0.02)	NR
CLEAR	Motzer (2022)	Pem + lenv	Suni	Fav	Disease specific HRQoL	FKSI-DRS. Mean change, LS mean difference	<1yr	110	124	NR	NR	Mean: -4.67 (SE 0.96)	Mean: -3.69 (SE 0.98)	-0.97 (-3.58, 1.61)
CheckMate 9ER	Cella (2023)	Cabo + nivo	Suni	Fav	Disease specific HRQoL	FKSI total, LS mean change score	1-2yr	74	72	NR	NR	NR	NR	-0.44 (-2.63, 1.75)
CLEAR	Motzer (2022)	Pem + lenv	Suni	Fav	Generic HRQoL	EQ5D-Index, Mean change, LS mean difference	<1yr	110	124	NR	NR	Mean: -8 (SE 1.4)	Mean: -6 (SE 1.5)	-2 (-6, 2)

Trial name	First author	Int name	Con name	Risk gp	Definition of event and censor variables	Measure	Follow-up time category	N (int)	N (con)	BL (int)	BL (con)	Outcome (int)	Outcome (con)	Mean diff (95%CI)
CLEAR	Motzer (2022)	Pem + lenv	Suni	Int/poor	Disease specific HRQoL	FKSI-DRS. Mean change, LS mean difference	<1yr	243	229	NR	NR	Mean: -0.72 (SE 0.86)	Mean: -1.42 (SE 0.96)	0.67 (-1.25, 2.58)
CheckMate 9ER	Cella (2023)	Cabo + nivo	Suni	Int/poor	Disease specific HRQoL	FKSI total, LS mean change score. HR is time to deterioration	1-2yr	249	256	NR	NR	NR	NR	3.33 (1.96, 4.70)
CheckMate 214	Motzer (2022)	Nivo + ipi	Suni	Int/poor	Disease specific HRQoL	FKSI-19 LS mean change	5yr+	425	422	NR	NR	Mean: 0.9 (SD NR)	Mean: -1.75 (SD NR)	2.65 (1.60, 3.70)
CLEAR	Motzer (2022)	Pem + lenv	Suni	Int/poor	Generic HRQoL	EQ5D-Index, Mean change, LS mean difference	<1yr	243	229	NR	NR	Mean: -3 (SE 1.5)	Mean: -7 (SE 1.7)	5 (1, 8)
CheckMate 214	Cella (2020)	Nivo + ipi	Suni	Int/poor	Generic HRQoL	EQ-5D VAS LS mean using MMRM	5yr+	425	422	NR	NR	NR	NR	3.3 (1.0, 5.6)
2L+														
METEOR	Cella (2018)	Cabo	Evero	All	Disease specific HRQoL	FKSI-19 LS mean change	<1yr	324	313	NR	NR	Mean: -3.483 (SD NR)	Mean: -2.214 (SD NR)	-1.269 (-1.864, -0.675)
AXIS	Motzer (2013)	Axi	Sora	All	Disease specific HRQoL	FKSI-15	1-2yr	NR	NR	43.2 (8.4)	43.3 (8.2	Mean: 38.9 (SD 9.5)	Mean: 39.1 (SD 8.9)	NR
CheckMate 025	Cella (2016)	Nivo	Evero	All	Disease specific HRQoL	FKSI-DRS mean change	1-2yr	361	343	30.2 (4.4)	30.8 (4.8)	NR	NR	1.6 (1.4, 1.9)
BERAT	Grunwald (2022)	Evero	Axi	All	Disease specific HRQoL	FKSI-10		2	1	16.25 (SD 5.0)	19.7 (SD 2.89)	Mean: 22 (SD 1.41)	Mean: 15 (SD NR)	NR
METEOR	Cella (2018)	Cabo	Evero	All	Generic HRQoL	EQ-5D Index LS mean change	<1yr	323	314	NR	NR	Mean: -0.02 (SD NR)	Mean: -0.02 (SD NR)	-0.002 (-0.018, 0.014)
CheckMate 025	Cella (2016)	Nivo	Evero	All	Generic HRQoL	EQ-5D mean change	1-2yr	361	344	0.78 (0.24)	0.78 (0.21)	NR	NR	0.04 (0.02, 0.07)
AXIS	Cella (2013)	Axi	Sora	All	Generic HRQoL	EQ-5D estimated using repeated measures analysis adjusting for time	NR	NR	NR	NR	NR	Mean: 0.71 (SD NR)	Mean: 0.69 (SD NR)	NR

Abbreviations: axi, axitinib; BL, baseline; cabo, cabozantinib; con, control; evero, everolimus; HRQoL, health-related quality of life; int, intervention; ipi, ipilimumab; IQR, interquartile range; lenv, lenvatinib; nivo, nivolumab; NR, not reported; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib;

3.4. Description and critique of the evidence presented by the company

The company submission for cabozantinib with nivolumab comprised a main submission, an appendix and a subsequent submission with updated efficacy data from CheckMate 9ER. The company also conducted a SLR to identify evidence relevant to the evaluation of cabozantinib with nivolumab. The company reported the synthesis of the identified evidence in a separate report, the findings of which we do not summarise in detail but contrast with our own network meta-analyses in Section 3.7.6. The EAG requested IPD from the company to enable the network meta-analysis and survival analysis to be run as robustly as possible, but this was not received.

3.4.1. Company's definition of the decision problem

The company's approach to the decision problem is presented in Table 22. The EAG broadly agreed with most decisions taken by the company, but disagreed on the full range of appropriate comparators, the relevance of time to next treatment, and the importance of risk group-specific analyses.

Table 22: Decision problem submitted by the company

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG response
Population	Patients with untreated advanced or metastatic renal cell carcinoma	Patients with untreated advanced or metastatic renal cell carcinoma	NA	The EAG agrees the scope has been fulfilled.
Intervention	Cabo+nivo as a 1L therapy in untreated advanced or metastatic renal cell carcinoma.	Cabo+nivo as a 1L therapy in untreated advanced or metastatic renal cell carcinoma.	NA	The EAG agrees the scope has been fulfilled.
Comparator(s)	• Pazo • Tivo • Suni • Cabo (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivo+ipi (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Pem+lenv (only for intermediate- or poor-risk disease as defined in the IMDC criteria)	• Pazo • Suni • Cabo (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivo+ipi (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Pem+lenv (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Ave+axi	Although currently in the CDF, ave+axi is available to an all-risk aRCC NHS England population. Significantly, ave+axi has been in the CDF for over four years now, an unusual length of time for the CDF. Additionally, as highlighted by a recent ABPI report, the majority of therapies (78%) exit the CDF into routine commissioning suggesting that ave+axi is also expected to enter routine commissioning. Therefore, ave+axi should be considered as a relevant comparator by NICE and is discussed as such in our submission. Tivo is not included as a comparator in this submission as the NMA that was conducted to support Ipsen HTA submissions for other countries determined tivo was not widely used in practice. There are data	The EAG disagrees that ave+axi is a relevant comparator for this appraisal. This is because it is not expected that axi with ave will exit managed access by the time the Committee discusses this specific access decision, as is consistent with the standard NICE position. While the EAG identified and synthesised clinical evidence relating to this drug combination, it stresses that this is for validation only and not on the basis of a comparison with routinely commissioned treatment. The EAG also disagrees that tivo should be excluded. While it could not readily be included in evidence networks for OS, it nevertheless is an important drug to be considered in this analysis. This was discussed in response to clarification question A1, where the company cited

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG response
	• Active surveillance		available to link and create a network. However, tivo has been assessed as an equivalent treatment to suni and pazo in previous NICE submissions. Active surveillance is not included in this submission; as discussed in the scoping call on 16th January 2023, active surveillance is usually used in 1L favourable risk patients and involves a wait-period before therapy is administered. Therefore, it is not relevant to this submission.	market share data to justify its exclusion. The EAG did not agree that this was an appropriate rationale. The UK RWE sourced by the EAG indicated tivo and cabo have a similar market share at 1L. Finally, the EAG agrees that active surveillance is not a relevant comparator in this appraisal.
Outcomes	• Overall survival • PFS • Response rates • DoR • Time on treatment/Time to next treatment • Adverse effects of treatment • HRQoL	• Overall survival • PFS • Response rates • DoR • Time on treatment • Adverse effects of treatment • HRQoL	Time to next treatment is not presented in this submission as it is not of relevance to the decision problem.	The EAG disagrees that time to next treatment is irrelevant. The receipt of subsequent lines of treatment is an important clinical outcome. This endpoint was considered relevant by the clinicians at the scoping workshop.
Groups to be considered	Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria	Patients with untreated advanced or metastatic renal cell carcinoma	Cabo+nivo is indicated for an all-risk population of 'patients with untreated advanced or metastatic renal cell carcinoma' and should be appraised in line with this indication [69,70]. The phase 3 CheckMate 9ER trial of cabo+nivo compared to suni demonstrated consistent clinical	The EAG disagrees with this assertion. Risk group is known to be an important prognostic factor as well as an important effect modifier across a range of RCC treatments. As a result, subgroup-specific evidence is highly probative. We also note that risk-based subgroups were

	Final scope issued by NICE	Decision problem addressed in the company submission	Company rationale if different from the final NICE scope	EAG response
			benefits across all patients, irrespective of prognostic risk profile.	considered in the previous MTA.[38]

Source: Company submission document A, table 1

Key: ABPI, The Association of the British Pharmaceutical Industry; aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; DoR, duration of response; HRQoL, Health Related Quality of Life; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MTA, multiple technology assessment; RCC, renal cell carcinoma; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFS, Progression Free Survival; TTD, time to discontinuation

3.4.2. Literature review methods used by the company

Ipsen carried out its original SLR in 2017, which they subsequently updated in 2018. A new search was then designed and conducted on 5th June 2020, and further updated on 29th October 2021. The latest update of the search—presented in the CS—was performed on 2nd December 2022.

Ipsen's review was developed to support indirect treatment comparisons against cabozantinib + nivolumab. Because the review was developed for a range of markets, including the UK, their analysis ultimately focused on the following comparators:

- Nivolumab + Ipilimumab
- Avelumab + axitinib
- Pembrolizumab + axitinib
- Pembrolizumab + lenvatinib
- Cabozantinib monotherapy
- Sunitinib monotherapy
- Pazopanib monotherapy

However, a wider range of comparators than the above list was included in the search. The interventions searched for by Ipsen broadly overlapped with the interventions included in the PenTAG search, except that Ipsen did not include everolimus (which was included in the PenTAG search), while they did include temsirolimus, bevacizumab, interferon-alpha, and sorafenib (which were not included in the PenTAG search). Tivozanib was included within the company search terms but was then not considered within the evidence reviews as the company considered that it was not widely used.

Ipsen carried out literature searches for clinical evidence in OVID MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations), Embase, the Cochrane Central Register of Controlled Trials via the Cochrane library, and the Health Technology Appraisal (HTA) Database (Ipsen Submission, Appendix C). They also performed a rapid appraisal search in the Cochrane library to identify existing systematic reviews in the topic area. The search strategies combine free-text and index terms for relevant cancers with free-text and index terms for relevant interventions. The Cochrane randomized controlled trial publication filter was used to limit the search results to RCTs (in MEDLINE and Embase). No language limits were applied.

Finally, Ipsen searched grey literature resources, including the trials registry ClinicalTrials.gov, online conference proceedings (searched only in updated search of October 2021), and the websites of national guideline and regulatory agencies, including NICE, Institute for Clinical and Economic Review (ICER), Haute Autorité de Santé (HAS), Gemeinsamer Bundesausschuss (G-BA), Canadian Agency For Drugs And Technologies In Health (CADTH) and International Network of Agencies for Health Technology Assessment (INAHTA), to identify European public assessment report (EPAR) and HTA documents (reviewed in the original search only).

In summary, Ipsen's literature searches use an appropriate range of databases and grey literature resources for the topic. The choice of free-text and index terms is also appropriate, and the searches have a reasonable balance of sensitivity and specificity.

The main difference between the reviews is the approach PenTAG took of first identifying systematic reviews and meta-analyses of the decision problem, followed by an update search since the search data of the most recent high quality systematic reviews. Ipsen, on the other hand, were updating their own initial 2017 literature review.

There are other small differences between the Ipsen and PenTAG searches. PenTAG only searched for HTA documents on the NICE website and the INAHTA database, while Ipsen also included ICER, HAS, G-BA, and CADTH (as their review is to be used to support submission across a wide range of markets). While in terms of clinical registries, Ipsen searched ClinicalTrials.gov only, while PenTAG searched ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP).

The search and review by Ipsen resulted in 142 reports being included in their NMA. When compared to the results of the PenTAG search, 76 of the 142 reports were retrieved by the PenTAG search, 49 were out of scope of the current decision problem, leaving 17 records in scope but not retrieved by the PenTAG search. These 17 records were appraised, and all added to the PenTAG review. Of the 17 records, 13 were conference abstracts (published from before the PenTAG RCT search), one was an FDA update in the Oncology Times, and three were full text journal articles (again from before the RCT search).

Only one of these 17 records contained new data not identified within the PenTAG search—a 2014 letter by Motzer et al[119] that contained the final overall survival outcomes of the COMPARZ trial.[91] This letter was included in the NMA of TA858 and was therefore also identified in citation chasing post the preliminary assessment report[38].

3.4.3. Analyses conducted by the company

CheckMate 9ER was a single-blind parallel group, RCT of cabozantinib + nivolumab comparing cabozantinib + nivolumab (n=323) against sunitinib (n=328). The trial included patients were those with advanced or metastatic RCC with a clear cell component (including patients with sarcomatoid features) who had also not received any prior systemic therapy. Patients could receive one prior adjuvant or neoadjuvant therapy if cancer recurrence was at least six months after the last dose (as is common across modern RCC trials) although only five patients did as use of adjuvant therapy was not common during the time of enrolment (Sept 2017 – May 2019). Though patients were required to have a Karnofsky performance score of at least 70%, all IMDC risk categories were included. Patients with active CNS metastases; active, known or suspected autoimmune disease; or with a range of comorbidities were excluded. CheckMate 9ER was conducted internationally across the USA, Europe and the Rest of the World with 21 patients enrolled from the UK.

A number of interim analyses were undertaken. In the company's original submission, the third database lock (median follow-up 32.9 months) was presented. This was later superseded by a fourth database lock with median follow-up of 44.0 months (minimum 36.5 for OS and PFS), which is the focus of discussion. The EAG regarded that controls for multiple analysis and multiple testing, including use of a hierarchical testing procedure, were appropriate. The EAG also regarded that assumptions underpinning sample size were, in some cases, unjustified (clarification response A7) but were not unreasonable given expected and observed trial results.

The primary outcome was PFS assessed via BICR according to FDA censoring rules. Analysis of the trial used standard methods. Differences between groups in survival outcomes used log-rank tests stratified by randomisation factors (IMDC category, PD-L1 tumour expression, and location of screening). Survival outcomes were further analysed using Cox proportional hazards models. In response to clarification question A21 on the validity of the proportional hazards assumption, the company provided results from tests on scaled Schoenfeld residuals and a check based on a visual examination of the log cumulative hazard plot. This was provided for OS and PFS outcomes in the ITT, intermediate/poor risk and favourable risk groups. The company argued based on these results that the assumption was met for all outcomes and groups except for OS in the favourable risk group. The EAG, however, believed that these assumptions were more tenuous than the company asserted; in the all-risk group, *p*-values from the tests of scaled Schoenfeld residuals were <0.10 for both outcomes, and it was not obvious

from any of the presented log-cumulative hazard plots that curves were indeed equidistant over the time horizon.

The EAG conducted quality assessment for all key trials, including CheckMate 9ER. This is presented in Section 3.3.2.5. The pivotal CheckMate 9ER trial was judged to have a high overall risk of bias because of a high risk of attrition bias (very high, differential overall attrition as well as dropouts due to discontinuation and disease progression, with reporting of single imputation of approaches to account for missing data). Random sequence generation was poorly reported, but pragmatically accepted as presenting low risk of bias due to the use of IxRS for randomisation. The EAG did not identify any specific additional conceptual concerns relating to the 44-month follow-up time point. However, the EAG noted that the company's explanation of the changes they made when they revised their data (clarification response A8) did not seem to encompass all of the changes made with minor differences observed for additional variables which were not noted as having been updated such as adverse events data. This creates some uncertainty related to data quality and consistency of definitions and datacuts.

The EAG noted several points in the outcome and design pattern of CheckMate 9ER that raise questions about the generalisability of this trial. Emerging observational evidence on the use of cabozantinib + nivolumab suggests that adverse event rates are possibly lower in routine practice than in the trial, with possible implications for observed effectiveness and relative dose intensity (clarification response A3). In addition, CheckMate 9ER enrolled a low number of UK patients (3.2%), which may indicate that effectiveness observed in the trial may not be reliably replicated in a UK treatment context (clarification response A5). CheckMate 9ER also included very few patients who had received a prior adjuvant treatment (n=5) due to the time period in which the trial was conducted, this does not align well with current and expected future practice in the UK following the recommendation of pembrolizumab in the adjuvant setting which impacts both on generalisability and on the achievability of the observed effect sizes. Finally, in response to clarification question A13, the company noted that [redacted] of patients receiving cabozantinib + nivolumab and [redacted] of patients receiving sunitinib continued to receive treatment post-progression, with mean duration of treatment beyond progression of [redacted] days and [redacted] days respectively. This is surprising given clinical advice that treatment generally ends at point of progression, and thus the trial may not reflect treatment patterns in the UK.

3.4.4. Results presented by the company

The EAG considered the most recent available data for each outcome to take precedence and therefore the focus of this section is the 44-month follow-up data, for which results are tabulated below (Table 23).

Table 23: Key results from 44-month follow up for CheckMate 9ER

Outcome	Cabo+nivo (n=323)	Suni (n=328)
BICR-observed PFS events	230	248
Median PFS months (95% CI)	16.56 (12.75, 19.48)	8.38 (6.97, 9.69)
Hazard ratio PFS (95% CI)	0.59 (0.49, 0.71), p<0.0001	
Median OS months (95% CI)	49.48 (40.31, N.E.)	35.52 (29.24, 42.25)
Hazard ratio OS (95% CI)	0.70 (0.56, 0.87)	
Increase in ORR (95% CI)	56.0% (50.4, 61.5)	28.0% (23.3, 33.2)
Median TTR months	2.83	4.32
Median DoR months	22.08 (17.97, 26.02)	16.07 (11.07, 19.35)
Median PFS-2 months	44.65 (35.94, N.A.)	25.07 (20.96, 32.36)
HR PFS-2 (95% CI)	0.63 (0.51, 0.78), p<0.0001	
Number of patients remaining on treatment[120]	57	32
Median TTD months	[redacted]	[redacted]
Number discontinued treatment	263 (82.2%)	288 (90.0%)
Proportion of discontinuers receiving a subsequent treatment	116/263 (44.1%)	148/288 (51.4%)
Most common type of subsequent therapy received	VEGF-targeted therapy (69/263; 26.2%)	Nivo-based or PD-(L)1 inhibitor-based regimen (101/288; 35.1%)
Median TTNT*	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation; TTR, time to response

Notes: this was not provided in line with the EAG requested definition and was instead defined as (1) the survival time from end of therapy in patients who never received subsequent systematic treatment, and (2) the time from end of therapy until subsequent systematic treatment in patients who received subsequent systematic treatment. An event was defined as receiving subsequent systematic treatment.

Data taken from the company submission and Burotto 2023[120]

By means of comparison, considering earlier follow-up points for the company's primary outcome, PFS rates were: 79.6% versus 59.9% at six months, 67.9% versus 48.3% at nine months, 57.8% versus 37.6% at 12 months, and 37.8% versus 21.7% at 24 months, for cabozantinib + nivolumab and sunitinib, respectively.

Subgroup analysis is provided by the company for a range of factors, including IMDC baseline prognostic risk, which was considered by the EAG to be the most pertinent subgroup analysis. Results were categorised by 0 (favourable), 1-2 (intermediate) and 3-6 (poor) and are presented below in Table 24. Combined intermediate/poor data were also provided for certain outcomes. In particular, it is notable that findings for OS [redacted] in favourable risk patients, in contrast to findings for patients with intermediate and poor risk. While the median OS had not yet been reached in the cabozantinib + nivolumab arm, there was a similar rate in mortality by the final follow-up (cabo+nivo: 30/74 [40.5%]; suni:27/72 [37.5%]). In addition subgroup analysis found [redacted] in the favourable risk group in HRQoL measured by the FKSI-19 with quality of life declining from baseline in both risk groups.[121] This [redacted] creates uncertainties in generalisability and in decision risk.

[redacted]

Table 24: Key 44-month results in CheckMate 9ER by IMDC prognostic risk status

Outcome	Favourable N =74 Int, 72 Con	Intermediate N = 188 Int, 188 Con	Poor N = 61 Int, 68 Con
Median PFS (95% CI)	Int: 21.42 (13.08-24.71) Con: 13.86 (9.56-16.66)	Int: 16.59 (11.86-20.04) Con: 8.67 (7.00-10.38)	Int: 9.92 (5.91-17.56) Con: 4.21 (2.92, 5.62)
Hazard ratio PFS (95% CI)	0.72 (0.49-1.05)	0.63 (0.49, 0.80)	0.37 (0.24, 0.57)
Median OS (95% CI)	Int: N.A. (40.67-N.A.) Con: 47.61 (43.63, N.A.)	Int: 49.48 (37.55, N.A.) Con: 36.17 (25.66, 45.96)	Int: 34.84 (21.36, N.A.) Con: 10.51 (6.83-20.63)
Hazard ratio OS (95% CI)	1.07 (0.63-1.79)	0.75 (0.56-1.00)	0.46 (0.30-0.72)
ORR % (95% CI)	Int: 67.6 (55.7, 78.0) Con: 45.8 (34.0, 58.0)	Int: 56.4 (49.0-63.6) Con: 27.7 (21.4-34.6)	Int: 41.0 (28.6-54.3) Con: 10.3 (4.2, 20.1)

Abbreviations: Int = intervention, cabozantinib with nivolumab. Con = control, sunitinib.

Treatment-related adverse events occurred in 97.2% patients receiving cabozantinib + nivolumab and 93.1% of patients receiving sunitinib with 66.9% versus 55.3% at Grade 3 or higher respectively. Treatment-related AEs led to discontinuation of either nivolumab or cabozantinib in 27.5% of patients versus 10.6% of patients in the sunitinib arm and [redacted] versus [redacted] of patients had at least 1 dose reduction of cabozantinib and sunitinib respectively. The most common treatment-related AEs were diarrhoea, HFS, hypertension, fatigue and hypothyroidism in both arms. Most immune-mediated AEs were low grade and hypothyroidism was the most common immune-mediated AE in both arms; 21.9% of patients treated with cabozantinib + nivolumab required corticosteroids (≥ 40 mg prednisone daily or equivalent) to manage immune-mediated AEs.

Analysis of HRQoL data collected via the FKSI demonstrated a benefit for cabozantinib + nivolumab on the FKSI-19 DRS-v1, 3·48 (1·58–5·39) and EQ-5D-3L UK utility index, 0·04 (0·01–0·07), reaching significance at most timepoints, with small to moderate effect sizes (0·2–0·5).[122] Patients were less likely to be bothered by side effects of for cabozantinib + nivolumab regardless of risk (intermediate / poor-risk odds ratio [OR], 0.50; 95% CI, 0.34–0.75; favourable-risk OR, 0.51; 95% CI, 0.28–0.91).[121] This analysis, however, needs to be considered in the context of the higher rates of discontinuation and dose reduction seen for cabozantinib + nivolumab.

3.5. Description and critique of the evidence presented by other stakeholders

3.5.1. Professional organisation submission

One professional organisation submission was received from the British Association of Urological Surgeons (BAUS).

The submission highlighted that the aim of treatment for RCC varies by disease stage (during Stages 1 to 3c, the aim is to cure, while for Stage 4 disease, the aim is to prolong life of a high quality). BAUS noted that the pathway of care for RCC was not well defined, and there was variation in treatment across different centres. The exact systemic anti-cancer therapy (SACT) and the sequence of treatments used at different points in the pathway will vary from centre to centre as there is currently no predictive tool/marker for each agent. This variation has been established by a recent NHS England-related audit commissioned by Kidney Cancer UK, and it

will soon be illustrated on a yearly basis by the National Kidney Cancer Audit. Nevertheless, the pathway presented in the NICE final scope was considered broadly representative of clinical practice in the UK. The submission highlights European Association of Urology (EAU),[123] European Society of Medical Oncology (ESMO),[43] and American Society of Clinical Oncology (ASCO)[44] guidelines as guidelines used in the treatment of the condition and noted that NICE has commissioned a guideline[124] in this area. Commissioning policies relevant to treatment may exist, but none were specified in the submission.

The BAUS considered that cabozantinib + nivolumab would be a welcome additional 1st line IO/TKI option in addition to the existing avelumab + axitinib combination and considered this to be the most likely treatment replaced as it is thought to be less effective than some of the other combinations. The EAG assumed that this comment related particularly to favourable risk patients for whom avelumab + axitinib was the only option available (via the CDF). They considered cabozantinib + nivolumab to represent only a “marginal gain”. They were not able to provide input to many of the questions related to the specifics of the technology and its impact compared to current care as they did not consider this to be their area of expertise.

3.5.2. Patient organisation submission

One patient organisation submission was received from Action Kidney Cancer.

The submission highlights that living with aRCC/mRCC presents significant challenges for patients and their families. The disease and the side effects of current treatments can have a profound impact, causing financial pressures, emotional distress, and a loss of confidence. Nephrectomy, a common treatment option, carries potential complications and requires a lengthy recovery period. Living with reduced kidney function can lead to long-term complications such as hypertension and chronic kidney disease. It is crucial to provide patients with treatment choices and maintain control to address these burdens effectively.

Family members and caregivers are noted to play a crucial role in supporting patients with aRCC/mRCC but face their own challenges, including financial burdens and the impact of frequent clinic visits. Access to treatments beyond the 1st line is complex and limited, leaving some patients with BSC as their only option. Improved access to new drugs, psychological support services, timely scan results, clinical nurse specialists, and personalised care plans is necessary to enhance overall care and patient experience.

The current treatment pathway for RCC in the UK was described as involving surgery or ablation for early-stage tumours, followed by adjuvant treatment with pembrolizumab where applicable. For aRCC/mRCC, a combination of immunotherapy or targeted therapies is administered. However, these treatments often come with significant side effects that impact the quality of life of patients and their families. Limited access to innovative cancer treatments in the UK may lead to poorer outcomes compared to other regions. Current treatments available on the NHS have their disadvantages, including toxicity, tolerability issues, debilitating side effects, frequent hospital visits for infusion sessions (e.g. with nivolumab), and additional medications for managing side effects. There are limited treatment options beyond the 4th line, which results in patients relying on BSC, with disease progression becoming inevitable.

Certain subtypes of RCC were noted to have poor prognoses and limited treatment responses (e.g. papillary RCC and RCC with sarcomatoid features), highlighting the need for better treatment options. In this regard, the EAG also noted the organisation's reference to hereditary renal cancer and renal medullary carcinoma but noted that these conditions were outside of the scope of this appraisal. Action Kidney Cancer highlight that the UK's cancer survival rates, including kidney cancer, lag behind those of other countries. Access to novel treatments is crucial to improve outcomes and reduce premature deaths. The absence of biomarkers for treatment selection emphasises the need for treatment alternatives in all disease stages. Offering a choice of treatments based on individual patient characteristics and needs is essential for disease management and maintaining quality of life.

The cabozantinib + nivolumab combination was considered to have shown promising results in the treatment of aRCC, improving survival rates and quality of life. Aligned with earlier clinical feedback to the EAG, the cabozantinib + nivolumab combination may be less beneficial for patients with significant co-morbidities or pre-existing autoimmune conditions, such as cardiovascular disease, hypothyroidism, or ulcerative colitis. Access to this combination is restricted for patients with these conditions due to the potential for SAEs or exacerbation of existing health issues. Immunotherapy like nivolumab can worsen autoimmune conditions, requiring lifelong treatment with IV immunosuppressants.

The organisation concludes that addressing the challenges of access, side effects, and limited treatment options is crucial to provide the best possible care and outcomes for patients with aRCC in the UK.

3.6. Critique of real-world evidence identified for this appraisal

3.6.1. Identified real-world evidence

The search and screening process for RWE is described in Section 3.1.2.

A total of four relevant databases were identified in the review of RWE (Table 26). Of these, data were only publicly available for the National Cancer Registration and Analysis Service [NCRAS] [#1][19] database. These data were included. Three databases (Systemic Anti-Cancer Therapy [SACT] dataset [#2][125]; Clinical Practice Research Datalink [CPRD] [#3][126]; Hospital Episode Statistics [HES] [#4][127]), were excluded as data were not available in the public domain and it would not have been possible to acquire the data within the necessary timeframe for this appraisal.

A total of 12 published reports that contained details of potentially relevant data sources were included for additional follow up to request access to data sets (Table 26). The authors for each of the 12 published reports containing potentially relevant data sources were contacted for access to additional data. A three-week period was allowed for a response, with one follow-up email sent. A total of four studies were excluded: four (Marchioni 2021 [#6];[128] International mRCC Database Consortium [IMDC, #7];[129] Schmidinger 2020 [#10];[34] Maroun 2018 [#8][130]) were excluded on geographical location as they reported data for non-UK participants and despite follow-up with the authors UK data could not be obtained, and one study (Olsson-Brown, 2020 [#15][131] was excluded on population as it reported data for a mixed population and data for the 335 participants with RCC could not be obtained from the corresponding author. A total of seven analyses were included: RECCORD (Wagstaff 2016)[22]; UK RWE 2022[53]; Nathan 2022 [132]; Brown 2021[133]; Hack, 2019[134]; Hawkins 2020[32]; NICE TA780[48]).

In addition to the data sets and studies identified in the EAG's review, a further four potential sources were identified in stakeholder and company submissions (Table 25). In addition, to these sources the company also provided hospital audit data 2022 from the same data set reported in Maroun (2018)[130] in its response to clarification question A1 (Table 25). Following scrutiny against the EAG's PICOS criteria specified in Section 3.1.2.3, two studies were excluded on geographical location as they did not report data for UK participants: one study was conducted in Germany (Hilser 2023) and one study was a multicentre study in 32 worldwide institutions (Santoni 2022). Three studies were included that met the specified PICOS criteria (Kidney Cancer UK: Quality Performance Audit of kidney cancer services in England[135]; Nathan

2023;[136] IQVIA hospital audit data 2022[137]). Given that no real-world evidence was identified evaluating the cabozantinib + nivolumab combination, the geographical criterion was relaxed to include the Hilser (2023)[138] study.

In total, 12 sources[19,22,32,48,53,132-138] A summary of the information sources scrutinised is provided in Table 25.

Table 25: Identified potential sources of real-world evidence

#	Name	Identified from	Included
Databases			
#1	National Cancer Registration and Analysis Service (NCRAS)[19]	Web search + Health Data Research UK Innovation Gateway	Yes. Publicly accessible data for the advanced RCC (aRCC) population.
#2	Systemic Anti-Cancer Therapy (SACT) dataset[125]	Web search + Health Data Research UK Innovation Gateway	No. Data that would be required from the SACT dataset for this project are not available in the public domain and cannot be accessed within the timescales of this project.
#3	Clinical Practice Research Datalink (CPRD)[126]	Web search + Health Data Research UK Innovation Gateway	No. Data that would be required from the CPRD for this project are not available in the public domain and cannot be accessed within the timescales of this project.
#4	Hospital Episode Statistics (HES)[127]	Web search + Health Data Research UK Innovation Gateway	No. Data that would be required from the HES dataset for this project are not available in the public domain and cannot be accessed within the timescales of this project.
Publications			
#5	RECCORD (Renal Cell Carcinoma Outcomes Research Dataset) registry (Wagstaff 2016)[22]	Observational studies search	Yes (full text)
#6	REMARCC (Registry for Metastatic RCC)[128]	Observational studies search	No. Study reported data for North American and European centres. The authors were contacted for data from the UK centres, but not data were provided.
#7	IMDC International mRCC Database Consortium[129]	Observational studies search + web search	No. The authors were contacted for data from the UK centres, but no data were provided.
#8	IQVIA real world oncology cross-sectional survey data (Maroun 2018)[130]	Observational studies search	No. Study published in Maroun 2018[130] reported data for European centres. The authors were contacted for data from the UK centres, but no data were provided. However, the company provided hospital audit data 2022 from the same data set in its

#	Name	Identified from	Included
			response to clarification question A1. These data were included (see below)
#9	UK RWE dataset 2022[53]	Observational studies search	Yes (access to data set). The authors were contacted and access to the dataset was granted following contact with authors of Challapalli et al. Patterns of care and outcomes of metastatic renal cell carcinoma (mRCC) patients with bone metastases (BM): A UK multicenter review [Challapalli 2022][139])
#10	Real-world Experience With Suni Treatment in Patients With mRCC: Clinical Outcome According to Risk Score (Schmidinger 2020)[34]	Observational studies search	No. Study reported data for European centres. The authors were contacted for data from the UK centres, but no data were provided.
#11	Ave + axi in advanced renal cell carcinoma (aRCC): 12-month interim results from a real-world observational study in the United Kingdom (Nathan, 2022)[132]	Observational studies search	Yes (conference abstract)
#12	Cabo and axi after VEGF therapy in patients with aRCC: A retrospective cohort study (Brown, 2021)[133]	Observational studies search	Yes (conference abstract)
#13	Real world experience of nivo therapy in metastatic renal cancer patients: A 3 year multi-centre review (Hack, 2019)[134]	Observational studies search	Yes (conference abstract)
#14	Treatment patterns and health outcomes in mRCC patients treated with targeted systemic therapies in the UK (Hawkins 2020)[32]	Observational studies search	Yes (full text)
#15	Real-world outcomes of immune-related adverse events in 2,125 patients managed with immunotherapy: A United Kingdom multicenter series (Olsson-Brown, 2020)[131]	Observational studies search	Yes. Study reported results for a mixed population; 335 participants had RCC. The authors were contacted for access to the RCC data. The authors were chased but no response was received (Feb to last contact, April). No data were provided.
#16	Information from SACT, collected as part of the CDF managed access arrangement, contained in NICE TA780[48]	During grey literature screening/data extraction	Yes (report)

#	Name	Identified from	Included
Stakeholder submissions (company and other stakeholders)			
#17	Kidney Cancer UK: Quality Performance Audit of kidney cancer services in England[135]	Stakeholder submission	Yes (report)
#18	Real-World Data on Cabo in Previously Treated Patients with mRCC: Focus on Sequences and Prognostic Factors (Santoni, 2019).[140]	Company submission	No. Study reported data for 32 worldwide centres, no data from UK centres reported
#19	Cabo + nivo in adult patients with aRCC or mRCC: A retrospective, non-interventional study in a real-world cohort (Hilser, 2023)[138]	Company submission	Yes. Study reported data for German centres only, no UK centres included in the study. Given the lack of evidence on the cabo + nivo combination the geographical setting criterion was relaxed in respect of this intervention
#20	Real-world treatment sequencing and outcomes in patients with aRCC. The CARINA interim analysis (Nathan 2023)[136]	Company response form	Yes (conference abstract + poster)
#21	IQVIA Hospital Audit Data[137]	Company clarification response to question A1	Yes. The company provided hospital audit data 2022 from the same data set as reported in Maroun 2018[130] in its response to clarification question A1. These data were included

Abbreviations: aRCC, advanced renal cell carcinoma; BM, bone metastases; CDF, Cancer Drugs Fund; CPRD, Clinical Practice Research Datalink; HES, hospital episode statistics; mRCC, metastatic renal cell carcinoma; NCRAS, National Cancer Registration and Analysis Service; NICE, National Institute for Health and Care Excellence; RCC, renal cell carcinoma; RECCORD, Renal Cell Carcinoma Outcomes Research Dataset; REMARCC, Registry for mRCC; SACT, Systemic Anti-Cancer Therapy; TA, technology appraisal; UK, United Kingdom; VEGF, vascular endothelial growth factor

Finally, the NICE team attempted to gain and share access to data generated specifically for this project via a healthcare data analytics company. However, no data were provided in time for the appraisal of cabozantinib + nivolumab. Data are expected to become available during the later phase of this project.

3.6.2. Description and critique of real-world evidence

3.6.2.1. Study characteristics

Available evidence comes from retrospective analyses, longitudinal cohort studies, prospective cohorts, registry data analysis, and audits predominantly from centres in the UK. The study periods vary across studies, but they generally cover a range of years data (2009 to 2022) and as such capture a substantial number of patients and treatment data. The study populations

include people with aRCC/mRCC. Sample sizes ranged from smaller cohorts, such as the Nathan 2022[132] study with an advanced population of 36 patients (N=36), to larger patient populations in the UK RWE,[53] which included 1,319 patients. Interventions assessed in the available evidence typically reflect the NICE recommendations during the data collection periods covered by the included evidence.

The Kidney Cancer UK report[135] provided results from a two-year retrospective audit using data extracted from the National Disease Registration Service (NDRS) pre-COVID-19 pandemic. Incident cases of RCC diagnosed between 1 January 2017 and 31 December 2018 were selected from the National Cancer Registration Dataset (NCRD). A total of 18,640 tumours were selected into the cohort, representing 18,421 distinct patients. The audit was conducted to assess the quality of services and to assess whether there was variation in service and treatment in England. There were six quality performance indicators assessed; of these, three provided information in PICO (post-operative 30-day and 12-month all-cause survival in M0 kidney cancer patients who undergo radical nephrectomy or nephron sparing surgery (NSS) and metastatic kidney cancers should receive SACT or active surveillance).[135]

Hospital audit data (IQVIA 2022[137]) were also provided by the company in response to clarification question A1, these data provide information on volume sales for RCC agents in the UK. Limited descriptive information on the data set was available.

The EAG had access to two data sets:

- The NCRAS dataset[19] provides publicly accessible data for the advanced RCC population. The NCRAS forms part of the National Disease Registration Service (NDRS) in NHS Digital. On 1 October 2021, responsibility for the management of the NDRS transferred from Public Health England (PHE) to NHS Digital. The EAG has extracted publicly available data from the NCRAS, specifically the 'Get Data Out' programme. The 'Kidney' dataset contains information on incidence, treatment rates, survival, routes to diagnosis (and other key outcomes) for patients with malignant kidney cancer in England from 2013 to 2019.
- The UK RWE dataset[53] (access kindly provided by the co-investigators: Amarnath Challapalli, Amit Bahl, Gihan Ratnayake, Ricky Frazer and John McGrane) included 1,319 mRCC participants from 15 UK centres, who commenced 1st line systemic therapies between June 2018 and August 2022. Access to the data set was provided following contact with the authors listed on a conference abstract identified in the searches (Challapalli 2022[139]). The EAG has been able to conduct its own analyses using this data set.

Summary study characteristics are provided in Table 26.

3.6.2.2. Baseline characteristics and risk scores

The included evidence all focused on people with aRCC or mRCC. Median age ranged from 59 years to 68 years[19,22,32,48,53,132-138] which broadly mirrored the populations included in the clinical trials (Table 9). Ten analyses reported sex, in these analyses the majority of participants were male.[22,32,48,53,132-136,138]

Of the 12 analyses, the RECCORD data set[22] included only patients with clear cell histology. Six analyses[32,48,53,132,136,138] included a mix of histologies, but clear cell RCC consistently appeared as the most prevalent histological subtype across the studies ranging from 67% in Hilser [2023][138] to 91% in SACT TA780[48] data. Four[22,53,134,138] of the 12 analyses reported the proportion of participants who had undergone prior nephrectomy; this ranged from 50%[22] to 67.9%[134]).

ECOG PS was reported in five analyses[48,132,133,136,138] and the majority of participants were ECOG PS 0 or 1. The proportion of participants with ECOG PS 0 or 1 ranged from 81% to 89% in four studies,[48,132,136,138] one analysis[133] reported only 20% of participants with ECOG PS 0 or 1. Of note, 8% of participants had missing data in the SACT TA780 data set.[48]

Risk score was reported in eight studies.[32,48,53,132,134,136-138] Risk distribution was measured by a combination of IMDC (or Heng criteria),[48,53,132,134,136-138] MSKCC,[32] risk criteria. For convenience, both sets of risk scoring methods are described as producing risk score classes as ‘favourable’, ‘intermediate’ or ‘poor’. The majority of participants across all studies were assessed as intermediate or poor risk categories for each of the scores used (ranging from 59% in Nathan 2022[132] to 100% in the SACT TA780[48] data set) (Table 27). The proportion of participants assessed as intermediate or poor risk broadly matched that in the clinical trial populations (Table 9).

Baseline characteristics are summarised in Table 27.

Table 26: Summary of study characteristics of included RWE

Study name	Study type	Country (number of centres)	Study period	Population	LOT	Interventions	Outcomes evaluated (per PICOS)
UK RWE 2022[53]	Multicentre UK retrospective analysis; patient level data	UK (17)	01/01/2018 to 23/08/2022	Metastatic (N=1,319)	1L; 2L; 3L; 4L 5L	Cabo; suni; pazo; tivo; nivo; evero; axi; ave+axi; lenv+evero; pem+lenv; cabo+nivo; nivo+ipi; nivo	Risk scores (IMDC); treatment patterns; OS; PFS; treatment discontinuation; TTNT; TTP; costs (information on RDI)
Hawkins 2020[32] Full text	Retrospective (longitudinal) cohort	England (2)	01/01/2008 to 31/12/2015	Metastatic (N=652)	1L; 2L; 3L	1L: suni; pazo; evero; Other 2L: suni; axi; evero; Other 3L: axi; evero; Other	Risk scores (MSKCC); treatment patterns; OS; treatment discontinuation
Wagstaff 2016 (RECCORD)[22]	Registry data (RECCORD). Retrospective non interventional study	UK (7: 5 in England; 1 in Wales and 1 in Scotland)	Mar 2009 to Nov 2012	Metastatic (N=514)	1L; 2L; 3L	1L: suni; pazo; evero; sora; tem; IL-2; IFNα; Other 2L: suni; pazo; evero; sora; tem; IL-2; Other 3L: evero; sora; axi; IFNα; Other	Treatment patterns; OS; treatment; discontinuation; TTNT; TTP
Brown 2021[133]	Retrospective cohort	England (NR)	01/01/2011 to 31/01/2020 (Cancer Analysis System)	Advanced (N=1,485)	2L+[a]	Cabo; axi	Treatment patterns; OS
Hack 2019[134]	Retrospective cohort	England (3)	Feb 2016 and Apr 2019	Advanced (N=109)	2L+[b]	Nivo	PFS; OS
Hilser 2023[138] Conference abstract	Retrospective non-interventional cohort	Germany (8)	NR	mRCC (N=67)	1L	Cabo+nivo	Risk scores (Heng); PFS; OS; TTP

Study name	Study type	Country (number of centres)	Study period	Population	LOT	Interventions	Outcomes evaluated (per PICOS)
Nathan 2022[132] Conference abstract	Prospective cohort	UK (4)	After 1 Aug 2019	Advanced (N=36)	1L	Ave+axi	Risk score (IMDC); PFS; OS
Nathan 2023[136] (CARINA: NCT04957160) Conference abstract + poster presentation	Retrospective, non-interventional cohort using CAS	England (6)	NR	Advanced (N=129) (cabo subgroup N=87)	2L	Any + subgroup analysis of 2L cabo	Treatment patterns; treatment discontinuation
NCRAS 2023[19]	UK Registry data (OS for mRCC collected from 2013 to 2019)	UK (England)	2013 to 2019	Advanced and metastatic (N=18,421)	1L+	Various	OS
IQVIA 2022[137]	Hospital pharmacy audit data	UK (England)	NR	RCC treated patients	1L+	[redacted]	Treatment patterns
Kidney Cancer UK (audit of kidney cancer services in England)[135]	Audit data	UK	1 Jan 2017 to Dec 2018	Advanced and metastatic (N=18,421)	1L+	Various	Post operative 30-day and 6-month all cause survival in M0 kidney cancer patients who undergo RN or NSS; variability in access to SACT for people with metastatic kidney cancer
NICE TA780:[48] SACT data report	Part of TA780 committee papers	England	5 April 2019 & 30 November 2020	Advanced (N=814)	2L	Any post 1L treatment with nivo+ipi	Risk scores (IMDC); treatment patterns; OS; TTNT; treatment discontinuation

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; ave, avelumab; axi, axitinib; CAS, Cancer Analysis System; cabo, cabozantinib; evero, everolimus; IFNα, interferon alfa; IL2, interleukin 2; IO, immunotherapy; ipi, ipilimumab; lenv, lenvatinib; LOT, line of treatment; mRCC, metastatic renal cell carcinoma; NCRAS, National Cancer Registration and Analysis Service; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; NR, not reported; OS, overall survival; pazo, pazopanib; PFS, progression free survival; RCC, renal cell carcinoma; RWE, real world evidence; SACT, Systemic Anti-cancer Therapy; sora, sorafenib; suni, sunitinib; TA, technology appraisal; tem, temsirolimus; tivo, tivozanib; TKI, tyrosine kinase inhibitor; UK, United Kingdom

Notes:

[a]Patients initiating 2L+ cabo (prior axi excluded) or axi (prior cabo excluded)

[b]69/109 (63.3%) received nivo as 2L; 30/109 (27.5%) received nivo as 3L; 9.2% (10/109) as 4L+

[c]Checkpoint inhibitor-based combination therapy as 1st line treatment in UK clinical practice

Table 27: Summary of baseline characteristics of included RWE

Study name	Intervention	Line of treatment	N	Age years, median (range)	Male n (%)	ECOG PS n (%)	Histology (% clear cell; % sarcomatoid)	IMDC (fav; int; poor) n (%)	Prior nephrectomy n (%)
UK RWE 2022[53]	Cabo; suni; pazo; tivo; nivo; evero; axi; ave+axi; lenv+evero; lenv+pem; cabo+nivo; nivo+ipi; nivo	1L: 687(52%); 2L: 415 (32%)[b]; 3L: 168 (13%)[b]; 4L 42 (3%); 5L: 7 (0.5%)	1,319	Mean 64.43 (min 21, max 90; SE 0.28)	936 (71%)	NR	Clear cell: 1,092 (82.8%); chromophobe: 11 (<1%); papillary 69 (5.2%); sarcomatoid 7 (); undifferentiated 6 (<1%); other 53 (<1%); missing/NA 81 (<1%)	Fav 294 (22.3%); Int/Poor 1,016 (77.0%); Missing 9 (<1%)	715 (54.2)
Hawkins 2020[32]	Suni (60.7%) (3.2% switched suni→pazo); pazo (37.7%) (5.7% switched suni→pazo); evero 4 (0.6%); Other 6 (0.9%)	1L	652	Mean 64.84 (SD 10.5)	426 (65.3%)	NR	Clear cell: 518 (79.5%); non-clear cell 70 (10.7%); other 22 (3.4%)	MSKCC: fav 73 (11.2%); int 380 (58.3%); poor 174 (26.7%); missing 25 (3.8%)	NR
	Axi (57.1%); evero (41.9%); suni 1 (0.5%); Other 1 (0.5%)	2L	184	Mean 62.97 (SD 10.3)	124 (67.4%)	NR	Clear cell: 141 (76.6%); non-clear cell 28 (15.2%); other 5 (2.7%)	MSKCC: fav 27 (14.7%); int 77 (41.9%); poor 59 (32.1%); missing 21 (11.4%)	NR
	Evero 13 (72.2%); axi 4 (22.2%); Other 1 (5.6%)	3L	18	Mean 65.06 (SD 8.9)	14 (77.8%)	NR	Clear cell: 13 (72.2%); non-clear cell 4 (22.2%); other 1 (5.6%)	MSKCC: fav 2 (11.1%); int 11 (61.1%); poor 2 (11.1%)	NR

Study name	Intervention	Line of treatment	N	Age years, median (range)	Male n (%)	ECOG PS n (%)	Histology (% clear cell; % sarcomatoid)	IMDC (fav; int; poor) n (%)	Prior nephrectomy n (%)
Wagstaff 2016 (RECCORD)[22]	Suni 404 (78.6%); pazo 60 (11.7%); evero 33 (6.4%); sora 6 (1.2%); tem 4 (0.8%); IL-2 3 (0.6%); IFNα 2 (0.4%); Other 2 (0.4%)[a]	1L	514	Mean 61.6 (SD 10.9)	341 (66.3%)	NR	Clear cell: 514 (100%) (clear cell patients only included in the trial)	NR	257 (50.0)
	Suni 12 (14.8%); pazo 8 (9.9%); evero 43 (53.1%); sora 3 (3.7%); tem 1 (1.2%); axi 4 (4.9%); IL-2 2 (2.5%); Other 8 (9.9%)	2L	81[b]	NR	NR	NR	NR	NR	NR
	Evero 8 (50.0%); sora 1 (6.3%); axi 5 (31.3%); IL-2 1 (6.3%); Other 1 (5.9%)	3L	16[b]	NR	NR	NR	NR	NR	NR
NCRAS 2023[19]	NR	NR	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
IQVIA 2022[137]	[redacted]	1L+	NR	NR	NR	NR	NR	NR	NR
Kidney Cancer UK (audit of kidney cancer services in	NR	1L+	18,421	68 (58, 77)	11,818 (63.4)	NR	NR	NR	NR

Study name	Intervention	Line of treatment	N	Age years, median (range)	Male n (%)	ECOG PS n (%)	Histology (% clear cell; % sarcomatoid)	IMDC (fav; int; poor) n (%)	Prior nephrectomy n (%)
England)[135]									
NICE TA780:[48] SACT data report	Nivo+ipi	1L	814	61 (NR) <40 to 80+ yrs[a]	596 (73%)	0: 285 (35%); 1: 420 (52%); ≥2: 42 (%); Missing 67 (8%)	Clear cell: 740 (91%); Other 74 (9%)	Int 533 (65%); Poor 281 (35%)	NR
Brown 2021[133]	Cabo	122 (27.7%) received ≥3L Tx	440	62.5 (NR)	258 (58.60%)	0-1: 80 (18.2%)	NR	NR	NR
	Axi	359 (34.4%) received ≥3L Tx	1,045	63.0 (NR)	556 (53.2%)	0-1: 213 (20.4%)	NR	NR	NR
Hack 2019[134]	Nivo	2L: 69/109 (63.3%); 3L 30/109 (27.5%); 4L+ 10/109 (9.2%)	109	59 (NR)	79 (72.5%)	NR	NR	Heng scores: fav 19.41%; int 61.2%; poor 18.3%	74 (67.9)
Hilser 2023[138]	Cabo+nivo	1L	67	67.6 (±30)[d]	42 (62.7)	≤1 51 (76.1)	Clear cell: 45 (67.2)	Fav: 15 (22.4); Int: 33 (49.3); Poor 10 (14.9)	38 (56.7)
Nathan 2022[132]	Ave+axi	1L	36	66.2 (39.8-84.1)	(78%)	0-1: 89%	Clear cell: 72%; Other 25%	Fav 39%; int 42%; poor 17%; unknown 3%	NR

Study name	Intervention	Line of treatment	N	Age years, median (range)	Male n (%)	ECOG PS n (%)	Histology (% clear cell; % sarcomatoid)	IMDC (fav; int; poor) n (%)	Prior nephrectomy n (%)
Nathan 2023[136] (CARINA: NCT04957160)	Cabo 80 (74.8%); suni 14 (13.1%); lenv+evero 1 (0.9%); tivo 3 (2.8%); pazo 3 (2.8%); axi 2 (1.9%); pem+axi 2 (1.9%); ave+axi 1 (0.9%); bev 1 (0.9%)[d]	2L	129	Mean 60 (9.9) [n=96][c]	97 (75.2%)	0: 34 (40.0%); 1: 47 (55.3%); ≥2 4 (4.7%) [n=85]	Clear cell: 75 (77.3%); Mixed clear-cell component 6 (6.2%); non-clear-cell 13 (13.4%); Other 3 (3.1%) [n=97]	Fav 12 (14.6%); Int 53 (64.6%); Poor 8 (15.4%) [n=82]	NR
	Cabo	2L	87	Mean 59.1 (9.8) [n=60][c]	64 (73.6%)	0: 22 (41.5%); 1: 30 (56.6%); ≥2 1 (1.9%) [n=53]	Clear cell: 48 (78.7%); Mixed clear-cell component 3 (4.9%); non-clear-cell 7 (11.5%); Other 3 (4.9%) [n=61]	Fav 8 (15.4%); Int 36 (69.2%); Poor 8 (15.4%) [n=52]	NR

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; ave, avelumab; axi, axitinib; bev, bevacizumab; cabo, cabozantinib; evero, everolimus; IFNα, interferon alfa; IL2, interleukin 2; IO, immunotherapy; ipi, ipilimumab; lenv, Lenvatinib; NCRAS, National Cancer Registration and Analysis Service; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; NR, not reported; OS, overall survival; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; SACT, Systemic Anti-cancer Therapy; SE, standard error; sora, sorafenib; suni, sunitinib; TA, technology appraisal; tem, temsirolimus; tivo, tivozanib; TKI, tyrosine kinase inhibitor; UK, United Kingdom

Notes:

[a]<40 yrs: 15 (2%); 40 to 49 yrs: 96 (12%); 50 to 59 yrs: 257 (32%); 60 to 69 yrs: 271 (33%); 70 to 79 yrs: 167 (21%); 80+ yrs 8 (1%)

[b]One additional patient was denoted as receiving 2nd line, 3rd line and 4th line treatment but no treatment type was specified

[c]For each year, patient numbers (population/incidence) were reported and stratified according to stage, age band, RCC type). Median/mean age not provided. Gender split, histology, IMDC risk category, prior nephrectomy not provided

[d]Reported in abstract as median (range)

3.6.2.3. Outcomes

The outcomes reported in the included real-world evidence are summarised in Table 28.

Table 28: Outcomes reported in the RWE

Trial name	Risk scores	OS + prognostic variables	PFS + prognostic variables	TTP	TTNT	Discontinuation	Tx patterns (subsequent Tx)	Health costs	HRQoL
UK RWE 2022	IMDC	X	X	X	X	X	X	X[d]	
Hawkins 2020[32]	MSKCC	X				X	X		
Wagstaff 2016 (RECCORD)[22]		X		X	X	X	X		
NICE TA780:[48] SACT data report	IMDC	X			X	X	X		
IQVIA 2022							X		
NCRAS 2023[19]		X[a]							
Kidney Cancer UK (audit of kidney cancer services in England)[135]		X[b]					X		
Brown 2021[133]		X					X		
Hack 2019[134]		X	X	X[c]					
Hilser 2023[138]	Heng	X	X						
Nathan 2022[132]	IMDC	X	X			X			
Nathan 2023[136] (CARINA: NCT04957160)	IMDC					X	X		

Abbreviations: HRQoL, health-related quality of life; MSKCC, Memorial Sloan-Kettering Cancer Center; NSS, nephron sparing surgery; OS, overall survival; PFS, progression free survival; RN, radical nephrectomy; RWE, real world evidence; SACT, Systemic Anti-cancer Therapy; TTNT, time to next treatment; TTP, time to progression; Tx, treatment

Notes:

[a]OS data yearly records (2013-2019) for Stage 1-4 clear cell RCC and RCC NOS patients with confirmed or unconfirmed diagnoses

[b]Reported post operative 30-day all cause survival in M0 kidney cancer patients who undergo radical nephrectomy (RN) or nephron sparing surgery (NSS) and post operative 12 months all cause survival in M0 kidney cancer patients who undergo RN or NSS

[c]Proportion with disease progression only

[d]Data on relative dosing intensity reported, included as dosing used to inform drug costs

3.6.2.4. Critical appraisal real world evidence studies

The DataSAT was completed for UK RWE (2022),[53] Hawkins (2020),[32] RECCORD (Wagstaff 2016[22]) and SACT TA780.[48] Note that the research team had access to the full data set only for UK RWE (2022)[53] and the remaining assessments were completed based on the publicly available information.

For the remaining studies, no assessment was completed as limited information was reported in the public domain to make a full assessment:

- Brown (2021),[133] Hack (2019),[134] Hilser (2023),[138] Nathan (2022),[132] and CARINA (Nathan 2023)[136] were only available as conference abstracts
- Kidney Cancer UK Audit report,[135] and the NCRAS data,[19] limited access to the data set based on information within reports available online.

The DataSAT assessments for the four appraised datasets[22,32,48,53] are summarised below with detail provided in Appendix L.

Data provenance: Data provenance refers to the documented history and origin of data, including its creation, transformation, and movement throughout its lifecycle. Data for three[22,32,53] of the analyses were derived from retrospective chart reviews conducted in various hospital settings in the UK, specifically focusing on patients with RCC. While specific details regarding data preparation, governance, and management are not provided, it can be inferred that the data collection process was clinically led and aligned with the objectives of the respective studies. Limited information is available on the procedures followed in these aspects.

In contrast, the SACT database served as a data source for one[48] of the analyses. This national database in England collects real-time information reported by NHS Trusts through electronic prescribing systems during patient care. The dataset undergoes regular reviews and updates, indicating ongoing efforts for data management and quality assurance. The SACT team, a part of the NCRAS, manages and ensures the quality of the reported data. Compliance with data protection requirements, such as the Data Protection Act 2018 and GDPR 2016, is ensured. Data submission requires completeness checks and adherence to national standards. Over time, data validation has been improving, although certain fields may still have issues related to ascertainment and completeness.

Regarding geographical settings, the data sources were hospital settings (secondary care) within the UK. The UK RWE (2022)[53] data set included patients from 15 UK hospitals who started 1st-line systemic therapy between January 2018 and August 2022. The Hawkins (2020)[32] analysis included patients who initiated 1st-line systemic therapy in two specific hospitals in Cambridge and Manchester between January 2008 and December 2015. The RECCORD data set (Wagstaff 2016)[22] included patients who began 1st-line systemic therapy from seven hospitals across England, Scotland, and Wales, with data collected between March 2009 and October 2012. The SACT database is a national database in England that collects and manages information about systemic anti-cancer therapy treatment. For the included analysis,[48] data from SACT for patients who received nivolumab + ipilimumab during the period of managed access following the NICE Appraisal Committee recommendation in TA581 were analysed.

It is worth noting that the EAG had access to the authors for the UK RWE (2022) dataset,[53] but no additional documents were available beyond those in the public domain for three of the four analyses,[22,32,48] limiting further insights into the data provenance.

Data quality: Across the UK RWE (2022)[53], Hawkins (2020)[32], RECCORD (Wagstaff 2016[22]), and SACT TA780[48] datasets, the included populations were assumed to be accurate, as they relied on information recorded in reliable medical records. Although specific diagnostic codes were not reported, clear inclusion criteria were stated, ensuring the accuracy of participant selection. The SACT TA780[48] dataset was slightly different to the other three datasets in that it selected participants based on Blueteq® applications for nivolumab + ipilimumab for which data were available in the SACT database (matched cohort SACT data to CDF Blueteq® applications for nivolumab plus ipilimumab between 5 April 2019 and 20 November 2020), and it is assumed that patients met the specified criteria for treatment.[48] In all datasets,[22,32,48,53] the majority of items linked to defining the population; e.g. histology type, previous treatments received were reported to have 100% completeness.

In terms of specific variables, the prognostic score assessed using IMDC or MSKCC risk scores typically showed a high level of completeness, albeit a small proportion of missing data reported in two studies.[32,53]

Similarly for treatments received (1st line and subsequent treatments), these data were considered accurate as the information was taken from medical records and linked prescribing

information. In addition, the data were considered complete as there was no indication of missing data in the datasets[22,32,48,53] among the participants who were recorded as having subsequent treatments.

Standard definitions were consistently used for outcomes such as OS, PFS, TTP, and TTNT, providing consistency and accuracy in measurements across the studies. In the SACT TA780 report in particular,[48] the calculation of OS was clearly reported and included vital status verification, tracing, and follow-up. The medical records were assumed to be accurate sources for determining survival time based on treatment start date. For outcomes which may have included some element of clinician judgment e.g. the assessment of progression, the EAG note there may have been some variability between centres and across studies. In most cases, the assessment was based on assessment of multiple markers, such as radiology, symptomatology, clinical investigation, and therapy changes, although primarily radiological assessment was used to determine progression. Medical records were assumed to be accurate sources for determining survival time relative to treatment start date.

It is important to note that for three studies, the completeness and accuracy assessments for study variables were based on the information reported in the publications. Therefore, the overall data quality assessment is based on the information provided in the studies. Overall, the four datasets[22,32,48,53] exhibited reasonable data quality, with a focus on accuracy, completeness, and were based on reliable data sources. The clear definitions and criteria employed in the studies further enhanced the reliability and robustness of the findings.

Data relevance: The four analyses[22,32,48,53] each included a significant number of patients, with sample sizes ranging from 514[22] to 1,319.[53] All four datasets[22,32,48,53] included data from treatment and monitoring in a UK secondary care setting. In three of the four analyses,[32,48,53] the majority of patients had clear cell histology, while one dataset[22] included only patients with clear cell histology. The majority of patients in the datasets were categorised as intermediate or poor risk[22,32,53] according to the IMDC criteria, with one dataset[48] specifically including only patients with intermediate or poor risk RCC. Sufficient data were reported in respect of the analysis populations for the EAG to conclude that the datasets reflected the appropriate population.

The UK RWE (2022)[53] dataset provided valuable insights into the population of RCC patients starting 1st-line systemic therapy in the UK. The data collection spanned from January 2018 to August 2022 and included comprehensive data from 15 UK centres. These data captured the

most recent routine practice in the NHS, reflecting the use of newer treatments recommended by NICE (**1st line:** cabozantinib TA542;[52] tivozanib (TA512);[51] nivolumab + ipilimumab [TA780 via CDF for the majority of the data collection period 2019 to 2022 TA581/TA780];[48] and avelumab + axitinib TA645 [via CDF];[46] **2nd line:** nivolumab TA417;[58] cabozantinib TA463;[55] and lenvatinib + everolimus TA498[56] [refer to Table 29]). The Hawkins (2020)[32] dataset focused on patients with mRCC and obtained data from two specialist centres in England between January 2008 and December 2015. Similarly, the RECCORD study (Wagstaff 2016[22]) analysed data from seven UK centres, providing insights into treatments and outcomes between March 2009 and October 2012. While the data collection periods for these datasets pre-date the recommendations for many current treatment options, comparing them with the more recent UK RWE (2022)[53] dataset can provide insights into the impact of newer treatments on outcomes and the treatment pathway. The SACT TA780[48] dataset specifically focused on patients who received nivolumab + ipilimumab treatment during the managed access period following the NICE appraisal. The dataset included 814 unique patients who applied for CDF funding, and 99% of them had a treatment record in the SACT database. The collection period covered 2019 to 2022 was also sufficient to capture many of the newer treatments recommended by NICE during that period).

Time-to-event outcomes, particularly OS, were assessed in all analyses.[22,32,48,53] In the SACT TA780 dataset[48] median OS had not been reached, but the follow-up period in SACT allowed for the collection of additional information beyond that captured in the trial period. The follow-up durations for each analysis were otherwise deemed sufficient to capture the specified outcomes beyond the trial period and to gather valuable insights into subsequent treatments.

Sample sizes ranged from 514[22] to 1,319[53] participants. The SACT TA780 dataset[48] provided a flow diagram for participants identified to participants included with reasons for not including participants. None of the analyses[22,32,48,53] conducted a sample size calculation as their primary objective was to collect descriptive information rather than test a specific research hypothesis.

Overall, the included datasets[22,32,48,53] provide relevant information from UK practice in terms of treatment patterns and efficacy outcomes (e.g. OS, PFS, TTNT, discontinuation, dosing information). However, in interpreting the information, it is crucial to consider the changes in the treatment landscape over time, given the differences in treatment pathways between the study periods and the present.

3.6.3. Results from real-world evidence

3.6.3.1. Treatment patterns

Feedback received in the both the professional and patient organisation submissions was that the pathway of care for RCC is not well-defined, leading to variation in treatment approaches across different centres. They noted that there is no established predictive tool or marker for each systemic anti-cancer therapy (SACT), resulting in different treatment sequences at different points in the pathway. A recent audit commissioned by Kidney Cancer UK[135] highlighted this variation, suggests that treatment policy is highly variable. The proportion of patients with metastatic kidney cancer who received SACT (with drugs) was widely inconsistent. When stratified by Cancer Alliance, the proportions of metastatic (M1) RCCs that received SACT one month before to any time after diagnosis ranged from 39.7% (95% CI [33.7, 46.1]) to 70.7% (95% CI [59.6, 79.8]). These variations were broadly similar from one month to four years after diagnosis (the cut off was May 2021).

Seven sources reported information on treatment patterns.

Three analyses reported the range of targeted systemic therapies recommended for use in mRCC patients in the UK across lines of therapy (RECCORD [Wagstaff 2016]; Hawkins 2020; UK RWE). The studies were all UK studies and were aligned with the NICE pathways for advanced and/or metastatic RCC, meaning that the received treatments were consistent with NICE-recommended systemic therapies. The broad time period across the three analyses (2008 to 2022) means that the treatments received in the studies vary relative to NICE recommendations at the time the studies were conducted which explains the differences in treatment practices.

The availability of interventions recommended by NICE during the data collection periods for each of the included studies is provided in Table 29. Drugs were considered to be available at the time of publication of final guidance by NICE either with a recommendation for routine commissioning or a recommendation to the Cancer Drugs Fund.

As noted, the interventions received by participants in the earlier data sets[22,32] reflected the treatments available during the study period; i.e. in both data sets the majority of participants received either sunitinib or pazopanib (78.6% and 11.7% and 60.7% and 37.7% in the Hawkins [2020][32] and RECCORD [Wagstaff 2016[22]] data sets, respectively). Subsequent treatments

were broadly similar in the two data sets with the majority of participants receiving everolimus (53.1% and 41.9% in the Hawkins [2020][32] and RECCORD [Wagstaff 2016[22]] data sets, respectively). The main difference being that a larger proportion of participants received axitinib in the later data set (57.1% vs 4.9% in the Hawkins [2020][32] and RECCORD [Wagstaff 2016[22]] data sets, respectively) reflecting the timing of the NICE recommendations. In 3rd line, the majority of participants received everolimus or axitinib (Table 30).

A summary of treatments used from 1st line to 4th line from three RWE sources (data collection period 2008 to 2022) are provided in Table 30. The EAG had access to UK RWE (2022) which includes data aligned with the majority of NICE recommendations. These data indicate that the following treatments are used at 1st line: avelumab + axitinib (13%), nivolumab + ipilimumab (23%), pazopanib (18%), sunitinib (25%), cabozantinib (9%) and tivozanib (8%) aligned with NICE recommendations. The data indicate a small proportion (5%) of patients are treated with interventions not recommended by NICE (e.g. in clinical trials). At 2nd line the data indicate the majority of patients are treated with cabozantinib (39%) or nivolumab (37%) with a smaller proportion of patients receiving lenvatinib + everolimus (5%) or axitinib (3%) and 16% of patients treated with interventions not recommended by NICE (e.g. in clinical trials). When stratified by risk group, the proportions treated were similar apart from a higher proportion of patients receiving nivolumab + ipilimumab in 1st line treatment in the intermediate/poor risk group as would be expected in line with NICE recommendations. Also of note was that, aligned with clinical feedback to the EAG, the proportion of participants receiving avelumab+axitinib was higher in the favourable risk group relative to the intermediate/poor risk group 21.43% vs 10.33%, respectively). A broader range of interventions were used in later lines with cabozantinib the most common treatment at 3rd line (48%) and axitinib the most common treatment at 4th line (43%). A full breakdown of interventions received in the cohort is provided in Appendix L. The EAG conducted an analysis to show the pathway of care from 1st line to 4th line treatment shown in Figure 9 (data are reported in Appendix L).

Table 29: Availability of interventions recommended by NICE during study data collection periods

Intervention		Suni	Pazo	Evero	Axi	Nivo	Cabo	Cabo	Lenv+ evero	Tivo	Nivo+ipi	Ave+axi	Pem+ lenv
NICE appraisal		TA169[49]	TA215[50]	TA219 → TA432[57]	TA333[54]	TA417[58]	TA463[55]	TA542[52]	TA498[56]	TA512[51]	TA780 (CDF review of TA581))[48]	TA645 (CDF)[46]	TA858[38]
Line of treatment recommended		1L (ECOG PS 0 or 1)	1L (no prior cytokine therapy; ECOG PS 0 or 1)	2L (after prior VEGF)	2L (after 1L TKI or a cytokine)	2L	2L (after prior VEGF)	1L (int or poor risk per IMDC criteria)	2L (after 1 prior VEGF and ECOG 0 or 1)	1L	1L (int or poor risk per IMDC criteria)	1L via CDF	1L (int or poor risk per IMDC criteria)
Published guidance date		2009	2011	2011 → 2017	2015	2016	2017	2018	2018	2018	2019 (via CDF); 2022 (CDF review)	2020	2023
Study	**Data collection period**												
RECCORD (Wagstaff 2016)[22]	Mar 2009 to Oct 2012	Y	Y	Y									
Hawkins 2020[32]	1 Jan 2008 to 31 Dec 2015	Y	Y	Y	Y								
UK RWE 2022	1 Jan 2018 to 23 Aug 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y (via CDF)	Y (via CDF)	
Brown 2021[133]	1 Jan 2011 to 31 Jan 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y (via CDF)	N (publ Sep 2020)	
SACT TA780[48]	4 Apr 2019 to	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y (via CDF)	Y(via CDF)	

	30 Nov 2020												
CARINA (Nathan 2023)[136]	15 Jan 2015 to Sept 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y (via CDF)	Y(via CDF)	

Abbreviations: 1L, 1st line; 2L 2nd line; ave, avelumab; axi, axitinib; cabo, cabozantinib; CDF, Cancer Drugs Fund; ECOG PS, Eastern Cooperative Oncology Group performance status; evero, everolimus; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; lenv, Lenvatinib; NICE, National Institute for Heath and Care Excellence; pazo, pazopanib; pem, pembrolizumab; publ, published; RWE, real world evidence; suni, sunitinib; TA, technology appraisal; tivo, tivozanib; TKI, tyrosine kinas inhibitor; UK, United Kingdom; VEGF, vascular endothelial growth factor

Table 30: Treatments used from 1st line to 4th line across three real world evidence studies

	RECCORD (Wagstaff 2016)	Hawkins 2020	UK RWE 2022
	%	n	%
1L			
Ave+axi	0	0	12.7
Cabo	0	0	8.6
Nivo+ipi	0	0	23.4
Pazo	11.7	37.7	17.7
Suni	78.6	60.7	24.7
Tivo	0	0	7.9
Other	9.8[a]	1.5	4.9
2L			
Axi	4.9	57.1	3.0
Cabo	0	0	38.8
Lenv+evero	0	0	4.6
Nivo	0	0	37.3
Evero	53.1	41.9	
TKI (suni, pazo)	24.7		
Other	17.3[a]	1.0	16.3
3L			
Axi	31.3	22.2	11.2
Cabo	0	0	48.1
Lenv+evero	0	0	13.1
Evero	50.0	72.2	4.2
Nivo+ipi	0	0	0.5
Nivo	0	0	19.6

	RECCORD (Wagstaff 2016)	Hawkins 2020	UK RWE 2022
Pazo	0	0	0.5
Suni	0	0	2.3
Tivo	0	0	0.5
Other	18.5	5.6	-
4L			
Axi	0	0	42.6
Belz	0	0	1.85
Cabo	0	0	14.81
Lenv+evero	0	0	9.26
Evero	0	0	20.37
Nivo	0	0	5.56
Other	0	0	3.7
Suni	0	0	1.85
5L			
Axi	0	0	42.86
Belz	0	0	57.14
Total	0	0	100

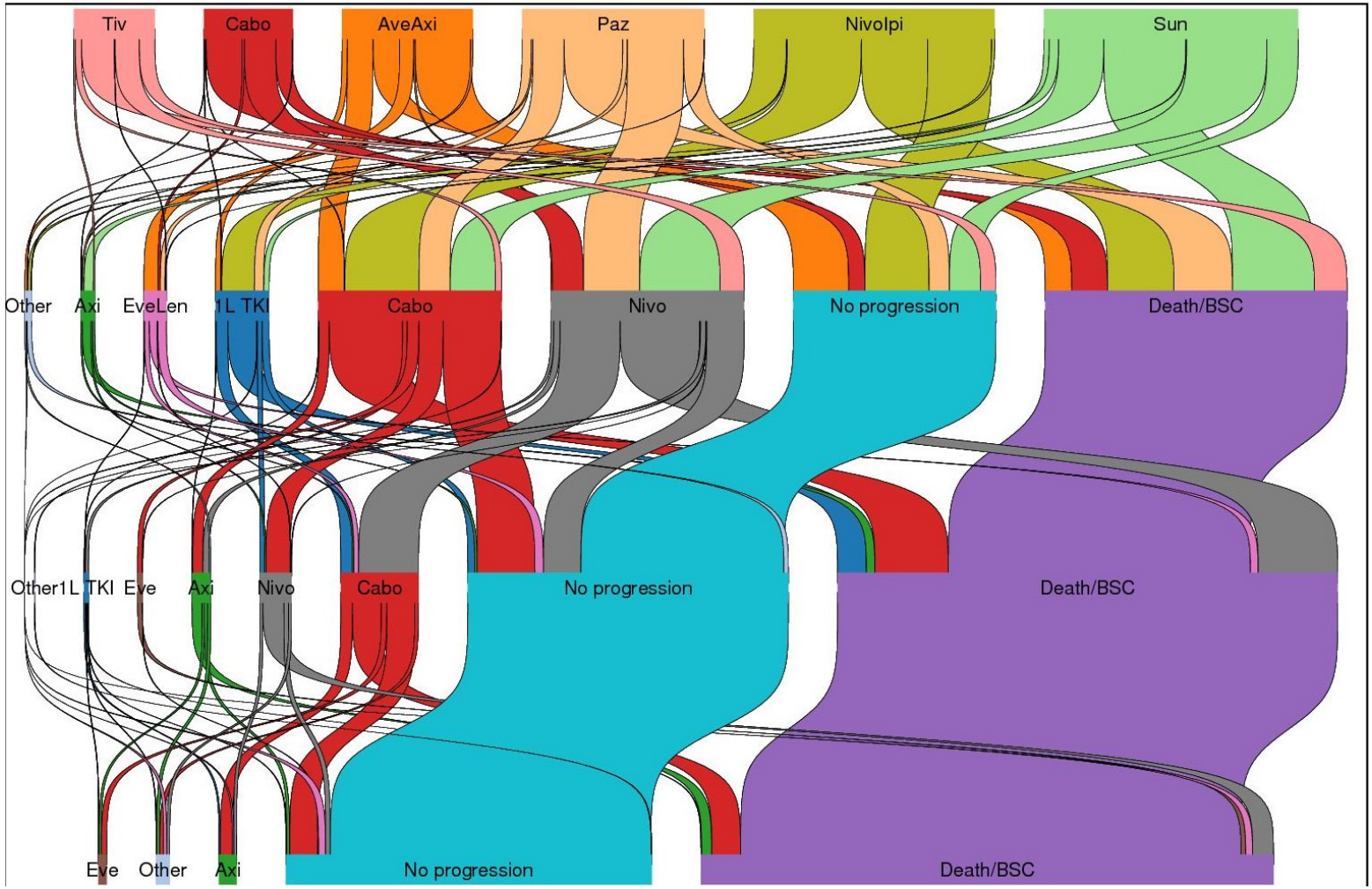
Abbreviations: axi, axitinib; ave, avelumab; belz, belzutifan; cabo, cabozantinib; evero, everolimus; ipi, ipilimumab; lenv, lenvatinib; nivo, nivolumab; pazo, pazopanib; RWE, real world evidence; sora, sorafenib; suni, sunitinib; tivo, tivozanib; UK, United Kingdom

Notes:

aOther grouping included treatments not recommended by NICE or not in the treatment pathway set out in Figure 6: 1L → evero 6.4%; sora 1.2%; tem 0.8%; IL-2 0.6%); IFNα 0.4%; Other 0.4%; 2L → sora 3.7%; tem 1.2%; IL-2 2.5%; other 9.9%

Sources: RECCORD (Wagstaff);[22] Hawkins 2020;[32] UK RWE 2022[53]

Figure 9: Sankey diagram for UK real-world evidence



Abbreviations: 1L, 1st line; Ave, avelumab; Axi, axitinib; BSC, best supportive care; Cabo, cabozantinib; Evero, everolimus; Evero+Len, everolimus + lenvatinib; Nivo+Ipi, nivolumab + ipilimumab; Paz, pazopanib; Sun, sunitinib; TIV, TKI, tyrosine kinase inhibitor

Notes: Patients receiving treatments not currently prescribed in the NHS have been removed from 1st line for readability.

Source: UK RWE 2022[53]

Hospital pharmacy audit data (IQVIA[137]) provided by the company in response to clarification question A1 were provided (Figure 10). These data suggest that [redacted] than other RCC agents in the UK. Although the data do not distinguish between lines of therapy or indication for the different tyrosine kinase inhibitors (TKIs), it can be seen that [redacted]. In addition, the EAG note the [redacted] and a [redacted].

Figure 10: Hospital pharmacy audit data: volume sales by product

[redacted]

Key: Cabometyx = cabo; Fotivda = tivo; Inlyta = axi; Kisplyx = lenv; Sutent = suni; Votrient = pazo
Abbreviations: axi, axitinib; cabo, cabozantinib; lenv, lenvatinib; pazo, pazopanib; suni, sunitinib; tivo, tivozanib
Source: IQVIA 2022[137] (provided by the company in response to clarification question A1

An additional three studies provided information on subsequent therapies following a defined 1st line therapy: two studies described subsequent treatment distributions following 1st line treatment with nivolumab + ipilimumab (SACT TA780[48]; CARINA [Nathan, 2023[136]]); one study described subsequent treatment distributions following treatment with axitinib + avelumab (CARINA [Nathan, 2023[136]]); and, a third study (Brown 2021[133]) described treatment patterns and sequence in patients who received 2nd line-plus cabozantinib or 2nd line-plus axitinib. A summary is provided in Table 31.

Table 31: Sequences described following defined 1st line therapy

	SACTTA780[48]	**Nathan 2023[136] (CARINA: NCT04957160)**		**Brown 2021[c133]**	
N	814	129		440	1,045
1L treatment					
Suni	-	-	-	N=186	N=422

	SACTTA780[48]	**Nathan 2023[136] (CARINA: NCT04957160)**		**Brown 2021[c133]**	
Pazo	-	-	-	N=178	N=500
Nivo+ipi	814 (100%)[a]	107 (82.9%)[b]	-		
Ave+axi	-	-	22 (17.1%)[b]		
Other	-	-	-		
N	**234 (29%)**	**107 (82.9%)**	**22 (17.1%)**	**NR**	**NR**
2L treatment					
Cabo	139 (59.4%)	80 (74.8%)	7 (31.8%)	N=377	0
Suni	31 (13.2%)	14 (13.1%)	1 (4.5%)	0	0
Pazo	28 (12%)	3 (2.8%)	0	0	0
Tivo	19 8.1%)	3 (2.8%)	1 (4.5%)	0	0
Axi	6 (2.6%)	2 (1.9%)	0	0	N=919
Nivo	0	0	2 (9.1%)	0	0
Bev	0	1 (0.9%)	0	0	0
Lenv+evero	5 (2.6%)	1 (0.9%)	10 (45.5%)	0	0
Dabref+tram	2 (0.9%)	0	0	0	0
Pem+carbo	1 (0.4%)	0	0	0	0
Pem+axi	0	2 (1.9%)	0	0	0
Ave+axi	0	1 (0.9%)	0	0	0
Nivo+ipi	0	0	1 (4.5%)	0	0
Evero	1 (0.4%)	0	0	0	0
Irin MDG Panit	1 (0.4%)	0	0	0	0
Trial	1 (0.4%)	0	0	0	0
N				27.7%	34.4%
3L Treatment					
Nivo				N=68	N=171
Axi				N=7	0
Cabo				0	N=49

Abbreviations: ave, avelumab; axi, axitinib; bev, bevacizumab; cabo, cabozantinib; carbo, carboplatin; CDF, Cancer Drugs Fund; dabref, dabrafenib; evero, everolimus; irin, irinotecan; lenv, lenvatinib; MDG, modified de gramont; NICE, National Institute for Heath and Care Excellence; nivo, nivolumab; panit, panitumumab; pazo, pazopanib; pem,, pembrolizumab; SACT, Systemic Anti-Cancer Therapy (data set); suni, sunitinib; TA, technology appraisal; tivo, tivozanib; tram, trametinib

Notes:

[a]Study cohort was participants who had received nivolumab + ipilimumab 1st line in the CDF

[b]Study cohort was participants who had received a 1st line combination therapy including a checkpoint inhibitor

[c]Total for cabo cohort n=440 and total for axitinib cohort n=1,045. The denominator for the reported sequences was unclear from the information available in the conference abstract and data are reported as seen

3.6.3.2. Overall survival

OS was reported in eight sources (Table 32). The studies evaluated various interventions and lines of therapy and typically reported median OS as well as OS rates at different time points, a summary is provided in Table 32.

OS data for RCC were sourced from the NCRAS-published 'Kidney' dataset via the Get Data Out (GDO) platform.[19] These data are reported in Section 2.2.

The Kidney Cancer UK audit report[135] reported post-operative 12-month all-cause survival in M0 kidney cancer patients who undergo radical nephrectomy (RN) or nephron sparing surgery (NSS). A total of 241 (2.8%) of M0 patients who had RN or NSS died in the 365 days after surgery. The most common underlying cause of death for M0 patients who were treated with RN or NSS in the year after their surgery was kidney cancer, accounting for 53.8%. Circulatory disease and other cancers were underlying causes for over 30 deaths each (14.3% and 13.4% of patients respectively).

In the UK RWE (2022[53]) data set, the median OS for patients who received 1st line treatment was [redacted] (95% CI [redacted]) months. The survival estimate was [redacted]% at 12 months falling to [redacted]% at 48 months. For those patients who received a 2nd line treatment, median OS from 2nd line treatment initiation was [redacted] months with a one-year survival estimate of [redacted]%. For those patients who received a 3rd line treatment, median OS from 3rd line treatment initiation was [redacted] months with a one-year survival estimate of [redacted]%. For those patients who received a 4th line treatment, median OS from 4th line treatment initiation was [redacted] months with a one-year survival estimate of [redacted]%. The analysis found that [redacted] (Figure 11). A log-rank test stratifying OS at 1st line by favourable or intermediate/poor status generated [redacted], with a Cox HR of [redacted] (95% CI [redacted]). Refer to Appendix L for Kaplan Meier curves of OS histology, line of treatment, treatment type (by line of treatment), treatment at 1st line by risk category.

Figure 11: UK RWE: Risk stratified overall survival at 1st line

Abbreviations: fav, favourable; int, intermediate; RWE, real world evidence; UK, United Kingdom

Similarly in the Hawkins (2020)[32] analysis median OS decreased with each subsequent treatment. The Hawkins (2020)[32] study found that the Memorial Sloan Kettering Cancer Centre (MSKCC) risk score had a significant impact on OS. Patients with a favourable-risk score had the best survival outcomes, while those with a poor-risk score had the lowest survival outcomes. In both 1st line treatment and 2nd line treatment, significant differences were observed between OS and MSKCC classification ($p<0.001$). At both lines of treatment, favourable-risk patients achieved the best survival outcomes (median OS; 39.7 months [1st line], 14.3 months [2nd line]), compared with intermediate-risk (median OS; 15.8 months [1st line]; 8.9 months [2nd line]), and poor-risk patients (median OS; 6.1 months [1st line] and 3.3 months [2nd line]). The year of treatment initiation also influenced survival, with better outcomes observed for patients treated between 2012 and 2015 (14.2 months) compared to those treated between 2008 and 2011 (11.8 months).

In the RECCORD (Wagstaff 2016[22]) data set, median OS was measured from 1st line treatment initiation and was 23.9 (95% CI 18.6–29.1) months over 13.8 months follow-up. Median OS of patients who received second-line treatment (33.0 months) was significantly longer ($p=0.008$) than that of patients who only received 1st-line treatment (20.9 months. Median OS was significantly longer in participants who switched to 2nd line treatment The authors note that this

may be due to selection bias (good prognosis patients are more likely to receive further therapy), an artefact of the relatively short follow-up period in the study, or because post 1st-line therapy is causing prolongation of survival. pattern was seen when considering the switch to third-line treatment, although it did not reach statistical significance, most likely due to the limited number of patients in this group. In addition, the time interval between diagnosis and systemic treatment was significantly associated with OS ($p<0.001$). Patients who received treatment within 100 days of diagnosis had a lower OS from the start of systemic treatment compared to those who initiated treatment 600 days or more after diagnosis. Toxicity-induced dose decreases also had a significant association with OS ($p=0.002$). Patients who experienced dose decreases in their 1st line treatment had a median survival time of 30.6 months, while for other patients, it was 19.8 months.

The OS observed in the Hawkins (2020)[32] analysis was found to be lower compared to the results reported in the earlier RECCORD database analysis, as well as in the UK RWE (2022)[53] dataset. Several factors could explain the lower median OS observed in Hawkins (2020) when compared to RECCORD and the UK RWE.

Firstly, the RECCORD (Wagstaff 2016)[22]study only included patients with clear cell RCC, which constituted 80% of the cohort in Hawkins (2020)[32] and 82% of the UK RWE dataset. Additionally, the median age of patients in the RECCORD study was younger at 61 years compared to 65 years (mean age) in the UK RWE dataset[53] and 64 years in the Hawkins (2020)[32] dataset. The difference in patient selection and in age distribution could contribute to variations in OS outcomes.

Another potential reason for the lower median OS observed in Hawkins (2020)[32] compared to RECCORD[22] is the inclusion of patients on clinical trials in the RECCORD[22] dataset, as well as a small number of patients receiving IL-2 or IFN-α. Hawkins (2020)[32] suggests that the inclusion of these patients in RECCORD[22] could have contributed to a higher median OS. Hawkins (2020)[32] conducted a subgroup analysis of 89 patients excluded from the main analysis because they received IL-2 or IFN-α at any point during the study. This analysis revealed a substantially longer median OS (47.5 vs. 12.9 months for 1st-line treatment) compared to patients treated exclusively with NICE/CDF-recommended systemic therapies. This discrepancy reflects the fact that the Manchester Centre, where the study took place, is a national treatment centre for high-dose IL-2, which can yield excellent outcomes in carefully selected patients. Furthermore, an additional 72 patients were excluded from the Hawkins (2020)[32] analysis

because they participated in clinical trials where systemic therapies were not administered within the standard of care. These excluded patients could have biased the OS in favour of better outcomes and may partially explain the shorter OS observed in the Hawkins (2020)[32] analysis compared to similar studies.

These differences (patient selection, age, treatment mix) could in part explain the differences between the median OS in the UK RWE (2022)[53] and the Hawkins (2020)[32] dataset, the longer median OS observed in the UK RWE could also potentially be attributed to the availability of newer treatments during the study period. In Hawkins (2020),[32] the majority of participants received sunitinib (60.7%) or pazopanib (37.7%), whereas the UK RWE[53] dataset showed a different distribution with participants receiving avelumab + axitinib (12.7%), nivolumab + ipilimumab (23.4%), cabozantinib (8.6%), tivozanib (7.9%), sunitinib (24.7%), and pazopanib (17.7%) (refer to Section 3.6.3.1 and Table 30).

Overall, the variations in patient selection, age distribution, inclusion of patients on clinical trials, use of specific treatments, and exclusion of certain subgroups can all contribute to the differences observed in median OS between the studies mentioned.

Four other studies reported median OS associated with specific interventions in the aRCC population:

- Nivolumab + ipilimumab as a 1st line treatment showed survival rates at six, 12 and 18 month timepoints of 80%, 69%, and 61%, respectively and median OS was not reached. Sensitivity analysis by IMDC score showed a similar pattern in survival rates at six, 12 and 18 month timepoints gave a median OS of 15 months for IMDC score 3-6 and median OS was not reached in patients with an IMDC score of 1-2;[48]
- Cabozantinib and axitinib as 2nd line treatments demonstrated similar median OS[133] Median OS was lower in RWE than in clinical trials for both cabozantinib (versus everolimus) and for axitinib (versus sorafenib) (Table 13)
- Nivolumab in 2nd and subsequent lines of treatment showed a 12-month survival rate of 56.88%. OS data not reported for CheckMate 025 (median OS not reached) with which to compare (Table 13);[134] and,

Avelumab + axitinib 1st line treatment showed a 12-month OS rate of 86%.[132] OS data not reported for JAVELIN Renal 101 (not estimable) with which to compare (Table 13).

Table 32: Overall survival estimates from RWE

Study	LOT	Intervention	OS definition	N	Median follow-up (95% CI)	Median OS months (95% CI)	OS rate at:
UK RWE 2022[53]	1L	Ave+axi; cabo; nivo+ipi; pazo; suni; tivo	Time from start of 1L treatment to death	1,319	16.8 months (15.8, 17.6)	[redacted]	12 mths: [redacted] 24 mths: [redacted] 36 mths: [redacted] 48 mths: [redacted]
	2L	Axi; cabo; lenv+evero; nivo; pazo; suni; tivo	Time from start of 2L treatment to death	632		[redacted]	12 mths: [redacted] 24 mths: [redacted] 36 mths: [redacted]
	3L	Axi; cabo; lenv+evero; nivo; suni	Time from start of 3L treatment to death	214		[redacted]	12 mths: [redacted] 24 mths: [redacted] 36 mths: [redacted]
	4L	Axi; evero	Time from start of 4L treatment to death	54		[redacted]	12 mths: [redacted] 24 mths: [redacted]
Hawkins 2020[32]	1L	Suni; pazo; evero; Other	Time from the start of 1L treatment to death	652	Mean 23.8 (22.2, 25.4)	12.9 (NR)	12 mths; 52.4% (48.6, 56.4%) 24 mths: 30.9% (27.3, 34.9%) 36 mths: 22.6% (19.3, 26.6%) 60 mths: 10.8% (8.0, 14.6%)
	2L	Suni; axi; evero; Other	Time from the start of 2L treatment to death	184	Mean 21.5 (NR)	6.51 (NR)	12 mths: 31.5% (25.2, 39.5%) 24 mths: 17.0% (11.8, 24.7%) 36 mths: 7.1% (3.1, 16.5%) 60 mths: 7.1% (3.1, 16.5%)
	2L	Suni; axi; evero; Other	Time from the start of 1L treatment to death	184	Mean 21.5 (NR)	20.8 (NR)	NR

Study	LOT	Intervention	OS definition	N	Median follow-up (95% CI)	Median OS months (95% CI)	OS rate at:
	3L	Axi; evero; other	Time from the start of 3L treatment to death	18	Mean 26.1 (NR)	5.91 (NR)	12 mths: 23.8% (10.1, 55.9%); 24 mths: 7.9% (1.3, 48.7%)
	3L	Axi; evero; other	Time from the start of 1L treatment to death	18	Mean 26.1 (NR)	36.7 (NR)	NR
Wagstaff 2016 (RECCORD)[22]	1L; 2L; 3L	As listed for 1L, 2L, and 3L	Time from the start of 1L treatment to death	431	13.1 (12.0, 14.1)	23.9 (18.6, 29.1)	NR
NICE TA780:[48] SACT data report	1L	Nivo+ipi	Time from the start of their treatment to death or censored date	814	3 (NR) (91 days)	Not reached	6 mths: 80% (77, 83%) 12 mths: 69% (65, 72%) 18 mths: 61% (57, 64%)
		Nivo+ipi (≥6 mths follow-up[b])		757	11.9 (NR)	Not reached	NR
		Nivo+ipi (IMDC Int, score 1 or 2)		533	8.7 (NR)	Not reached	6 mths: 88% (84%, 90%) 12 mths: 76% (72%, 80%) 18 mths: 69% (64%, 73%)
		Nivo+ipi (IMDC poor, score 3 or 4)		281	NR	15 (NR)	6 mths: 67% (61%, 72%) 12 mths: 55% (49%, 61%) 18 mths: 45% (38%, 51%)
Brown 2021[133]	≥2L	Cabo	NR	816	NR	11.24 (5.65, 27.98)[a]	NR
		Axi		1,483		10.39 (4.70, 22.03)[a]	NR
Hack 2019[134]	≥1L	Nivo	Time from the start of treatment to death	109	NR	NR	12 mths: 56.88% (NR)
Hilser 2023[138]	1L	Cabo+nivo	NR	67	8.3 (NR)	Not reached	NR
Nathan 2022[132]	1L	Ave+axi	NR	36	12 (NR)	NR	12 mths: 86% (74.8, 97.4%)

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; ave, avelumab; axi, axitinib; cabo, cabozantinib; CI, confidence interval; evero, everolimus; IFNα, interferon alfa; IL-2, interleukin 2; ipi, ipilimumab; mths, months; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; NR, not reported; OS, overall survival; pazo, pazopanib; RWE, real-world evidence; SACT, systemic anti cancer therapy; sora, sorafenib; suni, sunitinib; TA, technology appraisal; tem, temsirolimus; Tx, treatment; UK, United Kingdom

Notes:

Kidney Cancer UK audit report and the NCRAS data reported in a separate table as OS reported by disease stage or post-operative survival rather than by intervention

[a]Propensity score matching (IPW) was used to reduce baseline differences between the cohorts

[b]Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 5 April 2019 to 28 October 2020.

3.6.3.3. Progression-free survival

Four sources reported data on PFS. A summary is provided in Table 33.

The UK RWE (2022[53]) cohort reported a median PFS for 1st line treatment of [redacted] months (95% CI [redacted]) reducing to [redacted] months (95% CI [redacted]) in the cohort of patients receiving 4th line treatment (Table 33). Survival curves for PFS at 1st, 2nd, 3rd, and 4th line are provided in (Figure 12, Figure 13, Figure 14, and Figure 15, respectively). Refer to Appendix L for Kaplan Meier curves of PFS stratified by risk group, histology, treatment, and line of treatment, and post progression survival.

In a retrospective cohort study (Feb 2016 to Apr 2019; England) evaluating nivolumab in 2nd and subsequent lines of treatment (Hack 2019),[134] 31.5% showed a response to nivolumab, 9.3% had stable disease and 59.3% had disease progression. Reported median PFS from the start of nivolumab treatment was 5.4 months (Table 33).

In a retrospective cohort study (Hilser 2023)[138] evaluating patients with mRCC receiving cabozantinib + nivolumab 1st line the PFS rate at six months was 81.9% (Table 33). This was broadly aligned with the rate reported in the CheckMate 9ER trial for cabozantinib + nivolumab (79.6%) (Section 3.3.3.2).

A prospective cohort study (Aug 2019 to Jan 2022; UK) evaluating patients with aRCC receiving avelumab + axitinib 1st line via an early access scheme (Nathan 2022),[132] reported median duration of follow-up and PFS of 12 months (Table 33).

Three sources reported TTP:

- In the UK RWE (2022[53]) data set, median TTP at 1st line was [redacted] months (95% CI [redacted]). The correlation of TTD and PFS (1st line) and TTP (1st line) is [redacted] (Spearman's correlation). Refer to Appendix L for Kaplan Meier curves of time to progression by line of treatment, and for time to progression on 1st line treatment risk stratified.
- In the RECCORD study (Wagstaff 2016),[22] at the time of analysis, disease progression had been experienced by the majority (66.1%) of patients on 1st line therapy (median duration of follow-up: 13.1 months, 95% CI 12.0–14.1 months). Median time to disease progression was 8.8 months (95% CI 7.7–9.9 months). There was a significant association between the time from RCC diagnosis to 1st line treatment and disease progression (p=0.019). Estimated time to progression was shortest for patients who had started 1st line treatment within 100 days of diagnosis (16.8 months [95% CI 14.1–19.5 months]).
- Hack (2019)[134] reported 59.3% had disease progression in the cohort of mRCC patients who received nivolumab in 2nd line-plus treatment. TTP was not reported.

Figure 12: UK RWE: Pooled PFS at 1st line

Abbreviations: RWE, real world evidence; UK, United Kingdom

Figure 13: UK RWE: Pooled PFS at 2nd line

Abbreviations: RWE, real world evidence; UK, United Kingdom

Figure 14: UK RWE: Pooled PFS at 3rd line

Abbreviations: RWE, real world evidence; UK, United Kingdom

Figure 15: UK RWE: Pooled PFS at 4th line

Abbreviations: RWE, real world evidence; UK, United Kingdom

Table 33: Progression-free survival estimates from RWE

Study	LOT	Intervention	Median follow-up	Time on treatment	N	Median PFS mths (95% CI)	PFS rate %
UK RWE 2022[53]	1L	Suni; cabo; nivo+ipi; pazo; tivo	16.8 months (15.8, 17.6)	[redacted]	[redacted]	[redacted]	[redacted]
	2L	Axi; cabo; lenv+evero; nivo; pazo; suni; tivo		[redacted]	[redacted]	[redacted]	[redacted]
	3L	Axi; cabo; lenv+evero; nivo; suni		[redacted]	[redacted]	[redacted]	[redacted]
	4L	Axi; evero		[redacted]	[redacted]	[redacted]	[redacted]
Hack 2019[134]	2L; 3L; 4L+	Nivo	NR	NR	109	5.4 (NR)	NR
Hilser 2023[138]	1L	Cabo+nivo	8.3 (NR)	NR		NR	6 mths 81.9%
Nathan 2022[132]	1L	Ave+axi	12 (NR)	NR	36	12 (NR)	NR

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; ave, avelumab; axi, axitinib; cabo, cabozantinib; CI, confidence interval; evero, everolimus; IO, immune-oncology; ipi, ipilimumab; lenv, lenvatinib; LOT, line of treatment; mths, months; nivo, nivolumab; NR, not reported; pazo, pazopanib; PFS, progression free survival; RWE, real world evidence; suni, sunitinib; tivo, tivozanib; UK, United Kingdom

3.6.3.4. Time to next treatment

Three sources reported time to next treatment (Table 34).

Table 34: Time to next treatment estimates from RWE

Study, year	N	LOT → LOT	Median time (months) to next treatment (95% CI)
UK RWE 2022[53]	1,319 1L → 604 2L	1L → 2L	[redacted]
RECCORD Wagstaff 2016[22]	514 1L → 81 2L	1L → 2L	2009 to 2010: mean 17.4 (SD 11.8) 2010 to 2011: mean 12.3 (SD 7.1) 2011 to 2012 cohort: mean 6.3 (SD 3.7)
SACT TA780[48]	814 1L → 234 2L	1L → 2L	41 days (from last nivo+ipi cycle to next Tx); 148 days (from first nivo+ipi cycle to next Tx)

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; AE, adverse event; CI, confidence interval; evero, everolimus; IFNα, interferon alpha; IL2, interleukin 2; ipi, ipilimumab; LOT, line of treatment; nivo, nivolumab; NR, not reported; pazo, pazopanib; RWE, real world evidence; SACT, Systemic Anti- Cancer Therapy; SD, standard deviation; sora, sorafenib; suni, sunitinib; tem, temsirolimus; Tx, treatment

Notes:

[a]As a percentage of patients who already experienced one dose decrease

[b]Includes n=35 patients who changed to a different 1st line treatment due to toxicity

3.6.3.5. Discontinuation

Five sources reported data on discontinuation (Table 35).

Treatment duration by treatment type at 1st line, 2nd line, 3rd line, and 4th line for the UK RWE data set is provided in Appendix L

Table 35: Discontinuation estimates from RWE

Study, year	LOT	N	Median follow-up mths (95% CI)	Discontinuations, n (%)	Median TTD (months) to discontinuation (95% CI)	Reason for discontinuation n (%)
UK RWE 2022	1L	1,319	16.8 months (15.8, 17.6)	[redacted]	Treatment duration by treatment type at 1L in Appendix L	[redacted]
	2L	604		[redacted]	Treatment duration by treatment type at 2L in Appendix L	[redacted]
	3L	202		[redacted]	Treatment duration by treatment type at 3L in Appendix L	[redacted]
	4L	48		[redacted]	Treatment duration by treatment type at 4L in Appendix L	[redacted]
Hawkins 2020[32]	1L	652	23.8 (22.2, 25.4)	574 (88.0)	10.5 (9.5, 11.6)	Disease progression 411 (71.6); treatment toxicity/ AE 108 (18.8); Other 106 (18.5)
	2L	184		159 (86.4)	5.2 (4.2, 6.3)	Disease progression 115 (72.3); treatment toxicity/ AE 31 (19.5); Other 33 (20.8)
	3L	18		16 (88.9)	5.6 (1.7, 9.5)	Disease progression 11 (68.8); treatment toxicity/ AE 5 (31.3); Other 2 (12.5)
Wagstaff 2016[22]	1L	514	13.1 (12.0, 14.1)	97 (18.9) [b]; 27 (17.1)[a]	4.0 (0.2–5.8) (time to discontinuation of a 1st line drug)	NR
	2L	81		12 (14.8); 0 (0)	NR	NR
	3L	16		2 (12.5); 0 (0)	NR	NR

Study, year	LOT	N	Median follow-up mths (95% CI)	Discontinuations, n (%)	Median TTD (months) to discontinuation (95% CI)	Reason for discontinuation n (%)
SACT TA780[48]	1L	814	3 (NR)	NR	NR	At end of treatment: 469 (58%) stopped treatment: Died not on treatment 131 (28%); disease progression 128 (27%); toxicity 94 (20%); no treatment in at least 3 mths 65 (14%); died on treatment 24 (5%); completed as prescribed 23 (5); patient choice 2 (<1%); COVID 2 (<1%)
Nathan 2022[132]	1L	36	NR	5	NR	Disease progression 4 (11); toxicity 1 (3)
CARINA Nathan 2023[138]	1L	118	NR	NR	10.2 weeks (9.1, 17.1)	NR
	1L subgroup of cabo 2L	83	NR	NR	9.1 weeks (8.1, 12.0)	NR
	2L	129	NR	NR	23.6 weeks (14.0, 28.3)	NR
	2L cabo subgroup	87	NR	NR	28.1 weeks (20.1, 37.1)	NR

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; AE, adverse event; CI, confidence interval; LOT, line of treatment; mths, months; NR, not reported; RWE, real world evidence; SACT; Systemic Anti-Cancer Therapy (data set); TA, technology appraisal; TTD, to discontinuation

Notes:

[a]As a percentage of patients who already experienced one dose decrease
[b]Includes n=35 patients who changed to a different 1st line treatment due to toxicity

3.6.3.6. Health-related quality of life

None of the included real-world evidence studies reported HRQoL.

3.6.3.7. Costs

None of the included real-world evidence studies reported costs.

The UK RWE did report data that enabled the calculation of relative dosing intensity (RDI) which can be used to calculated drug costs, these data are provided in Appendix L.

3.7. Indirect comparisons

3.7.1. Methods

RCTs were synthesised using appropriate meta-analysis methods. Evidence networks for each outcome were formed by decision point on the pathway (i.e. line of treatment or class of prior treatment), combining 2nd, 3rd and 4th line RCC due to trials generally including patients who were previously treated at multiple lines and similar comparator sets.

The feasibility of network meta-analyses (NMAs) was considered by examining where possible the distribution of likely effect modifiers over the networks. Clinical advisors highlighted IMDC prognostic risk category, histology (though information is limited to clear cell vs non clear cell), whether the patient had a prior nephrectomy, and sarcomatoid features (discussed in Section 2.3). We further considered trial results (including interactions in forest plots), any relevant discussion from TA858, and information in the company submission. Due to clinical salience and consistency (and inconsistency) of reporting, we focused on risk, age, line, bone metastases, sarcomatoid features, prior nephrectomy and histology as key effect modifiers, including line where trials included combinations of treated and untreated patients. We did not judge that the feasibility of any NMAs was precluded, but note that relatively sparse evidence networks precludes formal testing via e.g. meta-regression for differences between groups, and consider how analyses might have been impacted by distribution of effect modifiers across the network (see Section 3.7.2.2). In some proportional hazards NMAs in 1st line, we sensitivity analysed findings excluding trials that did not enrol poor-risk patients, partly because several trials suggested that TKIs were not differently effective from more modern (IO or IO combinations) in favourable-risk patients.

Separate networks were formed by line of treatment (1st line or 2nd line-plus) and for 1st line treatment further stratified by IMDC risk subgroup.

If the network contained a clear reference treatment (placebo or standard of care or a central node) then baseline risk was compared across trials using PFS in the reference treatment. The baseline risk serves as a rough proxy for treatment effect modifiers across the trials, some of which may not have been measured or collated. Heterogeneity in baseline risk may point to variation in the distribution effect modifiers over the network, and therefore potential bias in network-based treatment effect estimates.

The set of selected trials from the search process (Section 3.3.1 and 3.3.2) were processed according to Steps two and three of the algorithm outlined by Dias et al.[141] namely: (2) identify all the trials that compare two or more comparators in the population of interest (3) remove trial arms that are not comparators of interest from trials with more than two arms.

Where necessary, connecting nodes were introduced which function to connect networks but do not in themselves represent comparators of interest, similar to the process in TA858.[38] As described above, these nodes were sorafenib and placebo.

NMAs were carried out for the following time-to-event outcomes: PFS and OS. Investigations on the feasibility of time-to-event NMAs for time-on-treatment and time-to-next-treatment indicated insufficient studies available.

Continuous and binary outcomes were further grouped with respect to similarity of follow-up times and combined using odds ratios, as appropriate. Time to event outcomes were analysed using two strategies: one primary and one exploratory. The exploratory strategy, for all time-to-event outcomes, relied on hazard ratios from longest follow-up combined after log transformation using an inverse variance method. We also describe these as ‘proportional hazards NMAs’.

The primary strategy, which focused on PFS as a priority outcome, used a parametric modelling method. OS was included as a secondary outcome. PFS was defined as the time from treatment initiation to the first of RECIST-defined progression or death assessed by BICR, with IA-assessed PFS used if BICR was not available.

3.7.1.1. Fractional polynomial NMAs

The first strategy used fractional polynomial analyses as, based on previous appraisals in RCC, it is expected that there may be issues in justifying proportional hazards for all endpoints. Model selection compared second-order fractional polynomials (except 'repeated powers') drawn from the set of powers defined by −2, −1, −0.5, 0, 0.5, 1, 2, 3 as standard.[142]

Pseudo-individual patient data (IPD) data for survival were requested from the submitting company who provided PFS and OS data for a subset of the EAG network. Further curves were digitised by the EAG. Grouped survival data were then formed in time intervals. The EAG attempted to use the planned grouping interval for survival data of one week (consistent with the model cycle length) but model fits were poor. The EAG elected to use eight weeks in order to obtain stable results and reduce coding manipulations (two months is the value coded by Wiksten[143]).

Initial fractional polynomial model selection used frequentist fixed effects models, identifying a candidate set of 'most likely' models on the basis of visual fit to observed data, clinical plausibility including elicited landmark survival estimates and biological considerations and statistical fit using Akaike Information Criterion (AIC).[143] Frequentist code was largely based on that provided by Wiksten.[143] The selected fractional polynomial model(s) were submitted to Bayesian analysis in the next stage.

A Bayesian analysis of selected models was carried out introducing random effects and comparing these to fixed effects models. Random effects were only be considered on the basis of 'time-invariant' heterogeneity, that is only using between-study variance on intercept terms.[142] The general framework used random effects in a Bayesian framework with Markov chain Monte Carlo estimation, including informative priors from Turner (2015)[144] where available and appropriate and vague or weakly informative priors otherwise. Turner 2015 offers priors for a set of generic scenarios in healthcare and associated types of outcomes. Specifically, an informative prior for the variance of LN(-3.95, 1.79^2) was used, which Turner offers for pharmacological vs pharmacological comparisons with outcomes relating to cause-specific mortality, major morbidity event and composite (mortality or morbidity) outcomes.

Estimation used two chains of 100,000 iterations with 20,000 iterations discarded as burn-in and thinning to every 10^{th} value. Bayesian model comparisons used Deviance Information Criterion

(DIC). Convergence was assessed using standard methods, including autocorrelation and Brooks-Gelman-Rubin diagnostic plots.

Bayesian coding utilised the gemtcPlus package.[145] Fitted curves were compared to the life-table estimates of the hazard following the equation given by Collett p29.[146]

To summarise, each fractional polynomial analysis fits 28 models under any risk and prior treatment subgroup, see for example Table 39 for the case line 1 PFS all risk. Any model selected from these fits is further fitted with fixed effect or random effect alternatives in a Bayesian analysis. An informed selection from these numerous models was made combining statistical criteria (selecting on the basis of smaller AIC or DIC) with clinical or logical plausibility. The steps were:

- Calculate AIC for all FP models with frequentist, fixed effects (FE) approach
- Select models with delta AIC≤5
- For each selected model, run Bayesian models (FE and random effects [RE]) and calculate
  - DIC
  - area under survival curve up to horizon (i.e. restricted mean survival time, or RMST)
- Select models where RMST > threshold for every treatment curve
- Select models best conforming to expert elicitation landmark distributions
- Select model with minimum DIC comparing random and fixed effects

Under expert elicitation the expected survival at five years (conditional on surviving to three) and 10 years (conditional on surviving to 5) were calculated for each model curve for the 1L intermediate/poor risk and 2nd line+ populations. These were compared with the elicitation distributions (Section 4.2). A good match to the expert elicitation was considered to be obtained when the point estimate for the FP NMA conditional survival fell within the 95% confidence interval of the expert elicitation result for that treatment. Models were selected where possible to maximise concordance with the expert elicitation noting that this was not possible in some cases.

Calculation of survival curves involved integration of the modelled hazard using the gemtcPlus package. Unstable results were obtained when the lower integration limit was set to near zero. The EAG attributes this to ‘end effects’ of fractional polynomials including singularities at 0 when exponents are negative. The EAG understands that the relevant gemtcPlus function effectively

applies a constant and finite initial hazard over a width determined by the user. The EAG set this to two weeks to avoid implausibly low survival curve estimates.

3.7.1.2. Proportional hazards NMAs and NMAs of other outcomes

Finally, meta-analyses on proportional hazards estimates were undertaken of survival outcomes, overall response rate, discontinuation due to adverse events and the risk of treatment-emergent adverse events of grade 3 or higher. The EAG also undertook a sensitivity analysis conducted using IA where available for the latest datacut. For trials which compared sequences of treatments, only the first treatment within the sequence was included within the analysis. Thus, for OS, the three relevant crossover trials (SWITCH, SWITCH II and CROSS-J-RCC) were excluded from the 1st line NMA. This is because (i) the results appeared to be reported as HRs for the difference between treatment sequences rather than between treatments (ii) as mentioned the crossover trials served only to connect tivozanib to the main network, and previous technology appraisals considered that an assumption of similar effectiveness to sunitinib was appropriate.[38,46]

The EAG used a Bayesian framework with 100,000 iterations per chain after 10,000 burn-in iterations were discarded and the resultant estimates thinned by using every tenth iteration. We used standard inconsistency and convergence checks on these models.

3.7.2. Characteristics and appraisal of trials identified and included in the indirect comparisons

The majority of included trials were associated with either 1st line or 2nd line-plus populations, but in one prioritised trial, TIVO-1,[103] the study population was mixed. In both cases analyses by line of treatment were available.

Networks were formed for 1st and 2nd line-plus treatments for the outcomes OS, PFS and ORR, taking into account availability of information (as HR, KM curves or response rates), and at 1st line for two IMDC risk categories: intermediate/poor and favourable. Network diagrams for 1st line PFS and OS (all risk) are shown in Figure 16 and Figure 17. Other networks in draft form are supplied in Appendix E.

Many networks are not complete. Following the precedent in TA858 and other previous RCC appraisals, two treatments (sorafenib, placebo) were introduced as connecting nodes. At 1st line, for PFS (Figure 4), this connects tivozanib and results in a complete network, but for OS

(Figure 5), tivozanib is excluded. This is in line with TA858 where the EAG considered that it was not possible to connect tivozanib to the OS network as the OS data required to connect the TIVO-1 trial came from crossover trials (CROSS-J-RCC, SWITCH and SWITCH II) which were not considered suitable as patients switched to the treatment they did not initially receive on progression. This is not considered to be a major issue given that the base case model structure does not use 1st line OS data and previous appraisals have considered that tivozanib is at best similar to pazopanib and sunitinib (TA858, TA645). The full results for excluded treatments with and without these connecting nodes are shown in the table in Appendix E.

For line 2+ networks under FP analyses, the BERAT trial was removed from the network; and indeed BERAT was only helpful for some network meta-analyses in other outcomes. The BERAT trial gives uninformative estimates of treatment effect (PFS HR for everolimus vs TKI was 1.0 (0.26 to 3.85) and OS HR was 1.12 (0.27 to 4.61)) relating to the small trial size (n=10). Inclusion of the trial caused instability in the FP NMA results. This trial also contains some design/reporting flaws, including lack of clarity about design (crossover or parallel group), no protocol available, no power calculation, and an apparent ad hoc extension beyond the planned treatment of axitinib to the class of TKI inhibitors (see the Clinical Trials Registry record for more details[147]). There are two corollaries: that (i) Inference to treatment with axitinib is lost, and that (ii) TIVO-1, TIVO-3 and AXIS trials are also removed, though these latter are not associated with treatments of primary interest. Similarly, for NMAs using proportional hazards and for other outcomes, our analyses relied substantially on the inclusion of BERAT as a linking trial between two components of the network: one defined by everolimus, nivolumab, placebo, everolimus with lenvatinib, and cabozantinib; and another defined by axitinib, sorafenib and tivozanib. This was an imperfect solution given the small size of the trial (n=5 in each arm) and documented issues with protocol administration. For ORR and discontinuation, problems with the data in BERAT (i.e. lack of events in one or both arms) meant that we could not connect both network components. In these analyses, we only present results for the first network component. We also had a disconnected network in our analysis for grade 3 or higher treatment-emergent adverse events, described below. Within subsequent cost-effectiveness analysis given the difficulties making comparison to axitinib within the NMA we test the assumption of equivalence with everolimus consistent with previous technology appraisals.

As can be seen in Figure 16 and Figure 17, for 1st line treatments sunitinib acts as a central node for all comparators of interest, with the exception of tivozanib. The networks are considerably more sparse for the risk subgroups (Appendix E) with no available risk subgroup

Kaplan-Meier curves for pembrolizumab + lenvatinib for PFS due to redaction in the NICE submission; in addition, OS subgroup data were not available for avelumab + axitinib. Risk subgroup Kaplan Meier curves were also not available for pazopanib for either OS of PFS. For the favourable risk subgroup the only trials of treatments recommended in this population where Kaplan Meier curves were available were CheckMate 9ER and JAVELIN Renal 101 and OS data was not available for JAVELIN Renal 101. Given this only time invariant NMA was conducted for the favourable risk subgroup. Proportional hazards NMAs at 2nd line-plus included all relevant comparators with the exception of pazopanib, as a reliable link could not be made to the network.

Figure 16: 1st line network diagram for PFS with summary HR and KM information

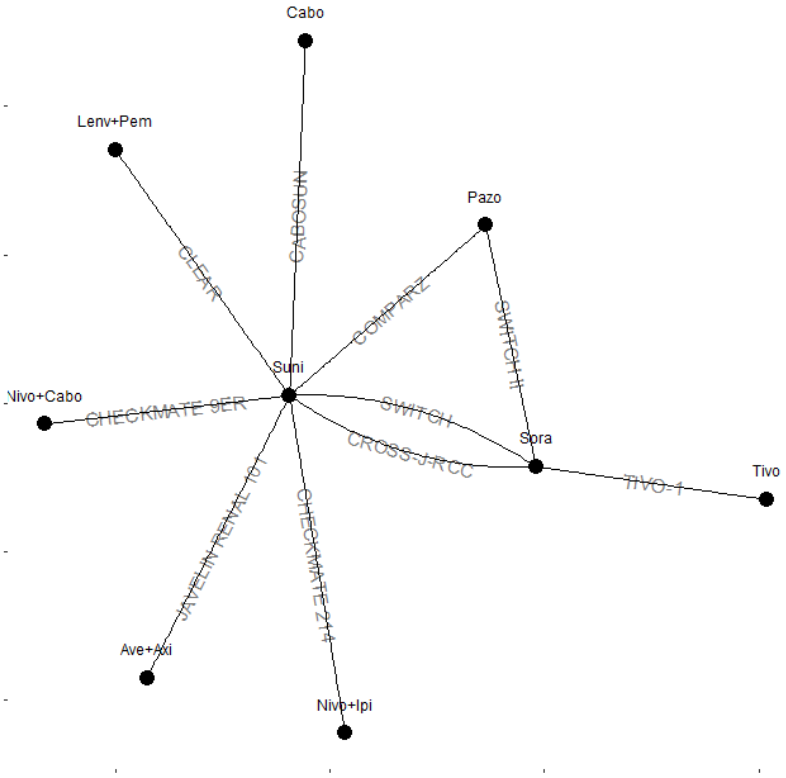
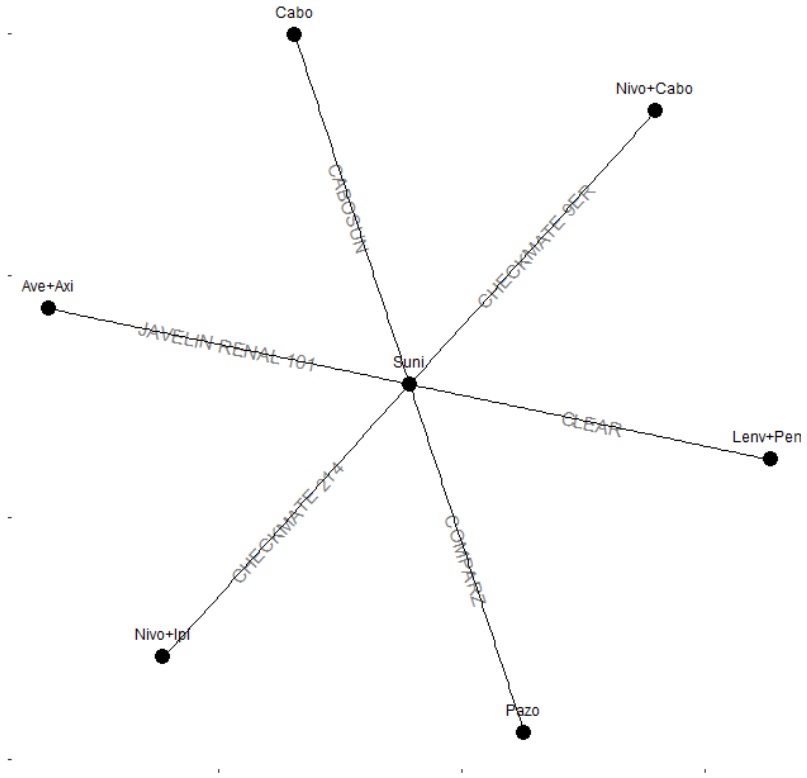


Figure 17: 1st line network diagram for OS with summary HR and KM information



3.7.2.1. Investigation of proportional hazards

Appendix E contains log cumulative hazard plots for included trials. Results of tests for proportional hazards using Schoenfeld residuals (i.e. Grambsch-Therneau tests) and based on EAG's digitisation of curves are provided in Table 36. Because these tests are based on our digitisations, there are likely small differences between the EAG's tests and published results; however, we were unable to precisely replicate results from CheckMate 9ER despite having IPD, possibly due to not being able to include stratifying factors in the analysis. In sum, there was clear and consistent evidence of non-proportional hazards across the network and for both outcomes. This is including with respect to key trials in the analysis, including CheckMate 9ER (also discussed in Section 3.4.3).

The EAG scrutinised log cumulative hazard plots alongside tests of proportional hazards. For PFS, visual assessment of proportional hazards was on several occasions at odds with significance tests. Aside from BERAT, where the small sample size meant a significance test would be underpowered, log cumulative hazard plots for CROSS-J-RCC, JAVELIN RENAL 101, SWITCH and TIVO-1 showed clear crossing of curves, in most cases on multiple time points. Plots with significant tests and visual checks suggesting non-proportionality included CheckMate 025, CheckMate 214, CheckMate 9ER, CLEAR, METEOR, and TIVO-3. Patterns in plots for CheckMate 025, CheckMate 214, CLEAR and TIVO-3 suggested crossing of hazards as well as a change in patterns over the time horizon. For CheckMate 025, CheckMate 214, and TIVO-3, hazards diverged over time, whereas for CLEAR hazards come closer together over time. Patterns in the plot for CheckMate 9ER (which had marginal significance in the EAG's test) suggested a clear separation of hazards over time and for METEOR a coming together of hazards over time.

For OS, findings between visual inspection and statistical tests largely matched, with the exception of TIVO-1, where the two trial arms crossed during the analysis time. Other plots with non-significant tests did not have visually obvious violations of proportional hazards. Visual inspection of plots for CLEAR showed a clear crossing and coming back together, and for CheckMate 9ER a clear separation and coming back together at the end of the analysis time.

These results indicate that an assumption of proportional hazards is unlikely to be valid within either the 1st line or 2nd line-plus aRCC setting.

Table 36: Results of tests for proportional hazards in the all-risk group using Cox regression

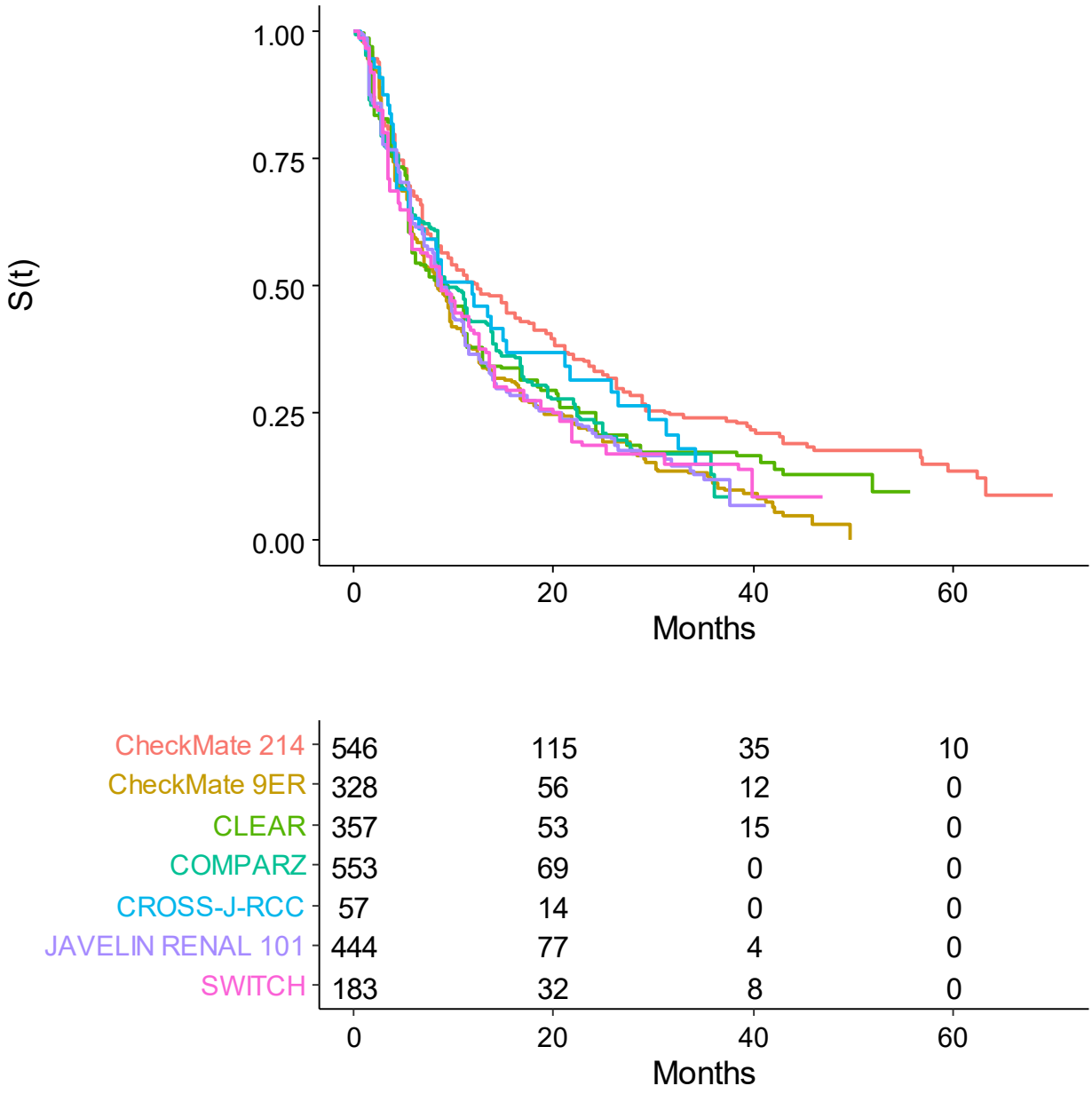
Study	P value: PFS	Visual check: PFS	P value: OS	Visual check: OS
AXIS	0.59	Yes	0.75	Yes
BERAT	0.13	No	NA	NA
CABOSUN	0.90	Yes	0.92	Yes
CheckMate 025	0.00016	No	0.34	Yes
CheckMate 214	0.000025	No	0.59	Yes
CheckMate 9ER	0.084	No	0.08	No
CLEAR	0.0027	No	0.00014	No
COMPARZ	0.25	Yes	0.44	Yes
CROSS-J-RCC	0.19	No	0.56	NA
JAVELIN RENAL 101	0.33	No	0.87	Yes
METEOR	0.032	No	0.56	Yes
NCT01136733	0.92	Yes	0.70	Yes
RECORD-1	0.66	Yes	0.31	Yes
SWITCH	0.15	No	0.32	NA
SWITCH II	0.72	Yes	0.43	NA
TIVO-1	0.29	No	0.83	No
TIVO-3	0.039	No	0.54	Yes

Note: Yes is no clear evidence of violation of proportional hazards; No represents evidence of violation of proportional hazards. Lenvatinib arm dropped from analysis for three-arm NCT01136733 trial

3.7.2.2. Effect modifiers across the network

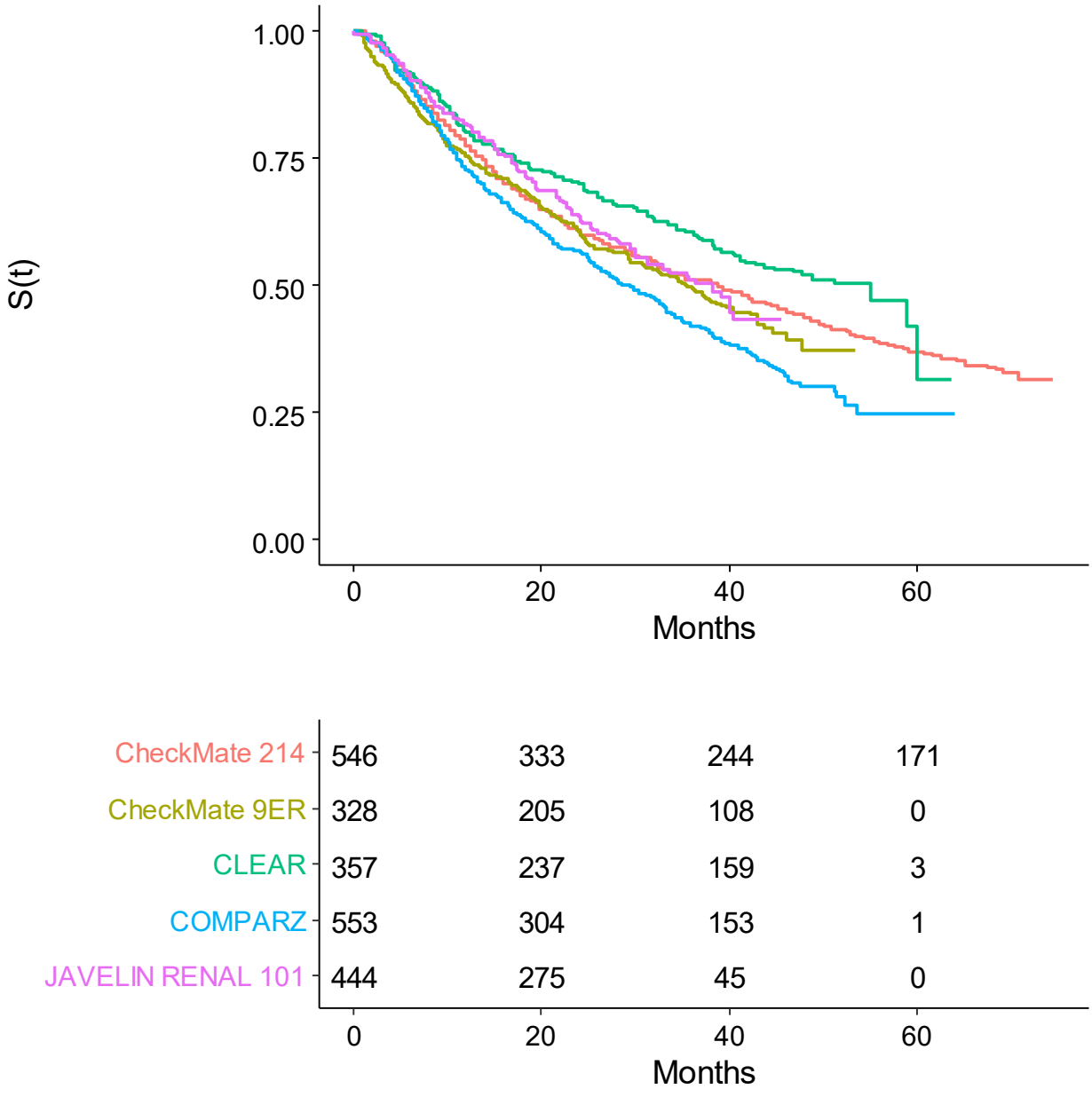
A central node within the network offers a common arm across the treatments which can be examined for heterogeneity in baseline risk. Survival data (PFS) for the sunitinib arms across the 1st line network are shown in Figure 18. Note that some digitisations were supplied at an earlier stage and may be updated with the final data-cut. There is some indication in the plot of anomalous PFS in the sunitinib arm of CheckMate214. There is no obvious explanation for this difference based on inclusion / exclusion criteria and baseline characteristics, and clinical experts consulted considered that this was most likely a chance observation; however, the EAG also noted that it could be due to use of investigator assessment for progression. For OS the COMPARZ trial looks to have anomalously low OS. This is to be expected as this trial was run prior to routine use of nivolumab as a subsequent therapy.

Figure 18: Survival data (PFS) for the central node (suni) of the 1st line network; all risk population



Abbreviations: PFS, progression free survival

Figure 19: Survival data (OS) for the central node (suni) of the 1st line network; all risk population

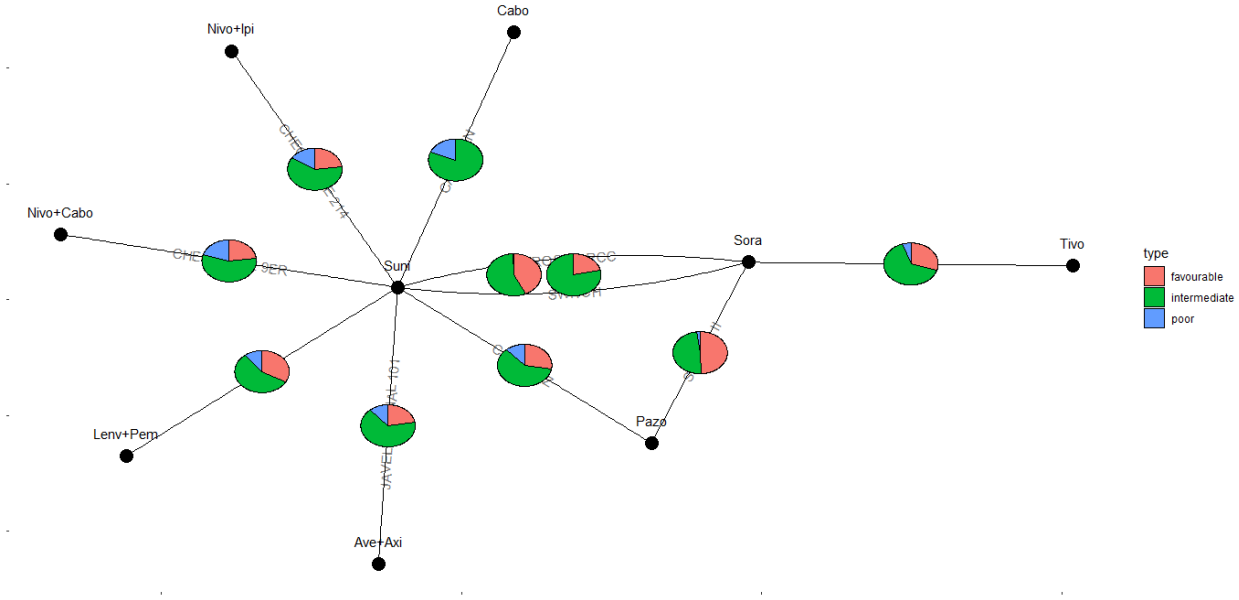


Abbreviations: OS, overall survival

Summary information for select potential effect modifiers is shown in Table 37. IMDC risk category is a primary effect modifier according to clinical advice.

A network graph for PFS of 1st line treatments overlaid with the proportions in risk subgroups is shown in Figure 20(following Cope et al[148]). This shows that the case mix is reasonably uniform across the network except for the three crossover trials that joined to the linking treatment sorafenib (which did not include poor risk patients) and the CABOSUN trial (which did not include favourable risk patients and is not recommended for use in this population). The expected impact of this is to bias towards tivozanib in the all risk population.

Figure 20: 1st line network with proportions of IMDC risk subgroups overlaid. The locations of pies are jittered when there are multiple trials between treatments



Notes: Three crossover trials (CROSS-J-RCC, SWITCH and SWITCH II) and one parallel group trial (TIVO-1) did not include (or included very few) poor risk patients, and the CABOSUN trial did not include favourable risk patients.

Abbreviations: Nivo: nivolumab; Ipi: ipilimumab; Cabo: cabozantinib; Sora: sorafenib; Tivo: tivozanib; Pazo: pazopanib; Ave: avelumab; Axi: axitinib; Lenv: lenvatinib; Pem: pembrolizumab

Table 37: Summary information for select effect modifiers

Trial name	Age (median) *	Risk status (%)¤			Line		Bone metastases (%) *	% clear cell	% prior nephrectomy	% sarcomatoid features
		Favourable	Intermediate	Poor	1L	2L+				
AXIS	61 | 61	20	64	16	0	100	NR	100	91	NR
BERAT	55	Included patients with up to 2 risk factors, split between favourable and intermediate not reported		0	0	100	NR	NR	20	NR
CABOSUN	63	0	81	19	100	0	NR	100	74.5	NR
CheckMate 025	62	36	49	15	0	100	18	100	88	NR
CheckMate 214	62 | 62	23	61	16	100	0	20 | 22	100	81.2	13
CheckMate 9ER	62 | 61	23	57	20	100	0	NR	100	69.9	11.9
CLEAR	64 | 62 | 61	32	55	10	100	0	24 | 24 | 27	100	74.6	6.8
COMPARZ	61 | 62	27	59	11	100	0	NR	100	83.2	NR
CROSS-J-RCC	67 | 67 | 66	21.7	78.3	0	100	0	23 | 33	100	88.3	NR
JAVELIN RENAL 101	62 | 61	22	62	16	100	0	NR	100	81.6	12
METEOR	62 | 63	46	42	13	0	100	22	100	85	NR
NCT01136733	61	23	37	40	0	100	27	100	88	NR
RECORD-1	61	29	56	14	0	100	35	100	97	NR
SWITCH	65	42	55	0.5	100	0	15	87	92	NR
SWITCH II	68 | 68	49	48	2	100	0	20	87	99	NR
TIVO-1	59 | 59	30	65	5	80	20	23 | 20	100	100	NR
TIVO-3	62 | 63	21	61	18	0	100	NR	100	NR	NR

Abbreviations: NR, not reported

* where results were available by arm the figures are shown separated by a bar (|).

¤ In some cases these do not add up to 100% due to rounding and risk status not having been recorded for some patients

Appendix E (Figures 17 to 23) presents the balance of other treatment effect modifiers across the 1st line network. The COMPARZ which links pazopanib to sunitinib has a lower proportion of patients with two or more metastatic sites than other studies which is likely to bias towards pazopanib. The SWITCH II and TIVO-1 trials had a larger proportion of patients with a prior nephrectomy which is likely to bias towards pazopanib and tivozanib. The TIVO-1 required a prior nephrectomy within the enrolment criteria. The CABOSUN trial had a larger proportion of patients with bone metastases enrolled; cabozantinib was considered by one of the experts consulted to be particularly effective in patients with bone metastases which may result in bias towards cabozantinib. Otherwise, patient characteristics were relatively well balanced across trials; particularly for trials of more recent treatments. Finally, the trials linking pazopanib and tivozanib to the network have a much lower proportion of subsequent IO use (or none) which will bias against these treatments when considering OS.

3.7.3. Results of time dependent NMA

The following sections contain summary results from frequentist and Bayesian analyses for all risk population and intermediate / poor risk population for OS and PFS at line 1. For line 1 PFS all risk, as the primary outcome, more detailed results are provided. Results for line 2+ are presented in Appendix E.

As explained above, sunitinib plays a central role in the 1st line networks and was selected as the reference treatment, along with CheckMate 9ER as the reference study. For 2nd line-plus networks, everolimus was chosen as the reference treatment and CheckMate 025 the reference study due to this being the treatment for which the longest follow-up was available.

A summary of the models selected by the process described in Section 3.7.1 is given in Table 38. As a note, AIC and DIC values that are lower reflect better fit compared to model complexity or parsimony. Generally, differences in AIC or DIC of between 3 and 5 values are considered noteworthy; however, the EAG generally preferred random effects models where these were supported by visual inspection and by the estimability of chosen models.

Table 38: Summary of final selected models for each line/risk/outcome subgroup

Outcome	Line	Risk group	Type	AIC	DIC	Exponent 1	Exponent 2
OS	1L	All	RE	1465.27	1466.5	-0.5	0.0
OS	2L+	All	RE	672.60	670.1	0.0	1.0

Outcome	Line	Risk group	Type	AIC	DIC	Exponent 1	Exponent 2
OS	1L	Intermediate/poor	FE	1121.26	1121.7	-0.5	0.5
PFS	1L	All	RE	1963.97	1982.0	-2.0	-0.5
PFS	2L+	All	RE	456.97	458.1	-0.5	0.5
PFS	1L	Intermediate/poor	RE	758.79	771.6	-2.0	-0.5

Abbreviations: 1L, 1st line; 2L+, 2nd line-plus; DIC: deviance information criterion; FE: fixed effects; OS: overall survival, PFS: progression free survival, RE: random effects

3.7.3.1. 1st line PFS all risk

The results of the frequentist model selection for PFS (1st line trials) are summarised in Table 39, which shows AIC values by the two exponents of each fractional polynomial fit. The model with lowest AIC has fractional polynomial exponents -2 and -0.5. In this instance, no other models attained AIC values within five points of the minimum.

Table 39: AIC values for fractional polynomial fit, 1st line PFS all risk

	-2	-1	-0.5	0	0.5	1	2	3
-2	-	1975.59	**1963.967**	1969.283	1996.790	2042.744	2148.740	2230.164
-1	-	-	1970.920	1994.467	2034.664	2085.816	2187.087	2258.683
-0.5	-	-	-	2021.301	2065.343	2115.107	2204.298	2262.540
0	-	-	-	-	2101.485	2144.774	2212.510	2250.925
0.5	-	-	-	-	-	2169.499	2209.582	2227.224
1	-	-	-	-	-	-	2200.388	2203.931
2	-	-	-	-	-	-	-	2185.450
3	-	-	-	-	-	-	-	-

Abbreviations: AIC: Akaike's information criterion; PFS: progression free survival

Notes: Row and column names correspond to exponent values. The model with lowest AIC is in bold. In this instance all other models had ΔAIC>5.

The fitted log-hazards under the NMA with the best-fitting (by AIC) fractional polynomial model are shown by trial in Figure 21. The trials approach a relatively constant hazard after about 20 to 40 months in each case. In some trials (e.g. CheckMate 9ER) there is an initial increase in hazard that inflects within the first 12 months.

A comparison of Bayesian model fits by fixed and random effects is shown in Table 40. In this case the random effects model has lower DIC. Hazard ratios from fitting by frequentist and Bayesian (random effects) methods are shown in Figure 22. Results are qualitatively similar. Survival curves under the Bayesian approach are shown in Figure 23 and Figure 24.

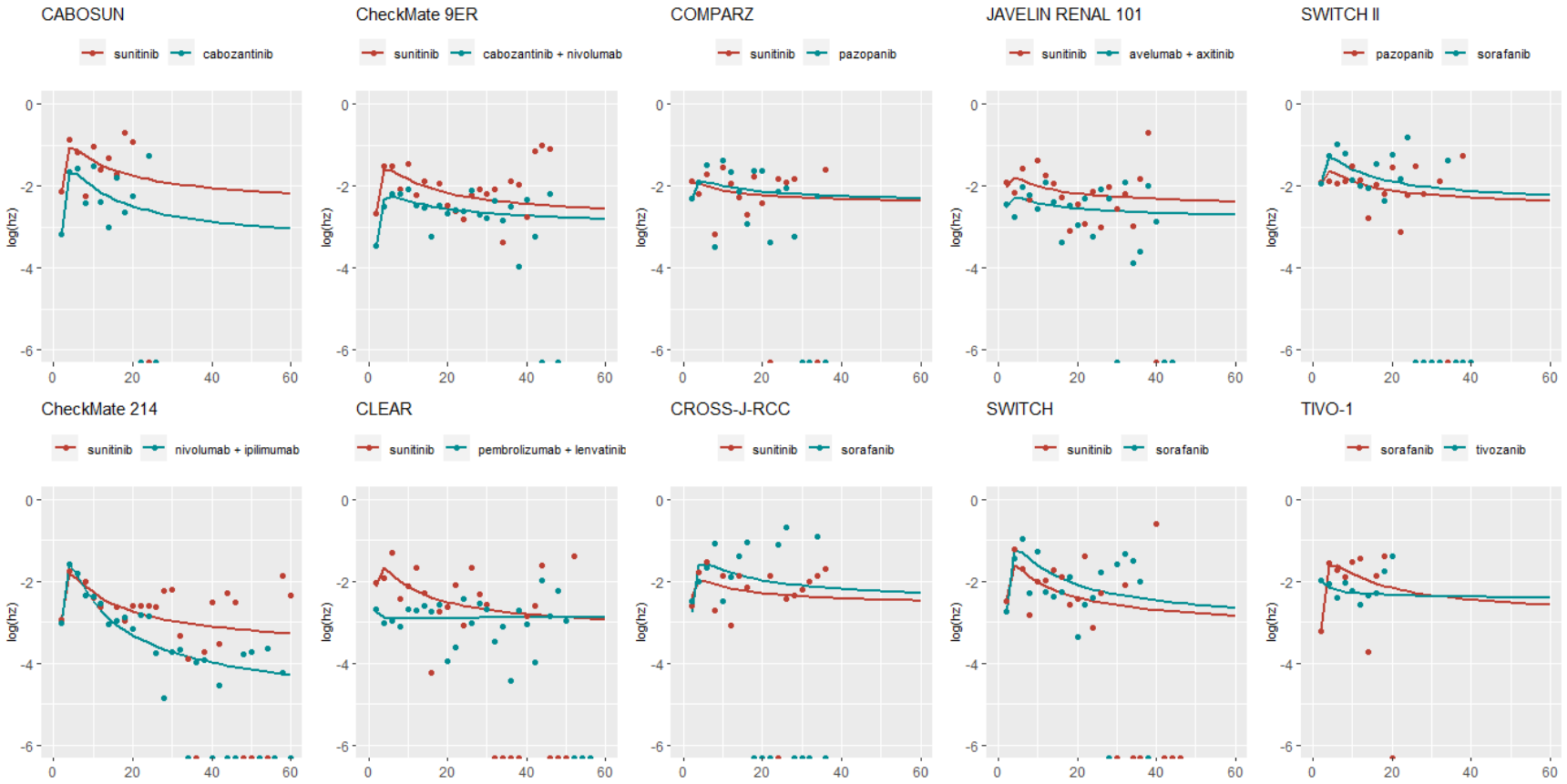
Table 40: Comparison of fixed and random effects Bayesian models for PFS for 1st line all risk

Model	Order	Exponents	DIC	pD	meanDev
FE	2	-2, -0.5	1983.2	53.9	1929.6
RE	2	-2, -0.5	1982	55	1927.1

Notes: using fractional polynomial model with exponents previously selected by frequentist methods.

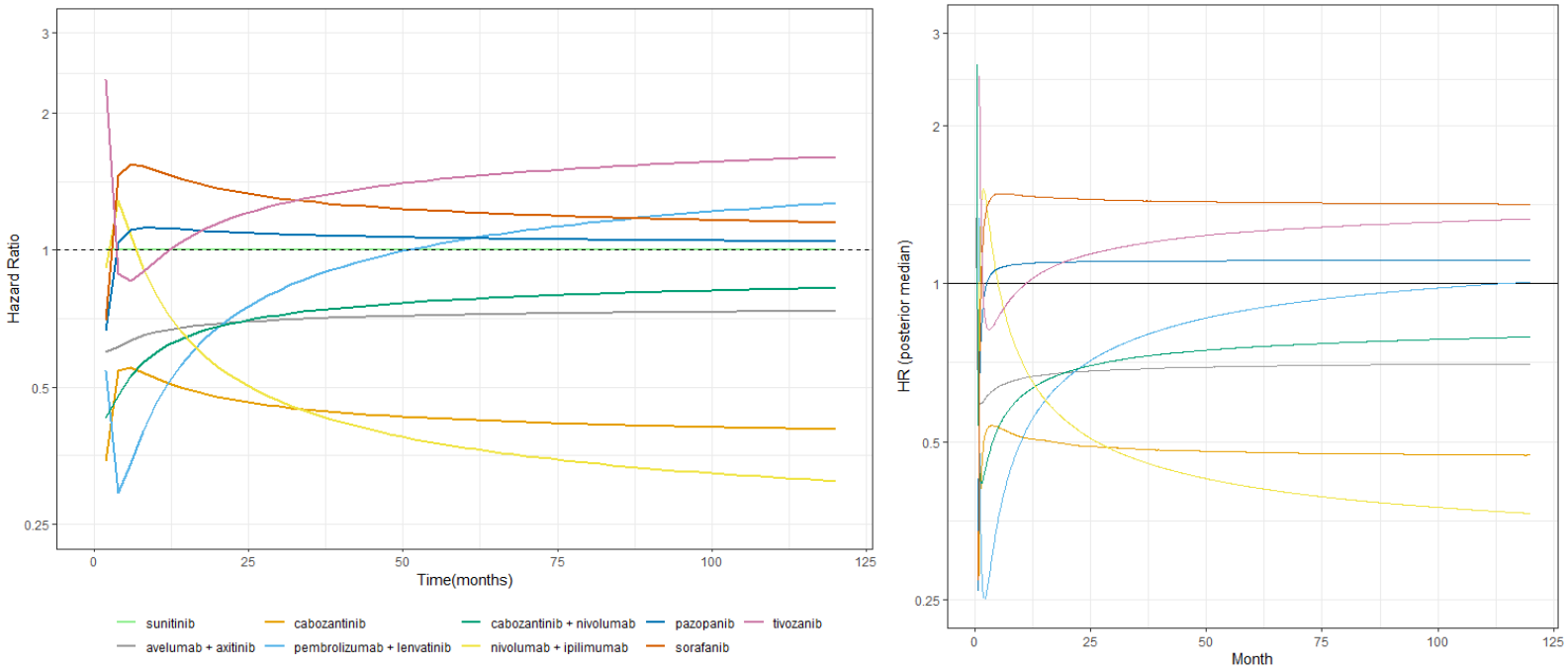
Abbreviations: DIC: Deviance Information Criteria, pD: effective number of parameters

Figure 21: Fitted log hazards for PFS for 1st line all risk



Notes: Fitted by fractional polynomial with exponents (-2, -0.5) across the network and extrapolated to 60 months. The points are logs of life-table estimates of the hazard (following Collett). Note that under sparse data the log hazard estimate is zero, which can be seen to the right of several plots as the event rate declines.

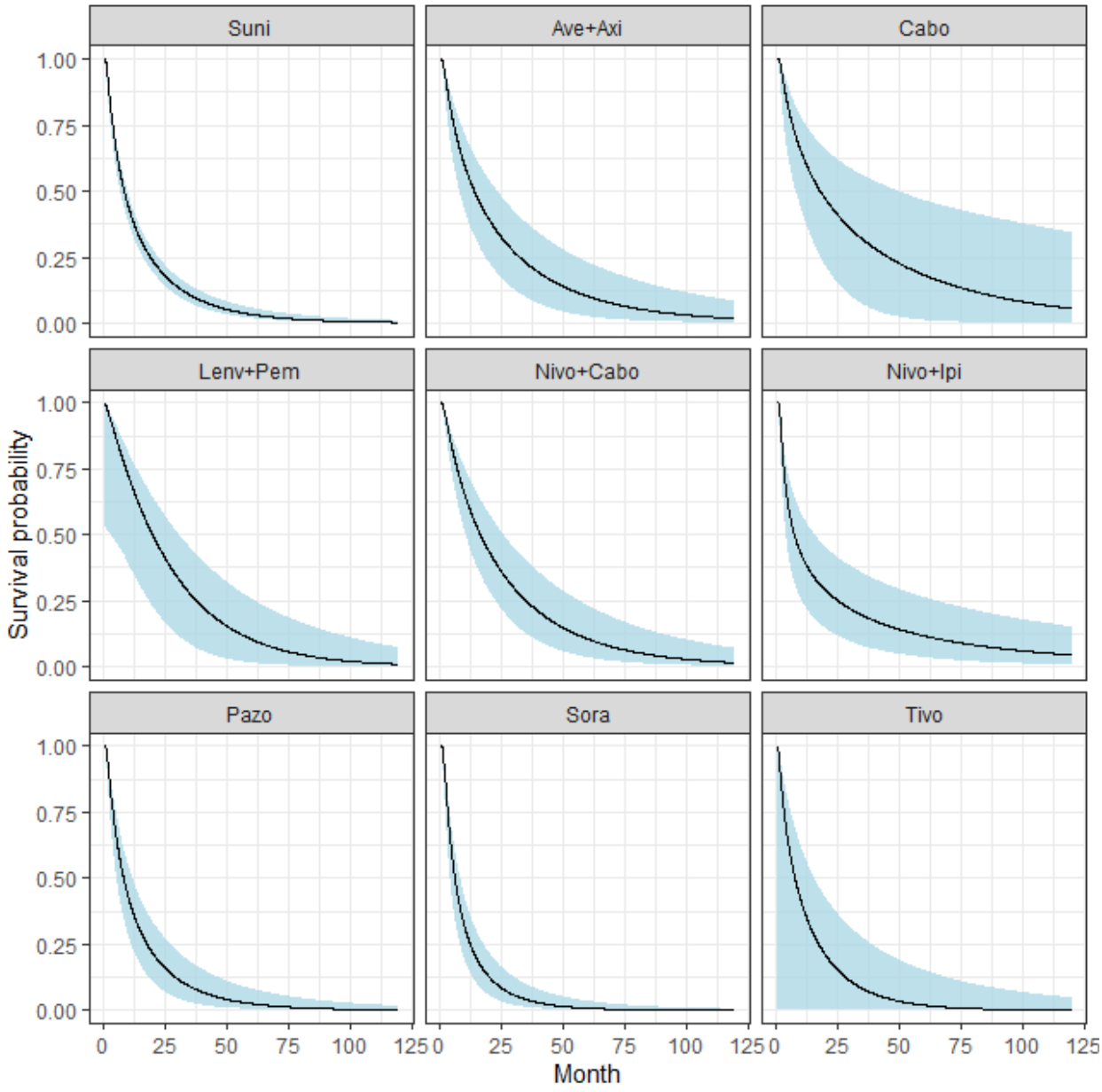
Figure 22: Time-dependent hazard ratios for PFS for 1st line all risk



Abbreviations: 1L, 1st line; PFS, progression free survival

Notes: Left : frequentist analysis. Right: Bayesian analysis (random effects). The reference treatment is sunitinib (central node in the network).

Figure 23: Survival curves by treatment from Bayesian fitting with the selected fractional polynomial model



Notes: Band is 95% credible interval.

A number of observations on the presented survival curves bear noting. First, HR plots in Figure 22 suggest that over time, treatments with higher HRs than sunitinib are other TKIs, whereas all other treatments than pembrolizumab + lenvatinib 'settle' into HRs less than 1 over the predicted time horizon. For cabozantinib + nivolumab the HR trends gradually upwards after the end of the observed data period, remaining below 1 during the first 60 months. Second, there is clear difference between treatments in the confidence bands surrounding fitted survival curves. This is perhaps most notable for cabozantinib and pembrolizumab + lenvatinib. For cabozantinib, this is likely due to the comparatively short timeframe included in analyses compared to other trials; whereas for pembrolizumab + lenvatinib, this may be due to comparatively poorer fit of the hazard function to the observed hazards in Figure 21. It should be noted that cabozantinib, nivolumab + ipilimumab, and pembrolizumab + lenvatinib are only recommended for intermediate and poor risk patients.

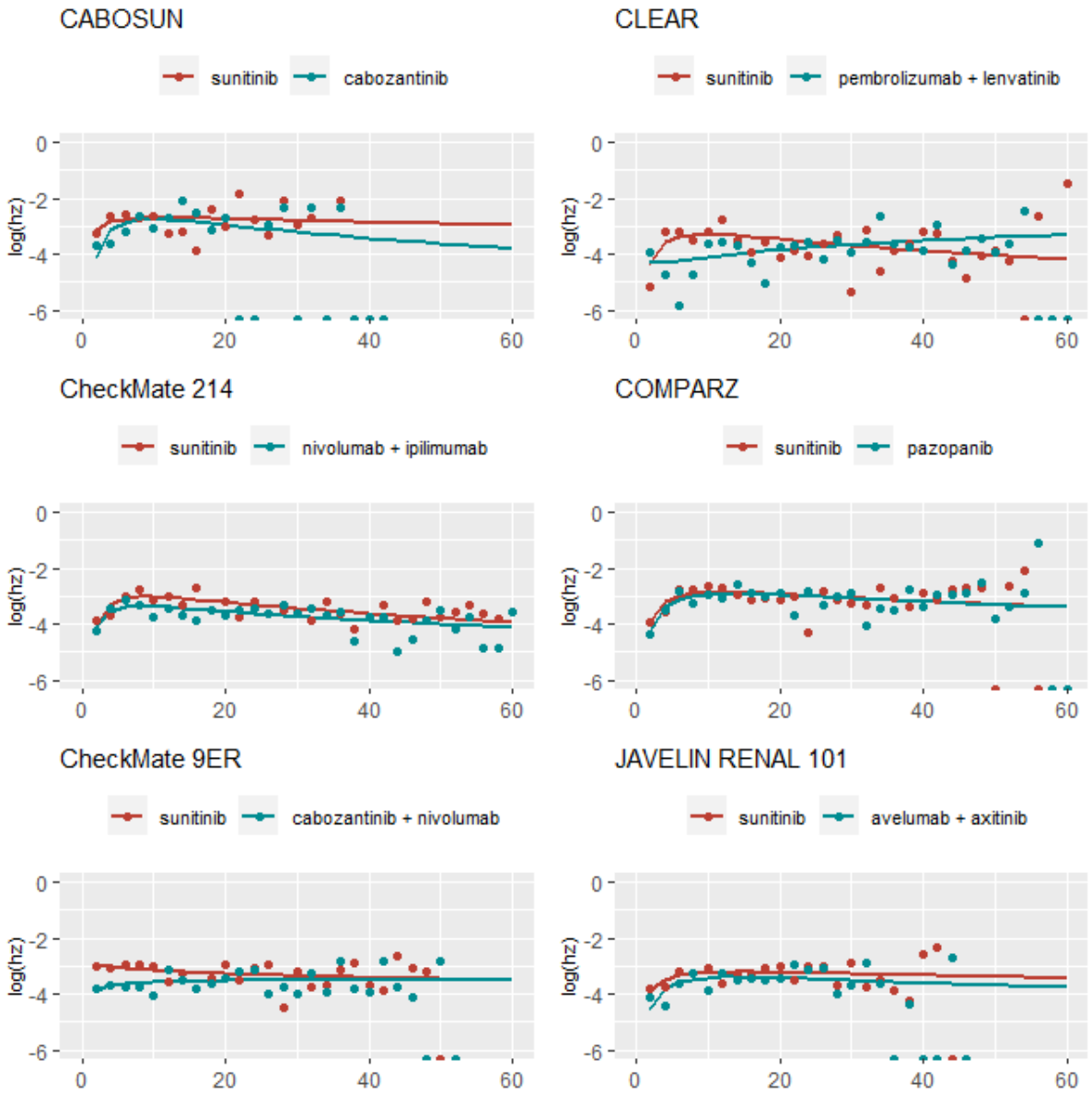
3.7.3.2. 1st line OS all risk

The selected model for first-line all risk OS had polynomial terms of -0.5 and 0. A number of models generated plausible AIC values; however, the chosen model had the best plausibility as assessed by the other criteria and based on input from expert elicitation. The very high initial HR for pembrolizumab + lenvatinib (

Figure 25) is associated with the unusual survival characteristics of the CLEAR trial, in which there were no or very few events in the sunitinib arm over the first two months (Motzer 2023).[149] The log-hazard (

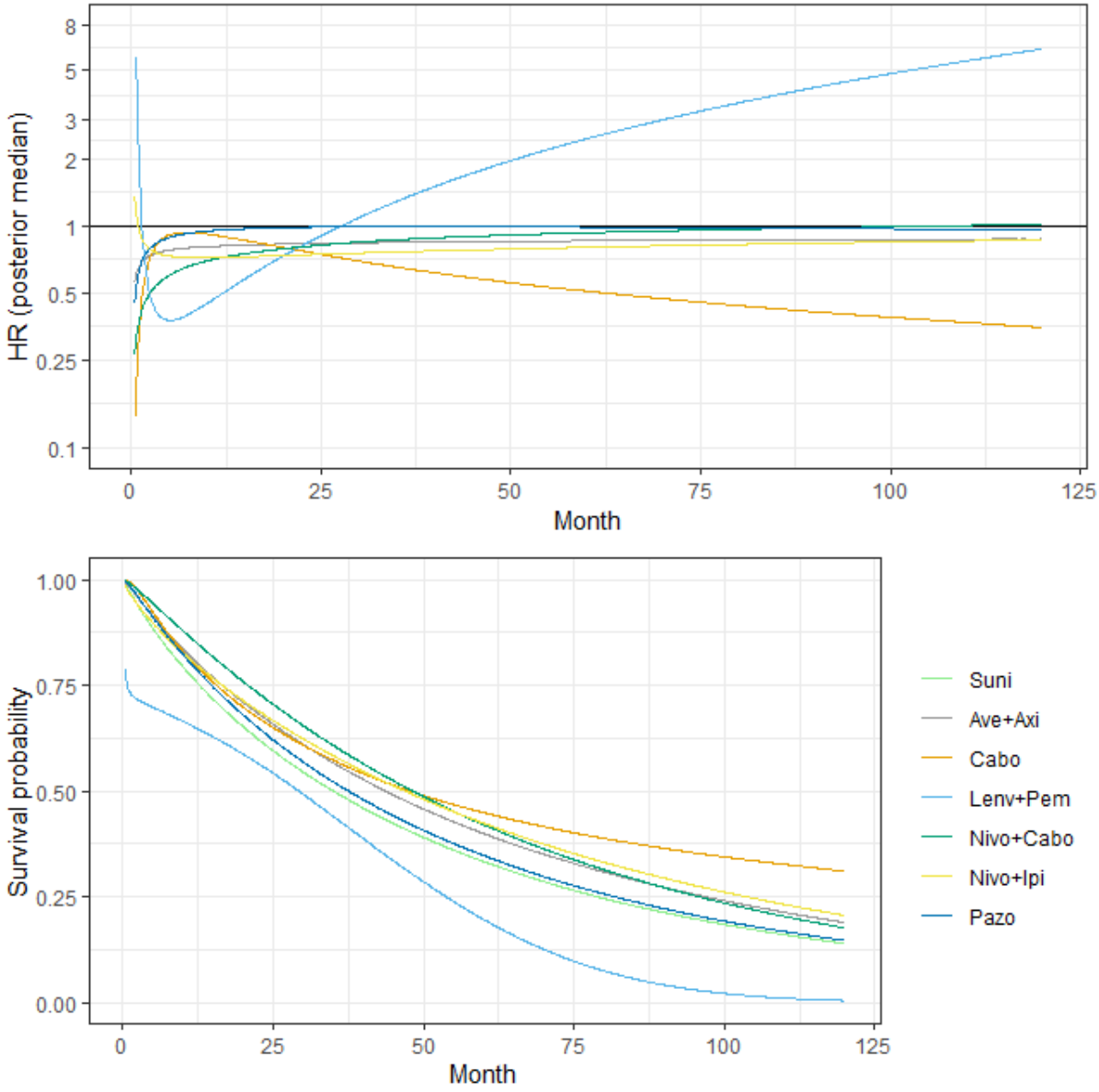
Figure 25) and survival curves (Figure 26) are qualitatively different to others in this subgroup, however, it should be noted that the expected survival for pembrolizumab + lenvatinib has high uncertainty, as can be seen in Figure 26. As with PFS in first line, cabozantinib has an unusually high level of uncertainty, likely due to the shorter timeframe of follow-up. Compared to PFS findings, findings for OS in this line are considerably more equivocal due possibly to the impact of subsequent treatments after progression; only cabozantinib appears to have a long-term HR substantially below 1 as compared to sunitinib. For cabozantinib + nivolumab again the HR trends gradually upwards after the end of the observed data period coming close to 1. There appears to be an early survival advantage for cabozantinib + nivolumab, especially relative to cabozantinib, that ends about month 50.

Figure 24: Log hazards for OS for 1st line all risk



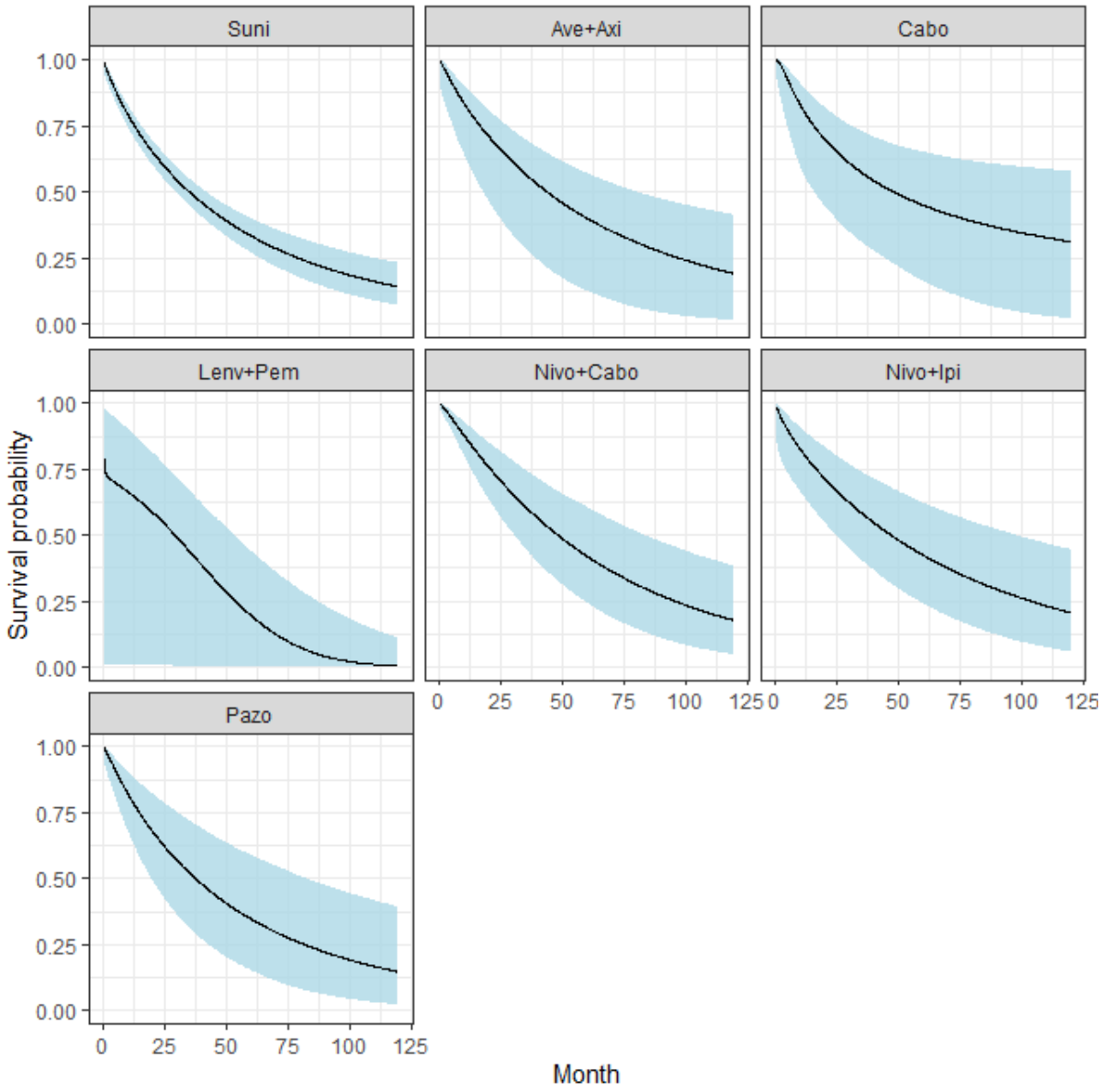
Abbreviations: 1L, 1st line; OS, overall survival

Figure 25: Hazard ratios and survival curves for OS for 1st line all risk (Bayesian analysis)



Abbreviations: Ave, avelumab; Axi, axitinib; Cabo, cabozantinib; Ipi, ipilimumab; Len, lenvatinib; Nivo, nivolumab; OS, overall survival; Pazo, pazopanib; Pem, pembrolizumab; Suni, sunitinib; vs, versus

Figure 26: Survival curves shown by treatment with 95% credible intervals.



Abbreviations: Ave, avelumab; Axi, axitinib; Cabo, cabozantinib; Ipi, ipilimumab; Len, lenvatinib; Nivo, nivolumab; Pazo, pazopanib; Pem, pembrolizumab; Suni, sunitinib

3.7.3.3. 1st line PFS intermediate/poor risk

Findings for PFS in first line for patients with intermediate or poor risk are presented in Figure 27 and Figure 28, with additional information in Appendix E (Figure 15, Table 11). The optimal model had polynomial terms of -2.0 and -0.5 and performed well in terms of AIC. The choice of model was also informed by expert elicitation, as estimates from these analyses better matched

the estimates from experts for novel therapies. We were unable to include pembrolizumab + lenvatinib in this analysis as Kaplan-Meier curves were not available for this subgroup. While all treatments show a long-term benefit in HRs as compared to sunitinib, these differences are unequal and highly uncertain for certain treatments. Time-varying HRs suggest that nivolumab with ipilimumab has a long-term lower HR than other treatments, reflected in a longer-term survival benefit emerging near the 60-month point. Cabozantinib monotherapy was predicted to have PFS similar to, or above, cabozantinib + nivolumab throughout the time period.

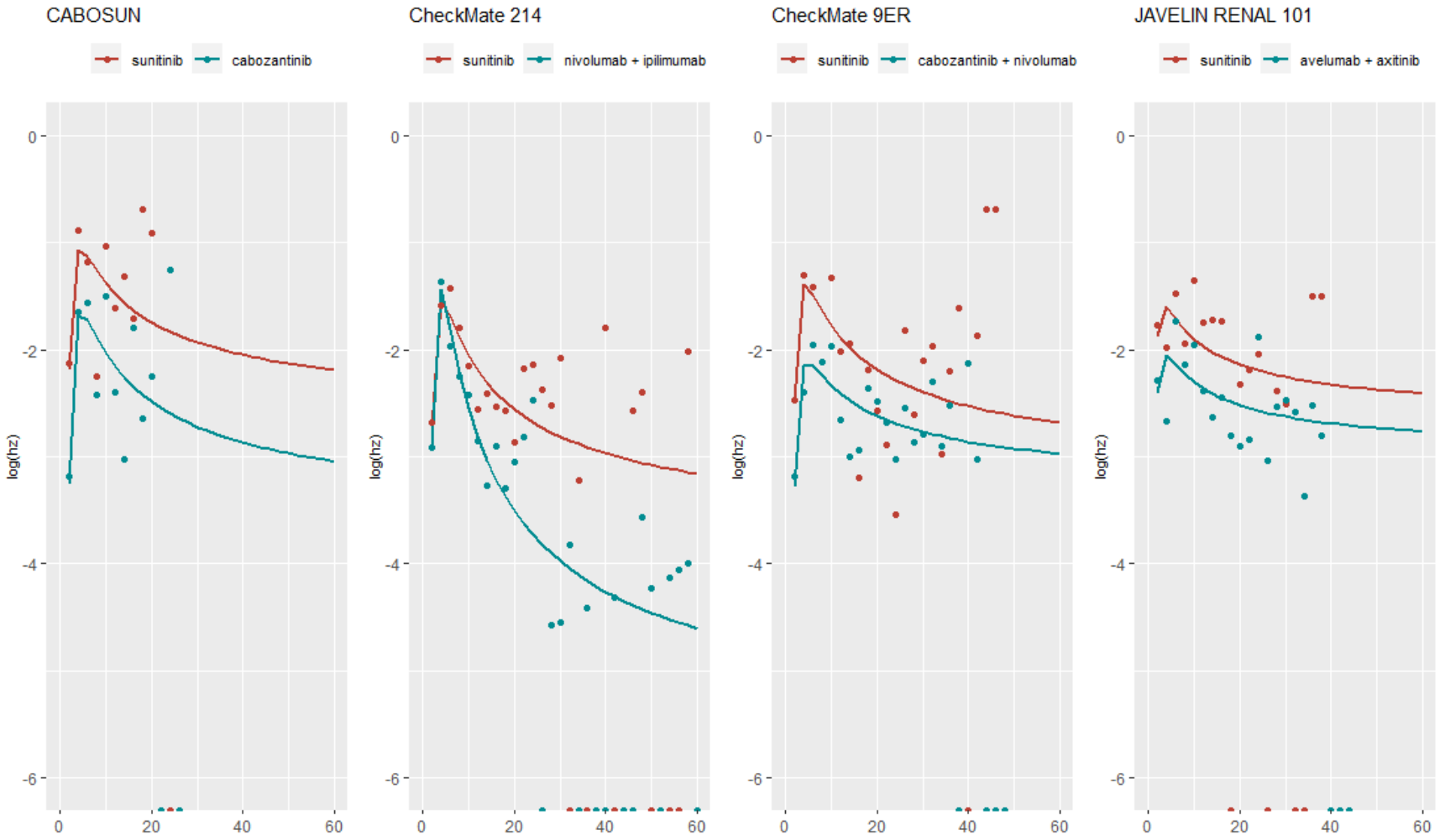
3.7.3.4. 1st line OS intermediate/poor risk

Findings for OS in first line for patients with intermediate or poor risk are presented in Figure 29 and Figure 30, with additional information in Appendix E (Figure 13, Table 12). The optimal model had polynomial terms of -0.5 and 0.5 and performed well relative to other models with AIC. Similar patterns of uncertainties in predicted survival curves were seen as in the analysis of PFS in intermediate and poor risk above. HR functions over time show a 'fanning out', with corresponding survival curves suggesting that different treatments have relatively better survival probabilities that change in order over the time horizon. Cabozantinib monotherapy was predicted to have OS similar to, or above, cabozantinib + nivolumab throughout the time period.

3.7.3.5. 2nd line-plus

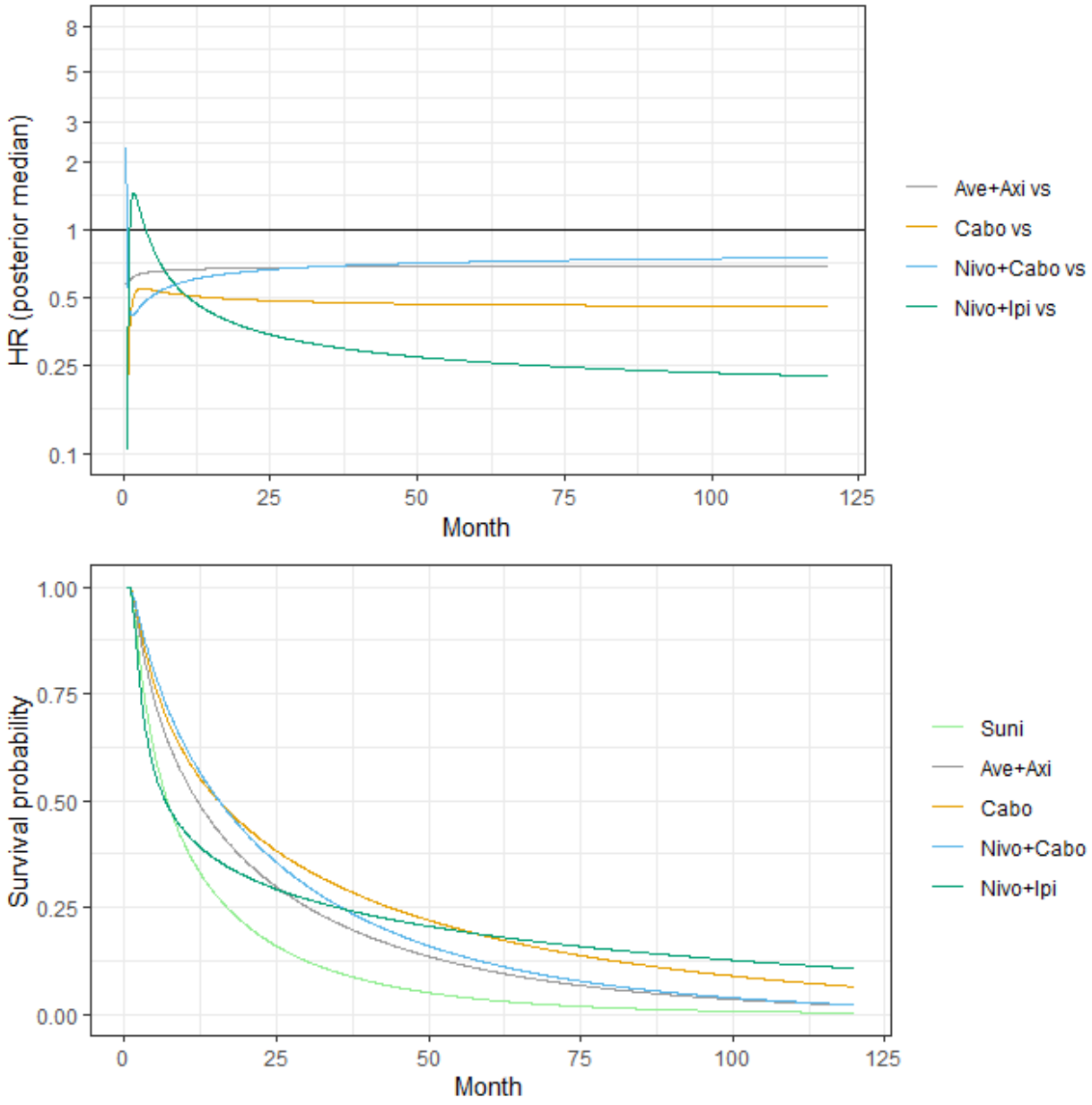
Findings for second-line and beyond outcomes are presented in Appendix E. We chose models that performed well in terms of AIC; furthermore, the PFS model was informed by expert elicitation to minimise the number of 0 or 1 probabilities in conditional survival at longer-term timepoints. Findings for PFS suggest a clear advantage in the survival function for lenvatinib plus everolimus until about 112 months, at which point it converges with nivolumab. Cabozantinib displays only limited improvement over everolimus which is unexpected given this is the 2nd line treatment favoured by clinicians. However, findings for OS suggest a different pattern, with cabozantinib possessing a long-term advantage in survival rates, followed by nivolumab. A contrasting misalignment was seen for everolimus plus lenvatinib, where PFS results were considerably more optimistic than OS results. In both situations, curves begin to display surprising results beyond the timepoints for which hazards where available, possibly due to the relatively limited follow-up time available from relevant trials to inform longer-term estimates. It should be stressed that predicted survival plots (Appendix E, Figure 14 and Figure 16) reflect substantial uncertainty.

Figure 27: Log hazards for PFS for 1st line intermediate/poor risk



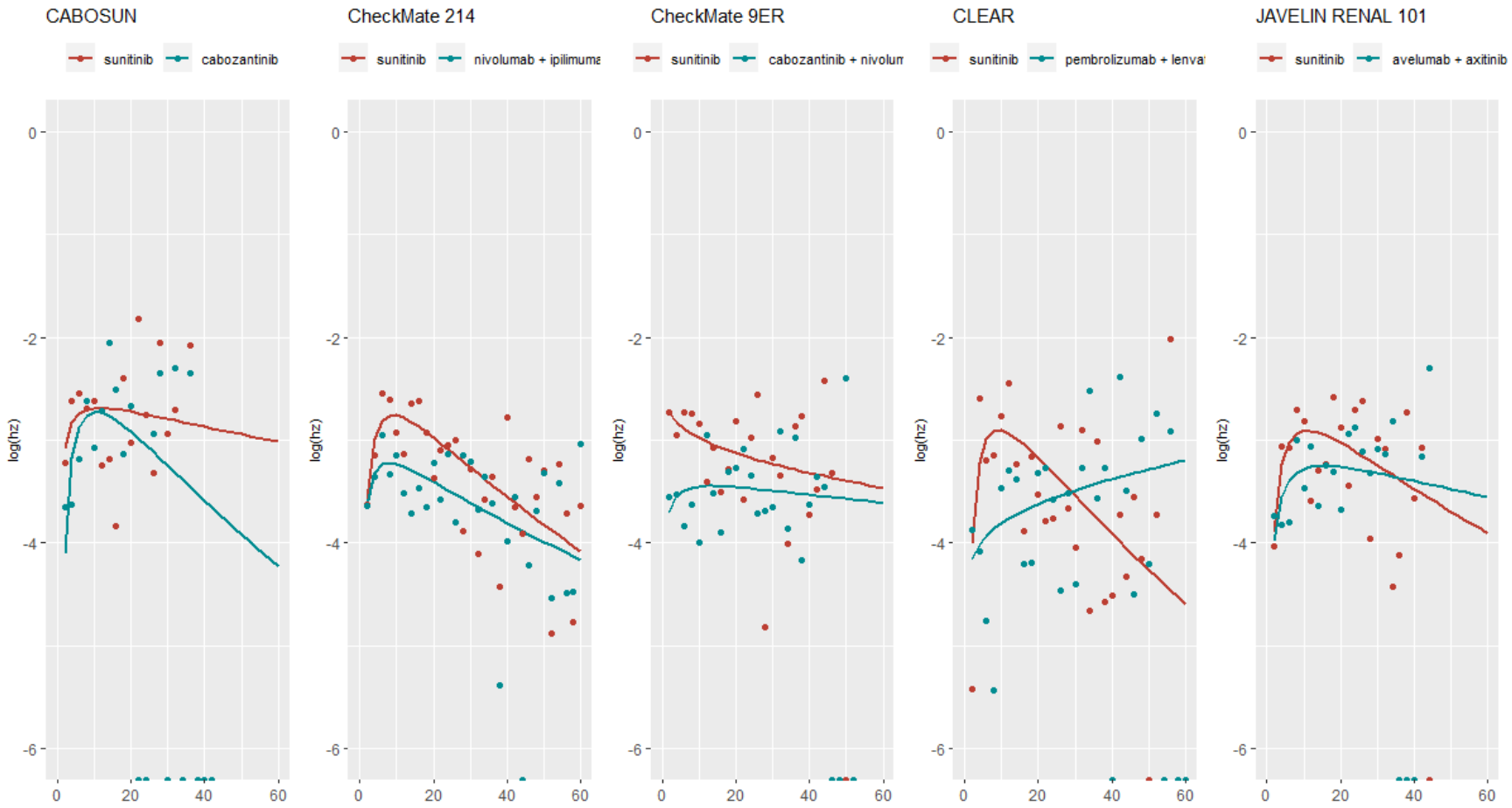
Abbreviations: PFS, progression free survival

Figure 28: Hazard ratios and survival curves for PFS for 1st line intermediate/poor risk (Bayesian analysis)



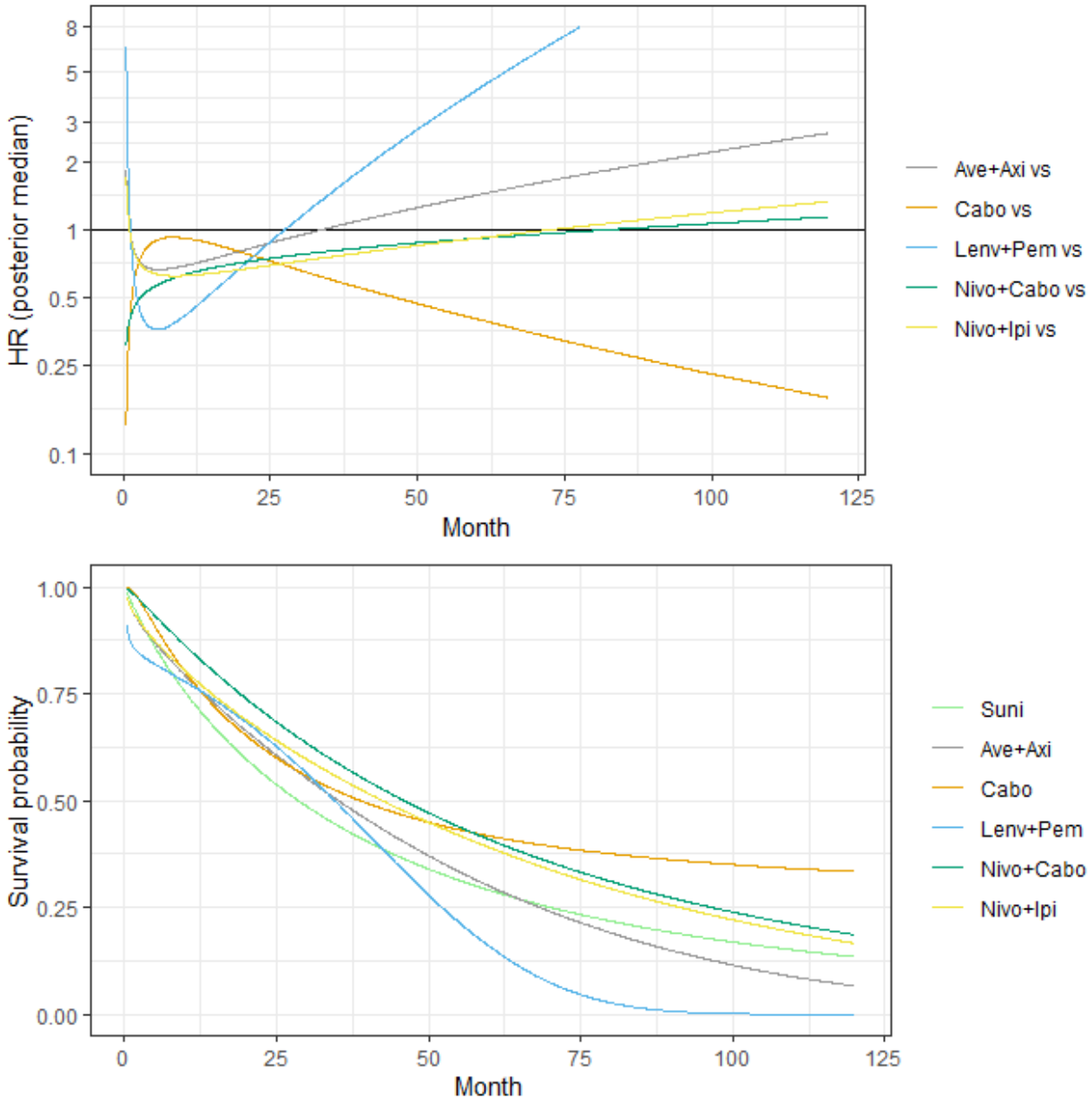
Abbreviations: Ave, avelumab; Axi, axitinib; Cabo, cabozantinib; Ipi, ipilimumab; Nivo, nivolumab; PFS, progression free survival; Suni, sunitinib

Figure 29: Log hazards for OS for 1st line intermediate/poor risk



Abbreviations: OS, overall survival

Figure 30: Hazard ratios and survival curves for OS for 1st line intermediate/poor risk (Bayesian analysis)



Abbreviations: Ave, avelumab; Axi, axitinib; Cabo, cabozantinib; Ipi, ipilimumab; Lenv, lenvatinib; Nivo, nivolumab; OS, overall survival; Pem, pembrolizumab; Suni, sunitinib

3.7.3.6. Interpretation and limitations

The EAG's fractional polynomial NMAs sought to compare different treatments in each network on the basis of time-varying HRs; i.e. by constructing the estimated HR for each treatment against a common comparator as a function of time. Using a multi-pronged assessment process, the EAG was able to select appropriate and justifiable models for each evidence network analysed. Importantly, the evidence of non-proportional hazards in a range of included trials (see Section 3.7.2.1) justified preference for a fractional polynomial method over a method assuming proportional hazards (i.e. inverse variance NMA using log HRs).

The EAG's analysis has a number of strengths. First, the use of a frequentist model selection stage followed by Bayesian analysis [143] of a subset meant it was practical for a large number of models to be efficiently assessed. At the frequentist model selection stage, all 2nd order fractional polynomial models (except repeated powers) were considered, creating 28 models per evidence network. At the Bayesian 'confirmatory' stage. a subset of models was used and compared for estimability and appropriateness, including a comparison of fixed effects and random effects (albeit time invariant). When random effects models were preferred by DIC, these generally offered only marginal improvement due to the large number of star networks analysed. However, in this analysis paradigm, time-invariant heterogeneity captured some of the difference between trials in common comparator hazards.

The EAG elected not to present a fractional polynomial NMA for the favourable risk group. This was justified on the basis of sparse availability of relevant Kaplan-Meier curves to support this analysis. Additionally, sparseness in networks, particularly in second-line plus, precluded inclusion of all relevant treatments; for example, axitinib could not be included in second-line and beyond. Moreover, differences in effect modifiers across network could cause bias in NMA. While the EAG did judge that NMAs were feasible, there was some broad variation over the network in effect modifiers identified through consultation, particularly in risk distribution. The CABOSUN trial was included in the 'all risk' population despite enrolling only intermediate/poor risk patients and the recommendation for cabozantinib being in the intermediate/poor risk population because the EAG did not regard that the difference between risk distributions was substantial enough to warrant its removal' however, it is notable as well that several trials did not enrol any poor risk patients. Uneven distributions of subsequent treatments may also have impacted interpretation of OS analyses in ways that are difficult to quantify across the network.

Finally, fractional polynomial NMAs require choice of model. While in some cases (particularly first-line all-risk PFS), AIC values clearly indicated the optimal model, in other cases AIC was not dispositive, and other sources of information were needed to determine optimal model choice. While expert elicitation for PFS outcomes was helpful, particularly at the five-year timepoint, it did not resolve all uncertainties in situations of multiple relevant choices. Thus, in the cost-effectiveness model, scenario analyses using proportional hazards NMAs are used as well.

3.7.4. Results of the time invariant NMA

We undertook NMAs for PFS, OS, ORR, discontinuation due to adverse events and risk of adverse events of grade 3 or higher. Adverse events data were only available in the ITT population. We present results for NMAs of the 1st line ITT population first, before presenting results for PFS, OS and ORR for intermediate/poor and favourable risk groups.

We interpreted the ITT population to be an 'all-comers' population and thus included all trials regardless of baseline risk distribution. This means, for example, that the CABOSUN trial was included despite only enrolling patients with intermediate or poor risk. We sensitivity analysed this assumption for the PFS outcome. Where we describe relevant treatments, we refer to those that are not included for linking (i.e. sorafenib) or for completeness (i.e. avelumab + axitinib). Finally, though all meta-analyses were undertaken in a Bayesian framework, we refer colloquially to 'statistical significance' where credible intervals do not include the point of unity.

3.7.4.1. Progression-free survival in 1st line ITT population

Base case analysis

Our proportional hazards NMA of PFS in the 1st line ITT population included all 10 relevant identified trials with 1st line groups. Because of the limited opportunities for estimation of heterogeneity in this NMA (one closed loop and only one comparison with more than one trial), we estimated this model as a fixed-effects analysis. Results are presented in Table 41 and suggested the numerical superiority of most relevant treatments against sunitinib except for pazopanib and tivozanib, but not a statistical difference of sunitinib against nivolumab + ipilimumab, pazopanib and tivozanib.

Cabozantinib + nivolumab was statistically better than nivolumab + ipilimumab, pazopanib, sunitinib and tivozanib, and was numerically, but not statistically, less effective than

cabozantinib alone and pembrolizumab + lenvatinib. However, it should be acknowledged that CABOSUN, the trial for cabozantinib alone vs sunitinib enrolled only intermediate or poor risk patients, for which the magnitude of treatment effects tends to be larger. Moreover, the CABOSUN trial used a higher dose of cabozantinib than other trials including this drug, which clinical advice suggests is linked to higher effectiveness in a dose-response relationship.

Because of the limited number of studies per comparison, we were unable to undertake network meta-regression to explore differences by study in key characteristics. However, we undertook two sensitivity analyses by assessor and presence of a poor-risk population.

We compared our model against an unrestricted mean effects model to evaluate the presence of inconsistency. The deviance information criterion (DIC) for our consistency model was 18.37, with a total residual deviance of 10.40. In contrast, the DIC for our unrestricted mean effects model was 18.74, with a total residual deviance of 9.72. This suggested that the consistency model was acceptable. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Preferring investigator-assessed PFS instead of blinded review PFS

Where PFS was presented at the latest datacut with both investigator-assessed and blinded independent central review, we preferred blinded review-based PFS. However, two trials (CABOSUN, COMPARZ) presented PFS at last datacut assessed via both methods. We used a fixed-effects analysis and found that results were very similar to the base case analysis (see Table 42).

We compared our model against an unrestricted mean effects model to evaluate the presence of inconsistency. The deviance information criterion (DIC) for our consistency model was 17.75, with a total residual deviance of 9.78. In contrast, the DIC for our unrestricted mean effects model was 18.58, with a total residual deviance of 9.64. This suggested that the consistency model was acceptable. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Excluding trials that did not enrol patients with poor risk

Three trials in our network (SWITCH, SWITCH II and CROSS-J-RCC) excluded patients with poor risk. We thus excluded these trials in a sensitivity analysis. The impact of this was to cause TIVO-1, and thus tivozanib, to be dropped from the network as all connecting trials evaluating

sorafenib were excluded. Results from this analysis are presented in Table 43. Findings for included treatments were very similar to the base case analysis.

No consistency results were generated as there were no closed loops in this network. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Table 41: PFS in 1st line ITT population (base case)

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+axi	-	1.136 (0.888,1.46)	1.405 (0.879,2.216)	0.78 (0.619,0.981)	0.668 (0.54,0.825)	1.425 (1.099,1.845)	0.491 (0.387,0.62)	0.671 (0.57,0.789)	0.65 (0.46,0.924)
Cabo+nivo	0.88 (0.685,1.126)	-	1.237 (0.765,1.98)	0.687 (0.538,0.882)	0.588 (0.467,0.742)	1.254 (0.948,1.646)	0.432 (0.336,0.557)	0.591 (0.49,0.711)	0.571 (0.401,0.825)
Cabo	0.712 (0.451,1.137)	0.809 (0.505,1.308)	-	0.556 (0.352,0.882)	0.476 (0.304,0.755)	1.012 (0.632,1.658)	0.349 (0.22,0.56)	0.478 (0.311,0.739)	0.462 (0.27,0.793)
Nivo+ipi	1.283 (1.019,1.615)	1.456 (1.134,1.859)	1.8 (1.134,2.839)	-	0.857 (0.693,1.053)	1.826 (1.411,2.364)	0.628 (0.497,0.794)	0.86 (0.732,1.009)	0.83 (0.586,1.185)
Pazo	1.496 (1.212,1.852)	1.701 (1.348,2.139)	2.101 (1.325,3.289)	1.167 (0.95,1.443)	-	2.134 (1.67,2.716)	0.734 (0.614,0.874)	1.005 (0.876,1.15)	0.974 (0.71,1.331)
Pem+lenv	0.702 (0.542,0.91)	0.797 (0.607,1.054)	0.989 (0.603,1.583)	0.548 (0.423,0.709)	0.469 (0.368,0.599)	-	0.344 (0.265,0.45)	0.471 (0.387,0.577)	0.456 (0.315,0.665)
Sora	2.036 (1.613,2.583)	2.317 (1.796,2.979)	2.864 (1.785,4.553)	1.592 (1.259,2.013)	1.362 (1.144,1.628)	2.91 (2.223,3.773)	-	1.368 (1.153,1.62)	1.322 (1.014,1.72)
Suni	1.49 (1.268,1.755)	1.692 (1.407,2.042)	2.092 (1.354,3.213)	1.162 (0.991,1.365)	0.995 (0.87,1.141)	2.124 (1.733,2.587)	0.731 (0.617,0.867)	-	0.967 (0.709,1.321)
Tivo	1.538 (1.083,2.176)	1.75 (1.212,2.494)	2.165 (1.261,3.699)	1.205 (0.844,1.707)	1.027 (0.752,1.409)	2.195 (1.505,3.174)	0.756 (0.581,0.986)	1.034 (0.757,1.411)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the HR metric. The comparison is the row-forming treatment against the column-forming treatment.

Table 42: PFS in 1st line ITT population (using investigator-assessed outcome at latest datacut)

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+axi	-	1.134 (0.89,1.453)	1.198 (0.777,1.863)	0.78 (0.624,0.977)	0.692 (0.562,0.856)	1.427 (1.105,1.846)	0.498 (0.396,0.634)	0.67 (0.571,0.787)	0.66 (0.466,0.94)
Cabo+nivo	0.882 (0.688,1.124)	-	1.055 (0.676,1.66)	0.686 (0.537,0.879)	0.61 (0.485,0.765)	1.259 (0.96,1.655)	0.439 (0.341,0.563)	0.59 (0.49,0.709)	0.583 (0.402,0.838)
Cabo	0.835 (0.537,1.288)	0.948 (0.602,1.479)	-	0.65 (0.421,1.014)	0.577 (0.376,0.884)	1.194 (0.757,1.885)	0.417 (0.268,0.646)	0.559 (0.372,0.843)	0.551 (0.33,0.923)
Nivo+ipi	1.283 (1.023,1.602)	1.457 (1.138,1.862)	1.537 (0.986,2.376)	-	0.888 (0.72,1.093)	1.832 (1.416,2.37)	0.64 (0.505,0.809)	0.859 (0.732,1.011)	0.848 (0.592,1.215)
Pazo	1.446 (1.168,1.781)	1.639 (1.307,2.061)	1.733 (1.132,2.656)	1.126 (0.915,1.388)	-	2.061 (1.63,2.626)	0.72 (0.605,0.859)	0.969 (0.848,1.106)	0.953 (0.696,1.313)
Pem+lenv	0.701 (0.542,0.905)	0.794 (0.604,1.042)	0.837 (0.53,1.321)	0.546 (0.422,0.706)	0.485 (0.381,0.614)	-	0.35 (0.266,0.457)	0.47 (0.385,0.573)	0.465 (0.317,0.676)
Sora	2.007 (1.578,2.527)	2.275 (1.776,2.937)	2.4 (1.549,3.729)	1.563 (1.236,1.978)	1.389 (1.164,1.653)	2.857 (2.189,3.763)	-	1.343 (1.132,1.599)	1.324 (1.023,1.729)
Suni	1.493 (1.271,1.752)	1.695 (1.41,2.04)	1.788 (1.187,2.688)	1.164 (0.989,1.365)	1.032 (0.904,1.18)	2.13 (1.744,2.596)	0.745 (0.626,0.883)	-	0.988 (0.72,1.356)
Tivo	1.515 (1.063,2.147)	1.716 (1.193,2.485)	1.814 (1.084,3.028)	1.179 (0.823,1.689)	1.049 (0.762,1.438)	2.152 (1.48,3.16)	0.755 (0.578,0.977)	1.013 (0.738,1.39)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the HR metric. The comparison is the row-forming treatment against the column-forming treatment.

Table 43: PFS in 1st line ITT population (excluding trials with poor risk exclusion)

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Suni
Ave+axi	-	1.137 (0.889,1.453)	1.393 (0.874,2.191)	0.778 (0.62,0.983)	0.638 (0.511,0.797)	1.426 (1.104,1.849)	0.67 (0.571,0.787)
Cabo+nivo	0.88 (0.688,1.124)	-	1.227 (0.764,1.971)	0.685 (0.537,0.877)	0.561 (0.44,0.715)	1.256 (0.956,1.648)	0.59 (0.49,0.71)
Cabo	0.718 (0.456,1.144)	0.815 (0.507,1.308)	-	0.558 (0.352,0.881)	0.457 (0.29,0.726)	1.024 (0.633,1.655)	0.48 (0.313,0.743)
Nivo+ipi	1.285 (1.018,1.612)	1.459 (1.14,1.863)	1.791 (1.135,2.843)	-	0.82 (0.655,1.02)	1.831 (1.416,2.366)	0.86 (0.73,1.011)
Pazo	1.567 (1.255,1.956)	1.781 (1.398,2.271)	2.189 (1.378,3.452)	1.22 (0.981,1.527)	-	2.236 (1.733,2.885)	1.05 (0.897,1.225)
Pem+lenv	0.701 (0.541,0.906)	0.796 (0.607,1.046)	0.976 (0.604,1.58)	0.546 (0.423,0.706)	0.447 (0.347,0.577)	-	0.47 (0.385,0.574)
Suni	1.492 (1.27,1.752)	1.696 (1.409,2.04)	2.083 (1.347,3.194)	1.163 (0.989,1.37)	0.952 (0.816,1.115)	2.126 (1.743,2.6)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the HR metric. The comparison is the row-forming treatment against the column-forming treatment.

3.7.4.2. Overall survival in 1st line ITT population

Our proportional hazards NMA of OS in the 1st line ITT population included six relevant identified trials with 1st line groups. We excluded trials testing sequences of treatments (CROSS-J-RCC, SWITCH, SWITCH II) as the OS estimates from these trials test sequences instead of individual treatments. As a result, we also excluded TIVO-1, and thus tivozanib, as this was now disconnected from the network. We estimated this model as a fixed-effects analysis as only one trial was available for each direct comparison, and we did not explore inconsistency as there were no closed loops in the network. Results are presented in Table 44 and suggested the numerical superiority of all treatments against sunitinib, though not the statistical superiority of cabozantinib or pazopanib. Results also did not suggest the superiority of any treatment against any other, with the exception of nivolumab with ipilimumab against pazopanib, though the pattern of effects suggested that cabozantinib with nivolumab was numerically superior to all other relevant treatments. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

3.7.4.3. Overall response rate in 1st line ITT population

Our NMA of ORR in the 1st line ITT population included all 10 relevant identified trials with 1st line groups. Because of the limited opportunities for heterogeneity in this NMA (one closed loop and only one comparison with more than one trial), we estimated this model as a fixed-effects analysis. We included the whole-population estimate from TIVO-1 in order to ensure tivozanib was represented in the network, since line-specific estimates for ORR were not available for this trial. Results are presented in Table 45 and suggested the numerical superiority of all relevant treatments against sunitinib, but not the statistical superiority of tivozanib. Cabozantinib with nivolumab was statistically superior to nivolumab with ipilimumab, pazopanib, sunitinib and tivozanib, numerically but not statistically superior to cabozantinib, and numerically but not statistically less effective than pembrolizumab with lenvatinib.

We compared our model against an unrestricted mean effects model to evaluate the presence of inconsistency. The deviance information criterion (DIC) for our consistency model was 39.53, with a total residual deviance of 21.47. In contrast, the DIC for our unrestricted mean effects model was 39.35, with a total residual deviance of 20.39. This suggested that the consistency model was acceptable. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Table 44: OS in 1st line ITT population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Suni
Ave+axi	-	1.128 (0.833,1.518)	0.984 (0.623,1.581)	1.096 (0.844,1.422)	0.859 (0.669,1.103)	0.999 (0.734,1.355)	0.789 (0.644,0.97)
Cabo+nivo	0.887 (0.659,1.2)	-	0.875 (0.552,1.404)	0.973 (0.744,1.278)	0.762 (0.585,1.001)	0.889 (0.641,1.215)	0.7 (0.56,0.878)
Cabo	1.016 (0.632,1.605)	1.143 (0.712,1.813)	-	1.113 (0.713,1.74)	0.873 (0.558,1.357)	1.012 (0.635,1.628)	0.804 (0.529,1.214)
Nivo+ipi	0.912 (0.703,1.185)	1.028 (0.783,1.345)	0.898 (0.575,1.403)	-	0.784 (0.631,0.973)	0.913 (0.69,1.193)	0.72 (0.614,0.843)
Pazo	1.164 (0.907,1.494)	1.312 (0.999,1.708)	1.145 (0.737,1.791)	1.276 (1.028,1.584)	-	1.165 (0.885,1.522)	0.92 (0.792,1.063)
Pem+lenv	1.001 (0.738,1.363)	1.125 (0.823,1.559)	0.988 (0.614,1.575)	1.096 (0.838,1.449)	0.858 (0.657,1.13)	-	0.789 (0.632,0.995)
Suni	1.267 (1.031,1.554)	1.428 (1.14,1.785)	1.243 (0.824,1.889)	1.39 (1.186,1.628)	1.087 (0.941,1.262)	1.267 (1.005,1.582)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the HR metric. The comparison is the row-forming treatment against the column-forming treatment.

Table 45: Overall response rate in 1st line ITT population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+ axi	-	0.961 (0.632,1.47)	1.174 (0.401,3.063)	2.306 (1.598,3.358)	2.163 (1.495,3.108)	0.732 (0.485,1.12)	3.813 (2.507,5.755)	3.14 (2.39,4.154)	2.339 (1.317,4.101)
Cabo+ nivo	1.041 (0.68,1.581)	-	1.234 (0.412,3.232)	2.415 (1.604,3.62)	2.254 (1.497,3.415)	0.765 (0.484,1.205)	3.975 (2.509,6.297)	3.277 (2.383,4.546)	2.438 (1.333,4.437)
Cabo	0.852 (0.326,2.49 7)	0.81 (0.309,2.42 9)	-	1.965 (0.768,5.726)	1.834 (0.71,5.397)	0.624 (0.241,1.863)	3.231 (1.231,9.67)	2.666 (1.085,7.527)	1.993 (0.712,6.341)
Nivo+ip i	0.434 (0.298,0.62 6)	0.414 (0.276,0.62 3)	0.509 (0.175,1.302)	-	0.936 (0.667,1.308)	0.316 (0.212,0.472)	1.65 (1.101,2.456)	1.36 (1.07,1.733)	1.011 (0.577,1.761)
Pazo	0.462 (0.322,0.66 9)	0.444 (0.293,0.66 8)	0.545 (0.185,1.409)	1.068 (0.764,1.5)	-	0.339 (0.227,0.502)	1.763 (1.284,2.425)	1.454 (1.146,1.849)	1.082 (0.653,1.776)
Pem+ lenv	1.367 (0.893,2.06 3)	1.307 (0.83,2.066)	1.603 (0.537,4.151)	3.16 (2.119,4.714)	2.954 (1.993,4.401)	-	5.205 (3.34,8.162)	4.288 (3.135,5.881)	3.193 (1.752,5.833)
Sora	0.262 (0.174,0.39 9)	0.252 (0.159,0.39 9)	0.31 (0.103,0.812)	0.606 (0.407,0.908)	0.567 (0.412,0.779)	0.192 (0.123,0.299)	-	0.825 (0.604,1.129)	0.615 (0.416,0.902)
Suni	0.318 (0.241,0.41 8)	0.305 (0.22,0.42)	0.375 (0.133,0.922)	0.735 (0.577,0.935)	0.688 (0.541,0.872)	0.233 (0.17,0.319)	1.212 (0.886,1.656)	-	0.745 (0.447,1.224)
Tivo	0.428 (0.244,0.75 9)	0.41 (0.225,0.75)	0.502 (0.158,1.404)	0.989 (0.568,1.734)	0.924 (0.563,1.531)	0.313 (0.171,0.571)	1.627 (1.109,2.406)	1.343 (0.817,2.235)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the OR metric. The comparison is the row-forming treatment against the column-forming treatment.

3.7.4.4. Discontinuation due to adverse events in 1st line ITT population

Our NMA of discontinuation due to AEs in the 1st line ITT population included all 10 relevant identified trials with 1st line groups. A fixed-effects model suggested inconsistency, with DIC (47.86) and total residual deviance (29.78) both higher than the corresponding values for the unrestricted mean effects model (DIC 38.70, total residual deviance 19.66). We then considered a random effects model using a stabilising prior distribution from Turner (2015[144]), in the form of a lognormal distribution with parameters (-2.29, 1.58^2). The resultant model showed satisfactory consistency when compared to an unrestricted mean effects model with the same informative prior distribution in respect of both DIC (39.68 vs 39.32) and total residual deviance (20.29 vs 19.76). One possible reason for this inconsistency is that evidence on discontinuation due to adverse events is inconsistently reported across included trials. In four trials, we extracted data from PRISMA flowcharts describing discontinuations due to adverse events; in another five trials, we extracted data from the text describing withdrawals or any treatment-emergent adverse event leading to treatment stop. It is possible that these outcome definitions generated some methodological heterogeneity in our NMA for this outcome. In addition, we included the whole-population estimate from TIVO-1 in order to ensure tivozanib was represented in the network, since line-specific estimates for discontinuation were not available for this trial.

Results are presented in Table 46. Nearly all credible intervals embraced 1, without a clear pattern of effects across treatments; comparisons between relevant treatments that were not sunitinib did not identify any statistically meaningful pairwise differences. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

3.7.4.5. Risk of treatment-emergent adverse events of grade 3 of higher in 1st line ITT population

Our NMA of risk of TEAEs of grade 3 or higher in the 1st line ITT population included all 10 relevant identified trials with 1st line groups. Because of the limited opportunities for heterogeneity in this NMA (one closed loop and only one comparison with more than one trial), we estimated this model as a fixed-effects analysis. We included the whole-population estimate from TIVO-1 in order to ensure tivozanib was represented in the network, since line-specific estimates for grade 3 or higher adverse events were not available for this trial. Results are presented in Table 47 and suggested a diverse pattern of effects. Cabozantinib with nivolumab had a statistically greater odds of TEAEs of grade 3 or higher as compared to nivolumab with ipilimumab, pazopanib, sunitinib, and tivozanib; numerically but not statistically greater odds

than cabozantinib; and numerically but not statistically lower odds than pembrolizumab with lenvatinib.

We compared our model against an unrestricted mean effects model to evaluate the presence of inconsistency. The deviance information criterion (DIC) for our consistency model was 37.42, with a total residual deviance of 19.23. In contrast, the DIC for our unrestricted mean effects model was 39.04, with a total residual deviance of 20.03. This suggested that the consistency model was acceptable. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Table 46: Discontinuation due to adverse events in 1st line ITT population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+axi	-	1.048 (0.314,3.367)	2.435 (0.612,9.354)	1.104 (0.341,3.614)	2.735 (0.945,8.014)	0.672 (0.211, 2.111)	2.741 (0.992,7.901)	2.393 (1.034,5.554)	2.634 (0.646,11.195)
Cabo+nivo	0.954 (0.297,3.18)	-	2.311 (0.585,9.078)	1.058 (0.324,3.456)	2.597 (0.909,7.622)	0.641 (0.197, 2.101)	2.612 (0.953,7.556)	2.296 (0.981,5.285)	2.513 (0.618,10.548)
Cabo	0.411 (0.107,1.635)	0.433 (0.11,1.709)	-	0.457 (0.117,1.76)	1.129 (0.331,3.994)	0.276 (0.07, 1.065)	1.138 (0.343,3.953)	0.989 (0.34,2.876)	1.085 (0.237,5.247)
Nivo+ipi	0.906 (0.277,2.929)	0.945 (0.289,3.083)	2.187 (0.568,8.516)	-	2.471 (0.838,7.282)	0.603 (0.192, 1.902)	2.489 (0.869,7.122)	2.166 (0.924,4.954)	2.414 (0.557,10.007)
Pazo	0.366 (0.125,1.058)	0.385 (0.131,1.1)	0.886 (0.25,3.023)	0.405 (0.137,1.193)	-	0.244 (0.085, 0.692)	1.009 (0.513,1.97)	0.881 (0.443,1.676)	0.975 (0.283,3.181)
Pem+lenv	1.488 (0.474, 4.732)	1.56 (0.476, 5.07)	3.617 (0.939, 14.26)	1.659 (0.526, 5.203)	4.091 (1.445, 11.829)	-	4.114 (1.46, 11.855)	3.564 (1.599, 8.196)	3.935 (0.871, 17.186)
Sora	0.365 (0.127,1.008)	0.383 (0.132,1.049)	0.879 (0.253,2.914)	0.402 (0.14,1.15)	0.991 (0.508,1.949)	0.243 (0.084, 0.685)	-	0.873 (0.463,1.586)	0.961 (0.348,2.645)
Suni	0.418 (0.18,0.967)	0.436 (0.189,1.019)	1.011 (0.348,2.943)	0.462 (0.202,1.082)	1.134 (0.597,2.256)	0.281 (0.122, 0.625)	1.145 (0.631,2.16)	-	1.1 (0.349,3.487)
Tivo	0.38 (0.089,1.547)	0.398 (0.095,1.618)	0.922 (0.191,4.215)	0.414 (0.1,1.797)	1.026 (0.314,3.534)	0.254 (0.058, 1.148)	1.041 (0.378,2.875)	0.909 (0.287,2.863)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the OR metric. The comparison is the row-forming treatment against the column-forming treatment.

Table 47: Risk of adverse events of grade 3 or higher in 1st line ITT population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+axi	-	0.702 (0.425,1.149)	0.891 (0.43,1.857)	1.818 (1.194,2.772)	1.114 (0.743,1.655)	0.576 (0.358,0.935)	1.348 (0.864,2.102)	1.197 (0.867,1.658)	1.966 (1.113,3.563)
Cabo+nivo	1.425 (0.87,2.353)	-	1.275 (0.594,2.714)	2.593 (1.641,4.121)	1.589 (1.01,2.509)	0.82 (0.49,1.385)	1.93 (1.182,3.132)	1.71 (1.167,2.518)	2.808 (1.531,5.179)
Cabo	1.122 (0.539,2.325)	0.784 (0.368,1.684)	-	2.042 (1.006,4.146)	1.252 (0.615,2.526)	0.646 (0.306,1.371)	1.516 (0.721,3.108)	1.342 (0.688,2.592)	2.205 (0.971,4.996)
Nivo+ipi	0.55 (0.361,0.838)	0.386 (0.243,0.609)	0.49 (0.241,0.994)	-	0.614 (0.427,0.878)	0.317 (0.205,0.491)	0.742 (0.497,1.106)	0.66 (0.501,0.86)	1.086 (0.631,1.88)
Pazo	0.898 (0.604,1.346)	0.629 (0.399,0.99)	0.799 (0.396,1.625)	1.628 (1.138,2.34)	-	0.518 (0.337,0.79)	1.209 (0.887,1.665)	1.076 (0.845,1.37)	1.769 (1.096,2.864)
Pem+lenv	1.736 (1.069,2.791)	1.22 (0.722,2.04)	1.548 (0.729,3.263)	3.156 (2.036,4.884)	1.93 (1.266,2.965)	-	2.342 (1.482,3.695)	2.078 (1.466,2.943)	3.425 (1.909,6.184)
Sora	0.742 (0.476,1.158)	0.518 (0.319,0.846)	0.66 (0.322,1.386)	1.347 (0.904,2.012)	0.827 (0.601,1.127)	0.427 (0.271,0.675)	-	0.887 (0.656,1.198)	1.462 (1.009,2.114)
Suni	0.836 (0.603,1.153)	0.585 (0.397,0.857)	0.745 (0.386,1.453)	1.514 (1.163,1.997)	0.929 (0.73,1.183)	0.481 (0.34,0.682)	1.128 (0.835,1.526)	-	1.646 (1.029,2.659)
Tivo	0.509 (0.281,0.899)	0.356 (0.193,0.653)	0.453 (0.2,1.03)	0.921 (0.532,1.586)	0.565 (0.349,0.912)	0.292 (0.162,0.524)	0.684 (0.473,0.991)	0.608 (0.376,0.972)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Notes: Findings are in the OR metric. The comparison is the row-forming treatment against the column-forming treatment.

3.7.4.6. Progression-free survival in 1st line intermediate or poor risk population

Our proportional hazards NMA of PFS in the 1st line intermediate or poor risk population included findings from nine trials (all 1st line trials except for SWITCH II). We included the estimate from TIVO-1 of PFS in the intermediate or poor risk population spanning 1st and 2nd line patients to ensure that tivozanib was represented in the network; otherwise, all estimates drew from 1st line patients only. The resultant network did not have any closed loops, and only the sunitinib-sorafenib comparison had more than one trial. Thus, we estimated a fixed-effects model. Results are presented in Table 48 and suggested all treatments were numerically superior to sunitinib, and statistically so for cabozantinib + nivolumab, cabozantinib, nivolumab + ipilimumab, and pembrolizumab + lenvatinib. Cabozantinib + nivolumab was statistically superior to pazopanib, sunitinib and tivozanib; numerically but not statistically superior to nivolumab + ipilimumab; and numerically but not statistically less effective than cabozantinib and pembrolizumab + lenvatinib. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

3.7.4.7. Overall survival in 1st line intermediate or poor risk population

Our proportional hazards NMA of OS in the 1st line intermediate or poor risk population included findings from six trials. Similar to the proportional hazards NMA of OS in the 1st line ITT population, we excluded CROSS-J-RCC and SWITCH. Findings from TIVO-1 and SWITCH II were not available for this outcome and risk group. The resultant network was star-shaped and no comparison had more than one trial in direct evidence. Thus, we estimated a fixed-effects model. Results are presented in Table 49 and suggested that all relevant treatments were superior to sunitinib. Cabozantinib + nivolumab was numerically superior to all relevant treatments, statistically so for pazopanib and sunitinib. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Table 48: PFS in 1st line intermediate/poor risk population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+axi	-	1.178 (0.904,1.542)	1.379 (0.863,2.176)	0.905 (0.704,1.168)	0.674 (0.517,0.879)	1.534 (1.142,2.062)	0.61 (0.426,0.87)	0.66 (0.552,0.789)	0.743 (0.479,1.146)
Cabo+nivo	0.849 (0.648,1.106)	-	1.168 (0.73,1.873)	0.767 (0.587,1.003)	0.572 (0.432,0.759)	1.303 (0.954,1.78)	0.516 (0.36,0.74)	0.561 (0.458,0.684)	0.629 (0.405,0.983)
Cabo	0.725 (0.46,1.159)	0.856 (0.534,1.369)	-	0.656 (0.414,1.034)	0.488 (0.305,0.778)	1.112 (0.691,1.815)	0.441 (0.263,0.747)	0.479 (0.313,0.735)	0.538 (0.299,0.963)
Nivo+ipi	1.105 (0.856,1.421)	1.304 (0.997,1.705)	1.525 (0.967,2.413)	-	0.746 (0.572,0.97)	1.699 (1.256,2.291)	0.672 (0.475,0.956)	0.729 (0.612,0.875)	0.82 (0.531,1.267)
Pazo	1.483 (1.137,1.935)	1.75 (1.318,2.316)	2.049 (1.285,3.284)	1.34 (1.031,1.75)	-	2.279 (1.682,3.098)	0.902 (0.629,1.308)	0.979 (0.803,1.198)	1.103 (0.706,1.731)
Pem+lenv	0.652 (0.485,0.876)	0.767 (0.562,1.049)	0.899 (0.551,1.448)	0.588 (0.437,0.796)	0.439 (0.323,0.595)	-	0.397 (0.269,0.579)	0.43 (0.339,0.547)	0.485 (0.301,0.765)
Sora	1.639 (1.149,2.345)	1.937 (1.352,2.779)	2.265 (1.34,3.804)	1.488 (1.046,2.106)	1.109 (0.764,1.59)	2.518 (1.728,3.719)	-	1.084 (0.803,1.469)	1.218 (0.946,1.58)
Suni	1.516 (1.267,1.81)	1.782 (1.463,2.186)	2.089 (1.361,3.195)	1.372 (1.143,1.635)	1.022 (0.834,1.245)	2.326 (1.829,2.946)	0.923 (0.681,1.245)	-	1.125 (0.755,1.674)
Tivo	1.345 (0.872,2.088)	1.59 (1.018,2.471)	1.858 (1.039,3.343)	1.22 (0.79,1.883)	0.907 (0.578,1.417)	2.063 (1.307,3.317)	0.821 (0.633,1.057)	0.889 (0.597,1.324)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

Table 49: OS in 1st line intermediate/poor risk population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pazo	Pem+lenv	Suni
Ave+axi	-	1.218 (0.877,1.669)	0.989 (0.622,1.578)	1.161 (0.885,1.526)	0.887 (0.67,1.179)	1.067 (0.761,1.495)	0.791 (0.636,0.982)
Cabo+nivo	0.821 (0.599,1.14)	-	0.814 (0.507,1.313)	0.958 (0.706,1.29)	0.73 (0.536,0.989)	0.882 (0.618,1.25)	0.651 (0.509,0.832)
Cabo	1.011 (0.634,1.608)	1.229 (0.762,1.974)	-	1.176 (0.759,1.832)	0.897 (0.579,1.399)	1.08 (0.671,1.746)	0.799 (0.533,1.206)
Nivo+ipi	0.861 (0.655,1.13)	1.044 (0.775,1.416)	0.851 (0.546,1.318)	-	0.763 (0.601,0.976)	0.92 (0.679,1.252)	0.68 (0.578,0.807)
Pazo	1.128 (0.848,1.492)	1.37 (1.011,1.864)	1.115 (0.715,1.727)	1.311 (1.024,1.663)	-	1.204 (0.887,1.637)	0.892 (0.749,1.061)
Pem+lenv	0.937 (0.669,1.315)	1.134 (0.8,1.619)	0.926 (0.573,1.491)	1.086 (0.799,1.474)	0.83 (0.611,1.128)	-	0.74 (0.574,0.959)
Suni	1.264 (1.019,1.572)	1.536 (1.201,1.965)	1.252 (0.829,1.876)	1.471 (1.24,1.731)	1.121 (0.942,1.336)	1.351 (1.043,1.743)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

3.7.4.8. Overall response rate in 1st line intermediate or poor risk population

Our NMA of ORR in the 1st line ITT population included findings from five trials (CABOSUN, CheckMate 214, CLEAR, JAVELIN Renal 101, CheckMate 9ER) for which data were available for this risk group, line and outcome. The resultant network was star-shaped and no comparison had more than one trial in direct evidence. Thus, we estimated a fixed-effects model. Results are presented in Appendix E and suggested that all treatments were superior to sunitinib. Cabozantinib + nivolumab was statistically superior to nivolumab + ipilimumab and sunitinib; numerically superior to cabozantinib; and statistically less effective than pembrolizumab + lenvatinib. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Table 50: Overall response rate in 1st line intermediate/poor risk population

	Ave+axi	Cabo+nivo	Cabo	Nivo+ipi	Pem+lenv	Suni
Ave+axi	-	0.851 (0.514,1.39)	1.197 (0.414,3.181)	1.609 (1.042,2.467)	0.485 (0.29,0.807)	3.17 (2.323,4.375)
Cabo+nivo	1.174 (0.72,1.946)	-	1.407 (0.482,3.862)	1.891 (1.175,3.047)	0.572 (0.325,0.994)	3.726 (2.542,5.518)
Cabo	0.835 (0.314,2.415)	0.711 (0.259,2.074)	-	1.347 (0.518,3.841)	0.406 (0.147,1.18)	2.662 (1.051,7.23)
Nivo+ipi	0.622 (0.405,0.96)	0.529 (0.328,0.851)	0.742 (0.26,1.93)	-	0.302 (0.184,0.49)	1.972 (1.483,2.636)
Pem+lenv	2.061 (1.24,3.449)	1.747 (1.006,3.079)	2.461 (0.848,6.783)	3.315 (2.04,5.442)	-	6.535 (4.418,9.821)
Suni	0.316 (0.229,0.43)	0.268 (0.181,0.393)	0.376 (0.138,0.951)	0.507 (0.379,0.674)	0.153 (0.102,0.226)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

3.7.4.9. PFS in 1st line favourable risk population

Our proportional hazards NMA of PFS in the 1st line favourable risk population included findings from eight of the nine trials that enrolled favourable risk patients (i.e. excluding SWITCH II). We included the estimate from TIVO-1 of PFS in the favourable risk population spanning 1st and 2nd line patients to ensure that tivozanib was represented in the network; otherwise, all estimates drew from 1st line patients only. The resultant network did not have any closed loops, and only the sunitinib-sorafenib comparison had more than one trial. Thus, we estimated a fixed-effects model. Results are presented in Table 51 and did not suggest a consistent pattern of effectiveness relative to sunitinib. Cabozantinib + nivolumab was numerically superior to all relevant treatments except for pembrolizumab + lenvatinib, and was statistically superior to

nivolumab + ipilimumab. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

3.7.4.10. OS in 1st line favourable risk population

Our proportional hazards NMA of OS in the 1st line favourable risk population included findings from five of the nine trials that enrolled favourable risk patients. Estimates were not available for TIVO-1, thus excluding tivozanib from the network, and we excluded both crossover trials for which estimates were available for this outcome (CROSS-J-RCC, SWITCH). The resultant network was star-shaped with one trial per comparison. Thus, we estimated a fixed-effects model. Results are presented in Table 52 and did not suggest any evidence of effectiveness relative to sunitinib. Cabozantinib + nivolumab was numerically, but not statistically, less effective than all relevant treatments. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

3.7.4.11. Overall response rate in 1st line favourable risk population

Our NMA of ORR in the 1st line favourable risk population included findings from four trials (CheckMate 214, CLEAR, JAVELIN Renal 101, CheckMate 9ER). The resultant network was star-shaped with one trial per comparison. Thus, we estimated a fixed-effects model. Results are presented in Table 53 and suggested that all treatments except for nivolumab + ipilimumab generated higher ORR in this population as compared to sunitinib; in contrast, nivolumab + ipilimumab generated worse ORR in this population. Cabozantinib + nivolumab was statistically superior to nivolumab + ipilimumab and sunitinib, and numerically superior to pembrolizumab + lenvatinib. Visual inspection of density plots and trace plots did not suggest non-convergence of our model.

Table 51: PFS in 1st line favourable risk population

	Ave+axi	Cabo+nivo	Nivo+ipi	Pazo	Pem+lenv	Sora	Suni	Tivo
Ave+axi	-	0.985 (0.591,1.662)	0.444 (0.267,0.732)	0.7 (0.441,1.121)	1.416 (0.856,2.328)	0.451 (0.255,0.799)	0.708 (0.496,1.025)	0.761 (0.37,1.586)
Cabo+nivo	1.015 (0.602,1.692)	-	0.45 (0.265,0.741)	0.711 (0.434,1.144)	1.435 (0.854,2.386)	0.458 (0.255,0.817)	0.721 (0.489,1.051)	0.774 (0.369,1.6)
Nivo+ipi	2.254 (1.366,3.739)	2.222 (1.35,3.779)	-	1.58 (0.988,2.518)	3.2 (1.954,5.192)	1.024 (0.585,1.744)	1.6 (1.135,2.244)	1.733 (0.836,3.497)
Pazo	1.428 (0.892,2.27)	1.406 (0.874,2.306)	0.633 (0.397,1.012)	-	2.026 (1.256,3.238)	0.644 (0.38,1.1)	1.013 (0.744,1.373)	1.091 (0.539,2.178)
Pem+lenv	0.706 (0.43,1.168)	0.697 (0.419,1.17)	0.313 (0.193,0.512)	0.494 (0.309,0.796)	-	0.318 (0.181,0.56)	0.501 (0.35,0.715)	0.539 (0.262,1.102)
Sora	2.217 (1.252,3.919)	2.183 (1.224,3.928)	0.976 (0.573,1.709)	1.554 (0.909,2.634)	3.145 (1.786,5.516)	-	1.57 (1.021,2.422)	1.695 (1.076,2.624)
Suni	1.413 (0.976,2.015)	1.388 (0.952,2.045)	0.625 (0.446,0.881)	0.987 (0.728,1.345)	1.996 (1.399,2.861)	0.637 (0.413,0.979)	-	1.077 (0.572,1.997)
Tivo	1.313 (0.63,2.7)	1.293 (0.625,2.707)	0.577 (0.286,1.196)	0.917 (0.459,1.857)	1.856 (0.907,3.814)	0.59 (0.381,0.929)	0.929 (0.501,1.747)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pazo, pazopanib; pem, pembrolizumab; tivo, tivozanib

Table 52: OS in 1st line favourable risk population

	Ave+axi	Cabo+nivo	Nivo+ipi	Pazo	Pem+lenv	Suni
Ave+axi	-	0.612 (0.276,1.385)	0.699 (0.345,1.447)	0.748 (0.371,1.499)	0.704 (0.325,1.557)	0.66 (0.359,1.216)
Cabo+nivo	1.633 (0.722,3.626)	-	1.138 (0.593,2.16)	1.218 (0.654,2.244)	1.149 (0.551,2.294)	1.074 (0.635,1.786)
Nivo+ipi	1.43 (0.691,2.896)	0.879 (0.463,1.687)	-	1.068 (0.65,1.762)	1.002 (0.545,1.832)	0.944 (0.645,1.384)
Pazo	1.336 (0.667,2.696)	0.821 (0.446,1.53)	0.936 (0.568,1.538)	-	0.936 (0.532,1.671)	0.881 (0.634,1.223)
Pem+lenv	1.42 (0.642,3.078)	0.87 (0.436,1.814)	0.998 (0.546,1.836)	1.068 (0.598,1.881)	-	0.941 (0.583,1.513)
Suni	1.516 (0.822,2.786)	0.931 (0.56,1.576)	1.06 (0.722,1.549)	1.135 (0.818,1.576)	1.063 (0.661,1.716)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pazo, pazopanib; pem, pembrolizumab

Table 53: Overall response rate in 1st line favourable risk population

	Ave+axi	Cabo+nivo	Nivo+ipi	Pem+lenv	Suni
Ave+axi	-	1.494 (0.597,3.786)	9.113 (4.068,20.436)	1.767 (0.791,4.028)	3.695 (2.02,6.99)
Cabo+nivo	0.669 (0.264,1.674)	-	6.08 (2.656,14.196)	1.189 (0.509,2.815)	2.484 (1.277,4.97)
Nivo+ipi	0.11 (0.049,0.246)	0.164 (0.07,0.376)	-	0.195 (0.093,0.403)	0.407 (0.243,0.683)
Pem+lenv	0.566 (0.248,1.265)	0.841 (0.355,1.963)	5.139 (2.483,10.734)	-	2.085 (1.225,3.562)
Suni	0.271 (0.143,0.495)	0.403 (0.201,0.783)	2.456 (1.465,4.12)	0.48 (0.281,0.817)	-

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; ipi, ipilimumab; ITT, intention to treat; lenv, lenvatinib; nivo, nivolumab; pazo, pazopanib; pem, pembrolizumab; tivo, tivozanib

3.7.5. Cross-cutting commentary on network meta-analyses

Our time-invariant NMAs have a number of caveats in their interpretation, in addition to the comments offered in Section 3.7.3.6. First, time-invariant NMAs using summary effect sizes for survival outcomes (i.e. for OS and PFS outcomes) rely on an assumption of proportionality within comparisons entered into each model. This assumption was violated multiple times in our network as the assumption of proportional hazards was tenuous for at least one outcome in each included trial. While it is possible to interpret the HR from a model where the proportional hazards assumption has been violated as a time-average effect, it is likely preferable to use survival curves directly in indirect treatment comparisons. This was the basis for our fractional polynomial NMA. However, a competing issue that is posed by fractional polynomial NMAs is the need to undertake model selection. Like all extrapolation analyses, this introduces a degree of subjectivity to the analysis, but is likely to provide 'higher-fidelity' estimates of relative treatment effects.

Second, we used the most mature datacut available for each trial in all NMAs. This is a challenge for both fractional polynomial and time-invariant NMAs. While this is unlikely to have made a substantial difference for binary outcomes beyond a point of maturity, we are aware that there is some debate that equivalent timepoints should have been used across trials for analysis, generally because more mature data (for example, for overall survival) may reveal relationships not in evidence in earlier datacuts. We did not take this approach for several reasons. First, using earlier datacuts even where trials are highly mature would discard valuable information contributing to precision of effect sizes. Second, we did not regard that there was a good basis *ex ante* for grouping trial follow-up times, and it is likely that this would have led to the exclusion of trials reporting inadequately similar follow-up times. Third, while we did identify some evidence of maturing HRs over time, we did not identify consistent patterns in evolving shape of survival curves and trends in effect size when we jointly considered different levels of trial maturity and different treatments. In Figure 31 and Figure 32, we present examples from OS and PFS estimates in sequential datacuts for key trials. For three out of four IO/TKI combinations (i.e. excepting avelumab + axitinib), there appears to be slippage in OS estimates with sequential datacuts; the same trend is less in evidence for the one IO/IO combination (nivolumab + ipilimumab). Of interest is that the same trend in IO/TKI combinations is less immediately obvious for PFS outcomes. The mechanisms underpinning this evolution over time, and the mismatch in evolution, are unclear and merit further investigation.

Figure 31: Plot of cumulative OS over sequential datacuts in key trials

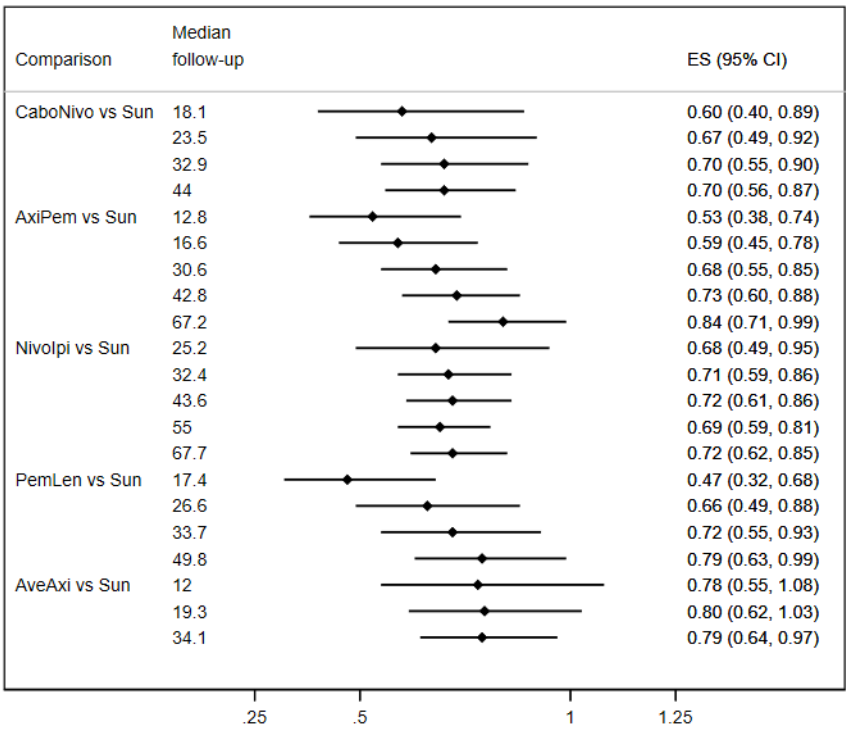
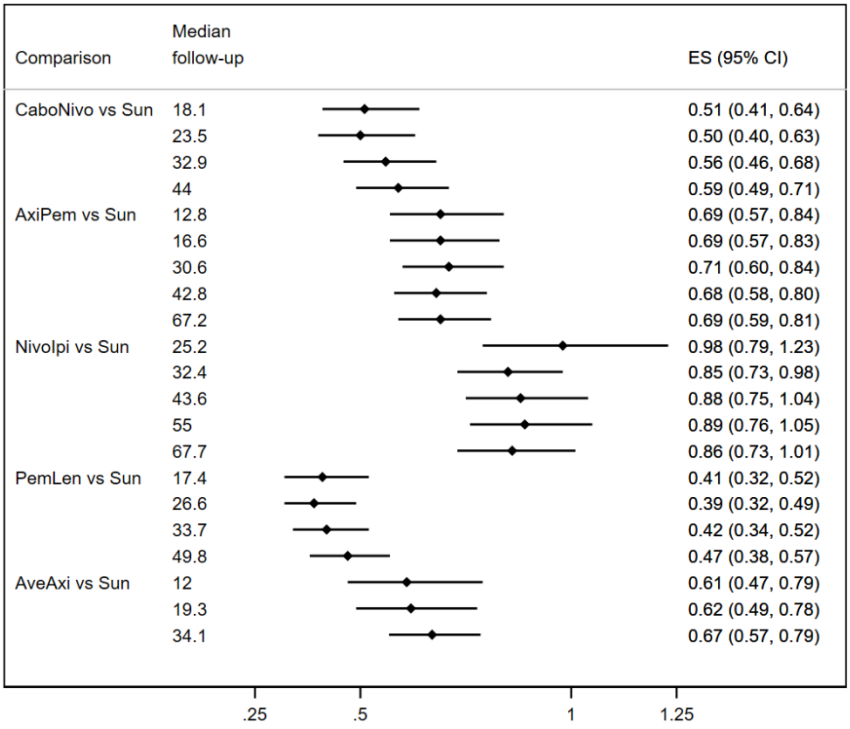


Figure 32: Plot of cumulative PFS over sequential datacuts in key trials



Third, most of our networks relied on one trial per direct comparison; even where networks had closed loops, these were sparse in the direct evidence available for each comparison. Again, this was a challenge for both fractional polynomial and time-invariant NMAs. The key limitation is that we were unable to account for differences over comparisons in the network in the distribution of potential effect modifiers.

Fourth, NMAs of safety outcomes are often unusually challenging given the diverse reporting of these outcomes. This is somewhat reflected in our findings relating to discontinuation due to AEs in the 1st line population. NMAs of safety outcomes should thus be regarded with some caution.

Finally, NMAs for 2nd line patient populations relied on a linking trial with a small sample size and documented issues with protocol administration. This mean that for some outcomes, networks were incomplete. These results should be interpreted in the view that not all relevant treatments were included in these meta-analyses.

3.7.6. Conclusions from the EAG NMAs

EAG NMAs included both fractional polynomial NMAs for OS and PFS and proportional hazards NMAs for the same outcomes, and NMAs for overall response rate and adverse event outcomes. On the whole, EAG NMAs reflected several challenges in this evidence base, including imbalanced distribution of effect modifiers, differences in follow-up, and challenges (particularly in second line) constructing evidence network, leading to the exclusion of tivozanib in some first line networks and axitinib and tivozanib in some second-line networks. However, both sets of NMAs reflect salient differences in effectiveness between treatments, particularly on PFS outcomes. As mentioned prior, inference on any differences in OS is complicated by subsequent treatment. A key issue comparing the NMAs was with respect to estimability in the CLEAR trial. The fractional polynomial NMA generated unreasonably pessimistic estimates of pembrolizumab + lenvatinib's effectiveness due to differences in events accumulated early in the time horizon, biasing results against this treatment; in contrast, the proportional hazards NMA provide an unduly favourable estimate of effectiveness given the convergence of hazards between treatment arms and the clear violations of the proportional hazards assumption.

Focusing on cabozantinib + nivolumab and the comparators relevant to the decision problem in each risk group, fractional polynomial NMAs for PFS and OS in the all risk group suggested that this combination was more effective than TKIs in first-line. Similarly, time-invariant NMAs for both OS and PFS reflected that cabozantinib + nivolumab was superior to TKIs.

In the intermediate/poor risk group, PFS for cabozantinib + nivolumab appeared to generate a predicted early survival benefit coterminous with cabozantinib up through about month 15, whereas for OS, cabozantinib + nivolumab generated an early survival advantage through 55 months, at which point survival curves with other treatments, including cabozantinib and nivolumab with ipilimumab, crossed. Time-invariant NMAs in the intermediate/poor risk population for both OS and PFS reflected that while cabozantinib + nivolumab was superior to TKIs, it was not generally statistically distinguishable from other novel treatments.

NMA estimates for the favourable risk group were only available from time-invariant NMAs. Cabozantinib + nivolumab was not generally distinguishable from other treatments in either OS or PFS analyses.

3.7.7. Comparison to other published network meta-analyses

To contextualise our findings, we compare our results to the ERG's NMAs in TA858, to the company's own NMAs, and to a recently published Cochrane review, all of which considered treatments in the 1st line. We also contrast our findings to the most recent NMA of 2nd line treatments in RCC, Liao 2022. Of note is that the only NMAs to also use a fractional polynomial method of those discussed below were presented by the company.

3.7.7.1. TA858

Our analysis strategy was similar to that undertaken in TA858, in that we undertook NMAs for PFS, OS, and ORR, and our analyses used a Bayesian framework. Similar to TA858, we preferred fixed effects models given the sparseness of included networks, and preferred blinded assessments of progression and response outcomes over investigator assessments. Unlike TA858, we interpreted the ITT population as an 'all-comers' group and thus included CABOSUN; we also considered all treatments for 1st line with available data in risk group analyses (e.g. even though sunitinib is not restricted by risk group, we included it in analyses of patients with intermediate or poor risk). We also used TIVO-1 to connect tivozanib to networks where estimates by line were unavailable, and were able to include JAVELIN-RENAL-101 and

CheckMate 9ER in our analyses. We further undertook NMAs of discontinuation due to AEs and risk of grade 3 or higher treatment-emergent adverse events as we were able to identify with appropriate reliability evidence from included RCTs. The ERG's concern in TA858 about the reliability of discontinuation evidence was somewhat reflected in the difficulties we faced with this analysis. Unlike TA858, we did not undertake sensitivity analysis by censoring rule used in PFS as we did not have the evidence available to undertake this. Specific comparison of results is limited both by differences in treatments included in each network and by the fact that we used different datacuts for several of the same trials used in TA858 (CheckMate 214, CLEAR).

3.7.7.2. Company-reported indirect treatment comparison

Our analysis strategy was also broadly similar to that undertaken in the company's NMA, including the use of a Bayesian framework. We used a proportional hazards NMA as an adjunct to additional methods for exploring differences between treatments in survival outcomes; however, we only considered fractional polynomial NMAs for survival outcomes as this was our protocol-specified method. We also did not consider proportion of intermediate or poor risk as a covariate due to the sparseness of the networks. A key difference between our NMAs and the NMAs reported by the company is that we included a systematically different set of trials. Unlike the company, we did not include KEYNOTE-426, which compared pembrolizumab with axitinib against sunitinib, as this was not a relevant comparator in this appraisal. We also did not consider the SUTENT trial (NCT01147822) separately from COMPARZ, as we used the pooled analyses from the COMPARZ studies in our NMAs. We also included data from the 1st line in crossover trials where these data were available (SWITCH, SWITCH II, CROSS-J-RCC), enabling use of TIVO-1 in several NMAs and thus including tivozanib in several networks. Where we undertook analyses of intermediate and poor risk patients, we pooled these groups as a result of our feasibility assessment. Finally, we included CABOSUN in our ITT population.

For fractional polynomial NMAs, our approach differed to the company in several ways. First, we used a frequentist model selection method to narrow down a wide range of polynomial terms and combinations to a smaller subset that would be taken through to Bayesian estimation. Second, as a result of that, we used a broader set of polynomial functions at model selection stage than the company used in any one meta-analysis, but used comparatively fewer at the model comparison stage. Third, we considered both fixed effects and random effects models in our analysis, but did not consider first-order polynomials. A final point of difference is that we included updated datacuts for a range of trials, including CheckMate 9ER. We also used expert

elicitation to guide in selection of curves. As a result, the EAG and the company chose different fractional polynomial distributions for each outcome, limiting direct comparability of findings.

However, a number of points merit discussion. For all-risk OS, the company's survival curves referenced against the CheckMate 9ER trial showed a similar set of curves, grouped as sunitinib and pazopanib with all other curves forming a second group. However, comparing the EAG's models to the company's models over 60 months, the EAG's fitted models appeared to show more variation between treatments early, with cabozantinib + nivolumab showing an advantage earlier in the time horizon that was not reflected in the company's analyses. Comparing HRs in all-risk PFS, both the company's and the EAG's analyses suggested that nivolumab + ipilimumab had a longer-term advantage over cabozantinib + nivolumab, though the EAG's analysis suggested that cabozantinib + nivolumab and avelumab + axitinib were closer together in effectiveness over the time horizon than the company's analysis indicated.

In the intermediate/poor risk group, the company's and EAG's analyses PFS analyses broadly aligned, though in the EAG's analysis, cabozantinib + nivolumab performs somewhat worse over the later time horizon as compared to cabozantinib. However, in the OS analyses, the EAG again found that cabozantinib + nivolumab had an early survival advantage that appeared to 'fade out'; in the company's analyses, curves for cabozantinib + nivolumab and cabozantinib are broadly coterminous over the time horizon.

Our proportional hazards analyses for OS and PFS aligned well with the results provided by the company. However, we considered ORR as the sum of complete and partial responses, whereas the company considered complete responses only. In addition, our NMA for discontinuation due to AEs used a random effects model and an informative prior distribution, whereas the company's model used fixed effects. This limited comparability. There was also a lack of comparability between NMAs on discontinuation outcomes. A possible reason for this is that we used updated datacuts for JAVELIN-RENAL-101, CLEAR and CheckMate 9ER. Unlike the company, we did not regard that meta-analysis of HRQoL was warranted given the available data.

3.7.7.3. Cochrane review

Next, we note a recently published Cochrane review that considered 1st line treatments for advanced RCC.[150] This review had a radically different scope than the current analysis as it sought to consider all published RCTs for this population, and used a frequentist analysis

paradigm. A total of 36 RCTs were included in this review, and NMAs were primarily estimated using random effects. In addition, searches were last undertaken in February 2022, which would have excluded a number of more recent datacuts we included for relevant trials. The NMA did, however, explore the impact of specific adverse events of clinical interest which could not be explored by the EAG within the timeframe for this appraisal (HFS, diarrhoea and fatigue) and was therefore considered useful for later us in the economic analyses.

3.7.7.4. Liao 2022

Finally, we compare our findings against the most recent NMA of 2nd line treatments identified. Our results are not comprehensively comparable. For example, our results may not be directly comparable for PFS as the definition used in Liao 2022,[77] 'time duration of disease progression, treatment cessation or end of the 2nd line treatment', did not align with ours, which specifically focused on time to radiological disease progression or death. Liao 2022 included nine trials, of which we regarded two as irrelevant due to not testing relevant comparators. Liao 2022 also included 2nd line data from two crossover trials, which we did not include in this NMA as second-period (i.e. post-progression comparisons) are not randomised. We also included TIVO-1 and analysed subgroup estimates where available, which this NMA did not; included BERAT and TIVO-3; and used more recent datacuts for CheckMate 025. However, where findings used similar datacuts, our NMA results were aligned.

3.8. Ongoing studies

Six relevant ongoing studies which have not year reported were identified prior to receipt of company data, including two from the trial registries search. These were:

- NCT05012371, which compares lenvatinib + everolimus against cabozantinib in a 2nd or 3rd line context after progression on a PD-1/PD-L1 checkpoint inhibitor[151];
- SUNNIFORECAST, which compares nivolumab + ipilimumab in combination against standard of care in a 1st line context in advanced non-clear cell RCC[152];
- A Study to Compare Treatments for a Type of Kidney Cancer Called TFE/Translocation Renal Cell Carcinoma (tRCC), which compares axitinib + nivolumab against nivolumab and against axitinib in a population with multiple lines[153];
- Cabozantinib or Sunitinib Malate in Treating Participants With Metastatic Variant Histology Renal Cell Carcinoma, comparing each treatment in a population with multiple lines.[154]
- REFINE, which is investigating an extended schedule for nivolumab following nivolumab + ipilimumab (8 weekly rather than 4 weekly) and is expected to produce results in 2025[155]

- A Study of Subcutaneous Nivolumab Monotherapy which is expected to complete in March 2025[156]

Three of these studies focus on the effectiveness of treatments in people with non-clear cell histologies. The NCT05012371 study is due to complete in April 2023 and is expected to provide highly relevant information on the comparative effectiveness of two treatments available for a previously treated population including data on their effectiveness after progression on a PD-1/PD-L1 checkpoint inhibitor, which is current standard practice. Unfortunately, however, this is a relatively small Phase 2 study (estimated enrolment of 90 participants). The other two studies looking at the mode and frequency of administration of nivolumab and could have a significant impact on the cost and cost-effectiveness of treatments for RCC when they report in 2025.

An additional ongoing study (RAMPART[157]) which started in 2018 was noted during clinical expert consultation as a UK study collecting information on the outcomes of adjuvant treatments in patients with a high or intermediate risk of relapse. The trial was set up to collect data on durvalumab, durvalumab + tremelimumab and active surveillance. We have been informed by clinical experts taking part in the structured expert elicitation exercise that data was also collected on patients who received adjuvant pembrolizumab in later phases of the trial. The primary completion date is noted as July 2024. It is unclear whether data is being collected within this study on the impact of treatments in the systemic, rather than adjuvant, setting and if they are when these data are likely to report.

3.9. Conclusions of the clinical effectiveness evidence

3.9.1. In relation to the decision problem and the company's submission

In the assessment of the clinical effectiveness evidence, the EAG scrutinised the company's submission, which included the CheckMate 9ER trial for first-line treatment in the target population. The EAG broadly agreed with most decisions taken by the company, but disagreed on the full range of appropriate comparators, the relevance of time to next treatment, and the importance of risk group-specific analyses. While the EAG regarded the trial as having high risk of attrition bias, the EAG also noted that the availability of 44-month follow-up was a potential strength. The EAG noted a number of potential issues with respect to generalisability of the trial (including high rates of treatment after progression) but was satisfied that the trial presented

evidence of effectiveness of cabozantinib plus nivolumab as compared to sunitinib across key outcomes, including OS, PFS and ORR. However, the EAG noted some evidence of effect modification by risk group for OS and PFS in particular, with favourable risk groups experiencing less effectiveness than intermediate and poor risk groups. Based both on the trial and on network meta-analyses (discussed below), the EAG agreed that overall, cabozantinib plus nivolumab is an effective treatment for first line RCC relative to existing treatment options and may be a consideration for patients in any risk group where a combination treatment is considered appropriate.

3.9.2. In relation to the EAG's syntheses

The EAG undertook its own SLR and identified 24 trials, of which 17 were prioritised for analysis. Collectively, the EAG's syntheses suggested that combination therapies (IO/TKI and IO/IO) were most effective at first-line, although they were also associated with high rates of adverse events, including a high rate of adverse events leading to discontinuation in the first-line setting. In the fractional polynomial NMAs, cabozantinib plus nivolumab, cabozantinib monotherapy, nivolumab plus ipilimumab, and avelumab plus axitinib all performed better than sunitinib in both the overall risk and intermediate/poor risk populations at first line. At second plus line in the overall risk population, lenvatinib plus everolimus, nivolumab monotherapy and cabozantinib monotherapy performed best. While proportional hazard analyses suggested that IO/TKI combinations outperformed IO/IO combination (nivolumab plus ipilimumab), this was not borne out in the fractional polynomial analyses.

However, despite the number of treatments available for RCC across lines and risk groups, the EAG considered that the evidence base in RCC was highly limited. With the exception of older treatments, shown in analyses to be less effective (e.g. sunitinib and sorafenib in the first line and everolimus monotherapy in the second plus line), most newer treatments were supported by only one trial. There was variation in some outcomes across trials that was not readily explained by known effect modifiers, and the EAG therefore concluded that there are some concerns about the comparability of effects across the evidence base. This is further magnified by evidence from observational sources suggesting that outcomes have improved over time, above and beyond the impact of any specific treatment. The paucity of evidence prevented statistical exploration of inconsistency in NMA and restricts confidence in any patterns in effect across potential effect modifiers. Moreover, many of the included trials conducted subgroup analyses to investigate patterns in treatment effect across risk subgroup and in the NHS,

clinicians frequently alter management according to risk category. However, analyses by risk group were limited due to the small sample sizes and a reduction in the availability of trial data (particularly in the favourable risk population). Overall, the EAG considered that there was a high degree of uncertainty in the clinical effectiveness results.

A further consideration for the clinical effectiveness results was that there was evidence of non-proportional hazards across outcomes, meaning that the results of proportional hazard NMAs are likely to be unreliable for some comparisons; at the same time, fractional polynomial NMAs were highly uncertain due to similar deficiencies in the evidence base. The narrative synthesis was also conducted based on hazard ratios that assumed proportional hazards, or on effects reported at a single follow-up timepoint, and therefore these findings may also be unreliable. Fractional polynomial NMAs were feasible for OS and PFS and suggested a different pattern of results than the other analyses. For example, while pembrolizumab and lenvatinib emerged as one of the strongest treatments across outcomes and risk groups (albeit with imprecision around the treatment effect) based on the proportional hazards analyses and the narrative synthesis, plots of hazards over time showed that this effect was being driven by a large effect in the short-term that then reduced (and even reversed) with longer follow-up; conversely, fractional polynomial NMAs produced results for pembrolizumab and lenvatinib biased in the other direction. Fractional polynomial NMAs were not conducted in the first-line favourable risk population due to data limitations.

Additional outcomes were narratively synthesised, including duration of response, time on treatment and health-related quality of life. These outcomes were not reported for all treatments and were generally restricted to analyses in an overall risk population. In the first line in an overall risk population, nivolumab plus ipilimumab, cabozantinib plus nivolumab, pembrolizumab plus lenvatinib and avelumab plus axitinib all showed a longer duration of response relative to sunitinib. The findings reported for time on treatment were not considered to be informative due to sparsity of data. No treatments were found to offer meaningful benefits for HRQoL over their comparators. In general, HRQoL was found to decrease following treatment irrespective of treatment received, and relative differences between treatments in overall response were not borne out in meaningful differences in HRQoL.

Going beyond challenges with the evidence base itself, the presented syntheses leave open a number of questions, with the most pressing relating to histology and prior treatments. First, most trials were restricted to people with clear cell RCC, which is known to have improved

treatment outcomes compared to non-clear cell histologies. The licence for cabozantinib plus nivolumab, similar to other combination treatments, does not restrict use in people with non-clear cell RCC, though the CheckMate 9ER trial was also restricted to those with clear cell disease. Based on the studies identified as part of this appraisal, there is little understanding of how treatment effects may vary in people with alternative histology RCC although the EAG does not an increase in trials being conducted in this area. Second, we were unable to explore the importance of adjuvant pembrolizumab on outcomes within this appraisal, given the availability of evidence. Clinical advice to the EAG is that receipt of adjuvant pembrolizumab may be beneficial for the population in general, but that it may reduce the benefit exhibited in subsequent treatments involving IOs. This may be particularly true in the favourable risk population, since more low risk patients can be identified in the routine scanning after adjuvant pembrolizumab.

Clinical advice to the EAG and consideration of relevant evidence highlights that optimal treatment sequencing following novel treatments at first line (i.e. IO/IO or IO/TKI combinations) remains an area of uncertainty. An exploration of the role of prior treatments in subsequent treatment outcomes will be conducted as part of Phase 2 of this appraisal, however, the evidence base appears relatively sparse.

3.9.3. In relation to real-world evidence

The EAG identified a number of real-world evidence sources and completed full assessments of quality for four sources. The EAG ultimately determined that the UK RWE dataset provided the most robust and relevant natural history data for use in an economic model. Median PFS data from the UK RWE was consistent with those reported in clinical trials, though median OS from UK patients was generally shorter than was reported in the trials. On the basis of the baseline characteristics reported or the UK RWE, the EAG was unable to identify meaningful differences in data sets that may influence OS, and this was not a primary aim within the remit of this appraisal. In general, evidence based on RCTs is considered to lack external validity due to the artificial procedures used in the trials relative to clinical practice, and a tendency for trials to exclude people with higher risk or more complex disease. The EAG considered it plausible that treatment effects, both in terms of absolute survival and relative effects, reported in the clinical trials would therefore vary from those that would be seen in clinical practice. Where appropriate and feasible, learnings from RWE will be integrated into Phase 2 of this pilot.

4. COST-EFFECTIVENESS MODEL DEVELOPMENT

4.1. Published cost-effectiveness studies

4.1.1. Search strategies

Systematic searches of the health economic literature were undertaken to identify 1) economic evaluations of relevant interventions and comparators, 2) studies reporting quality of life data in the form of utilities, and 3) UK cost and resource use studies. Search strategies are provided in Appendix A.

Search strategies were developed by an information specialist and the final strategies were peer reviewed by another information specialist within our team. The search strategies used relevant search terms, comprising a combination of indexed keywords (e.g., Medical Subject Headings, MeSH) and free-text terms appearing in the titles and/or abstracts of database records and were adapted according to the configuration of each database. No publication status (published, unpublished, in-press, and in-progress) limits were applied.

Alongside the Medline and Embase searches detailed below, the following databases were searched to identify general economic studies: INAHTA, CEA registry, ScHCARRHUD, NHS EED, EQ-5D documents, and the NICE website. All were searched from 2009 (aligning with the publication of the first NICE appraisal in RCC) to 2023. We also searched RePEc via EconPapers. Given the lack of an export functionality in EconPapers, we reviewed the first 30 hits online. Finding no unique, in-scope citations among these 30, we added no documents from RePEc.

Abstracts and titles of references retrieved by the electronic searches were screened by two reviewers for relevance against the criteria specified in Table 54. Full paper copies of potentially relevant studies were then obtained and assessed for inclusion by two reviewers using the pre-specified inclusion/exclusion criteria. At both stages, discrepancies were resolved by discussion, with involvement of a third reviewer, where necessary. All duplicate papers were double checked and excluded.

Included studies were extracted by one reviewer into a bespoke database for each search. The quality of cost-effectiveness studies evaluating cabozantinib + nivolumab was assessed using the Philips 2004 checklist for decision analytical models.[158]

Table 54: Inclusion and exclusion criteria for economic studies

PICOS item	Include	Exclude
Population	Studies of participants with advanced (stage 3 unresectable and stage 4) RCC	Studies of participants with early stage (not advanced) RCC
Intervention (economic evaluation searches only)	Cabo+nivo, pazo, tivo, suni, cabo, nivo+ipi, pem+lenv, axi, lenv+evero, evero, nivo, ave+axi*	Any other treatments not listed under inclusion Treatments used in the adjuvant setting
Comparator (economic evaluation searches only)	Any of the other interventions listed above (i.e. head-to-head studies) Usual care / physicians' choice / best supportive care	Any other treatments
Outcomes	Economic evaluations Incremental Cost Effectiveness Ratio expressed as cost per life year gained or cost per QALY Cost savings (cost-minimisation studies only) Utility studies Quality of life data expressed in the form of utilities regardless of the method of elicitation and valuation Cost and resource use studies Resource use data from UK studies Cost data from UK studies	Studies not reporting an included outcome
Study design	Economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost-minimisation) Systematic reviews of economic evaluations or utilities Conference abstracts will be included unless data are superseded by another conference abstract or full journal article	Abstracts with insufficient methodological details Editorials and commentaries
Data limits	Economic evaluations: 2009 Utility studies: 2009 Cost and resource use studies: 2017	

Abbreviations: QALY, quality-adjusted life year; RCC, renal cell carcinoma

Notes: * as belzutifan was included within the NICE draft scope it was included within the search terms for the searches conducted, these studies will, however, not be included during screening

4.1.1.1. Searches for economic evaluations

Searches for economic evaluations were carried out in Medline and Embase, using the SIGN economics filter.[82] The same terms were used for the economic evaluation searches as for the clinical RCT searches in respect of the population and interventions. Searches were limited to 2009 onwards, aligning with the publication of the first NICE appraisal in RCC. No limits by language were used.

Conference abstracts were included for the following conferences: American Association for Cancer Research, American Society of Clinical Oncology, American Urological Association,

European Society for Medical Oncology, European Association of Urology, Genitourinary Cancers Symposium, International Conference on Translational Cancer Medicine and The International Society for Pharmacoeconomics and Outcomes Research.

4.1.1.2. Searches for health utilities

The utilities searches in Medline and Embase used the same population terms, but no intervention terms were used. Rather, population terms were combined with the CADTH utilities filter.[75] As with the economic evaluations search, searches were limited from 2009 onwards, and the same conferences were included as above. No language limits were imposed.

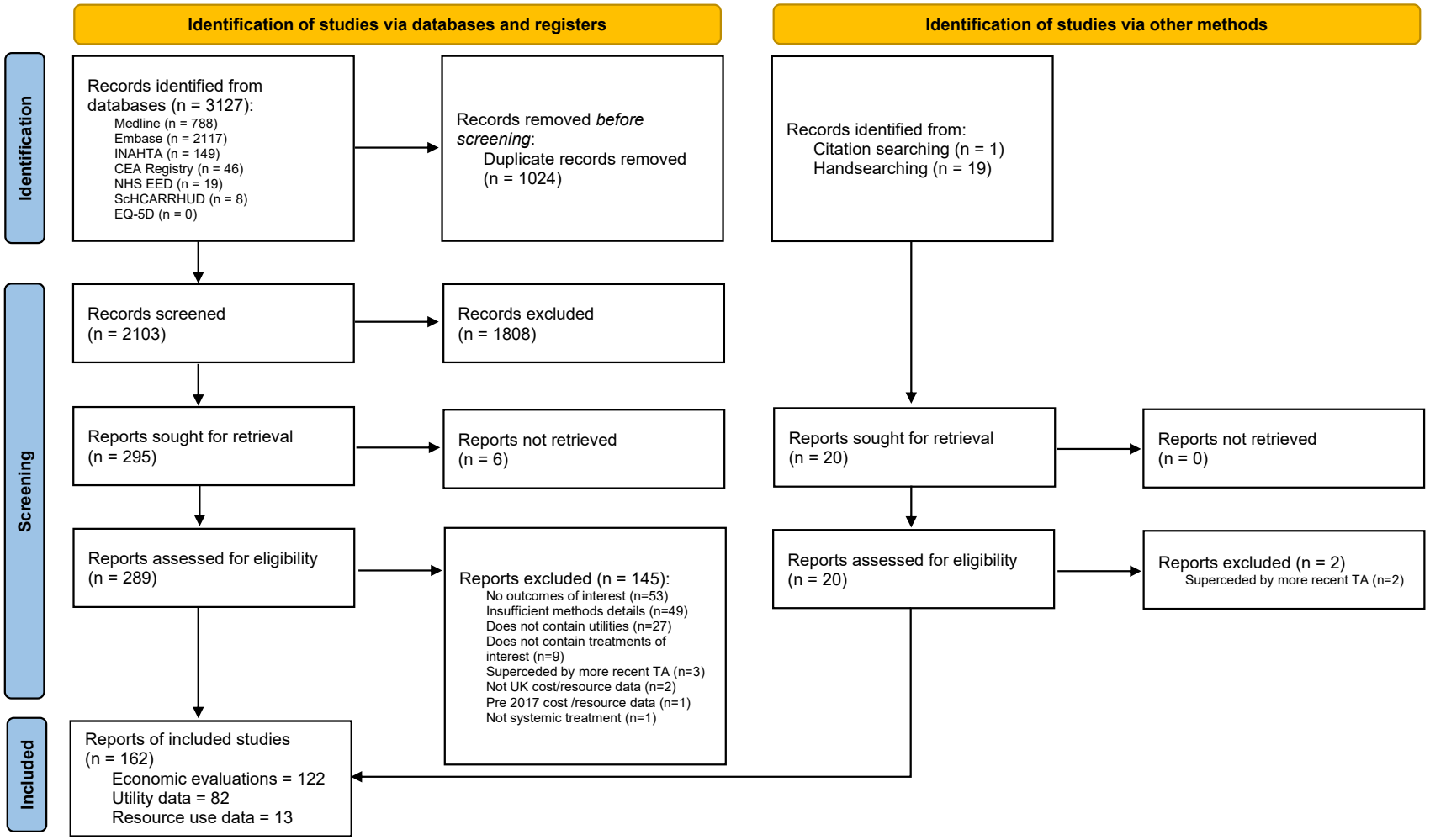
4.1.1.3. Searches for UK cost and resource use studies

UK cost and resource use searches in Medline and Embase combined population terms with the Cochrane cost of illness filter[159] and the NICE UK filter.[83] Studies were included from 2017 onwards, to ensure that only relevant data are found (aligning with the entry of immuno-oncology options into clinical practice post TA417[58]). Again, no language limits were imposed.

4.1.2. Results of the searches

In total, 162 papers were identified across the three searches (Figure 33). Some publications contained information relating to more than one review. 122 papers containing relevant economic evaluations were identified, 82 papers were identified containing utility data (discussed in Section 4.3.7) and 13 containing cost and resource use data (discussed in Section 4.3.8)

Figure 33: Economic literature review PRISMA



Abbreviations: INAHTA = International Network of Agencies for Health Technology Assessment; NHS EED = The NHS Economic Evaluation Database; ScHCARRHUD = School of Health and Related Research Health Utilities Database. Note: a number of studies qualified for more than one of the economic reviews and therefore the total across each of the 3 reviews (122 + 82 + 13) sums to more than the number of reports included (n=162)

Of the 122 economic evaluations identified, the EAG prioritised inclusion within this report to the following types of studies:

- Previous NICE technology appraisals from 2017 onward – 10 included
- Systematic reviews of cost-effectiveness studies from 2017 onward – two included
- Studies evaluating cabozantinib + nivolumab – seven included
- Sequencing models – six included
- Western (Europe, US, Canada, Australia and New Zealand) studies by recency of data – 44 included

The data extraction grid can be found in Appendix D. Data was extracted into the pre-specified data extraction sheet by one reviewer and 10% of records were checked by a second reviewer.

4.1.2.1. Learnings from previous technology appraisals

Table 55 provides a summary of economic evaluations used in previous NICE technology appraisals in RCC.

The vast majority of previous NICE technology appraisals used a simple three-state partitioned survival (PartSA) model based upon progression status. This aligns with company preferences for oncology modelling as discussed in TSD 19.[160] The use of this structure may not, however, have been ideal as within a number of these appraisals (TA780,[48] TA650,[47] TA645,[46] TA512,[51] TA417[58]) the Committee raised concerns around the way that subsequent therapy was accounted for, expressing a clear preference that costs and effectiveness of subsequent lines should match and that Committee preference was to use UK data for both. This type of analysis would be very difficult to achieve in a PartSA model without access to patient-level data for all involved treatments to allow statistical adjustment of OS. Within a state transition model, although evidence gaps would still remain, there is the flexibility to test the impact of different assumptions rather than having unquantifiable, and sometimes unacknowledged, uncertainty relating to the mismatch between subsequent treatments within trials and practice and the impact of this on effectiveness.

Another issue identified within previous appraisals relates to inconsistency in the evidence base. Different trial arms have been used to represent the reference treatment across appraisals and previous appraisals generally used HRQoL from the trial for the treatment currently being appraised. There are therefore different estimates of baseline risk for progression, death and HRQoL being used for the same population and same treatment across appraisals.

The EAG also note that the evolution of appraisals within RCC and lack of use of a common model and set of comparators has already led to some potentially counterintuitive decisions. Specifically, TA780[48] (a CDF re-review) did not compare nivolumab + ipilimumab to cabozantinib (the only other option available specifically for intermediate and poor risk disease) as it was not in scope of the original appraisal in line with standard process at the time. TA858[38] then found nivolumab + ipilimumab not to be cost-effective versus cabozantinib with pembrolizumab + lenvatinib recommended on the basis of cost-effectiveness versus nivolumab + ipilimumab and not cabozantinib due to high levels of usage of nivolumab + ipilimumab in practice.

Table 55: Summary of previous technology appraisals

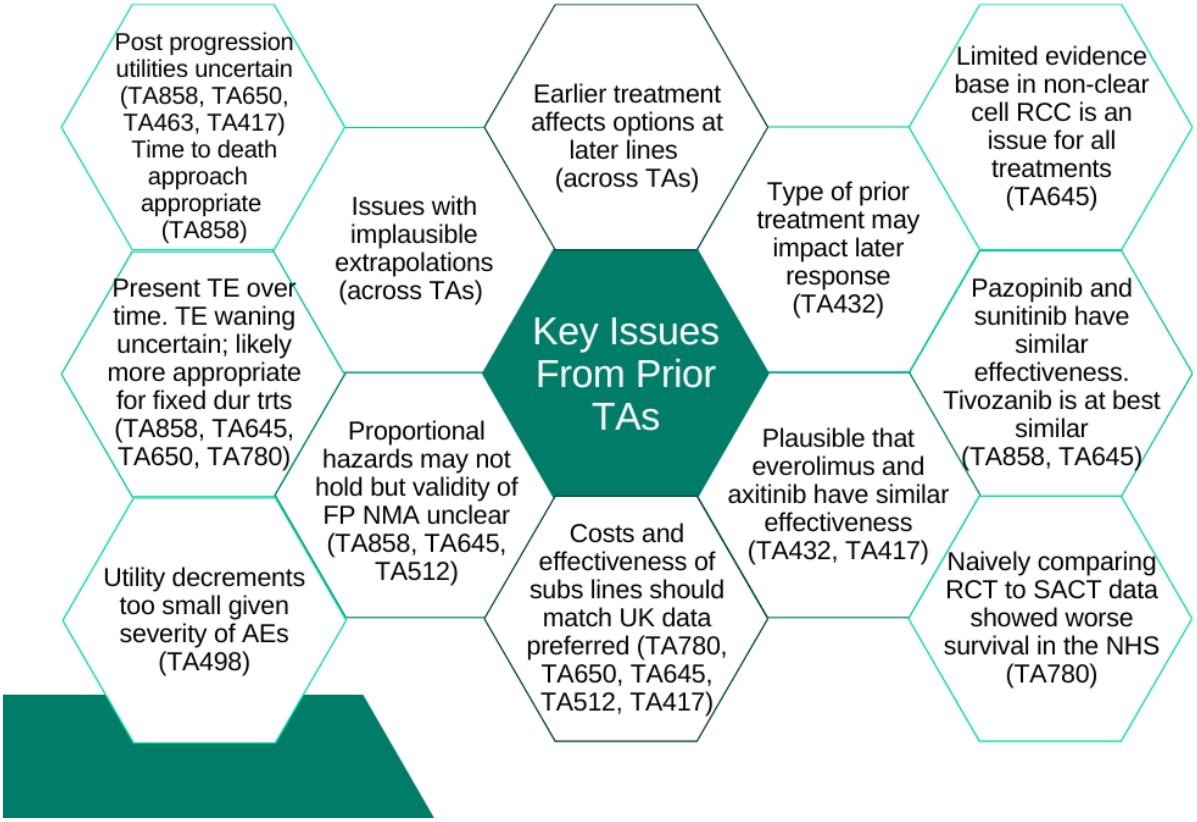
TA	Year	Recommendation population	Model type	Intervention	Comparators in final analysis	Source of HRQoL data	Committee ICER
TA858 (MTA)[38]	2023	1L int/poor risk, where nivo+ipi would otherwise be offered	3 state PartSA	Pem+lenv	Int/poor risk: cabo, nivo+ipi Favourable risk: suni, pazo, tivo	CLEAR	EAG vs nivo+ipi = £133,362 vs cabo = £166,249 (list price analyses) Not c/e vs cabo
TA830[39]	2022	Adjuvant: increased risk of recurrence after nephrectomy	State transition: DF, LR, DM and death	Pem	Routine surveillance	KEYNOTE-426 for advanced RCC	NA
TA780[48] (CDF review of TA581)	2022	1L int/poor risk	6 state PartSA (prog and tx states, terminal care, death)	Nivo+ipi	Suni, pazo	CheckMate 214	vs suni = £25,897 - £36,041 vs pazo = £24,653 - £34,132
TA650[47]	2020	1L (not recommended)	3 state PartSA	Pem+axi	Pazo, suni, tivo, cabo (int/poor risk)	KEYNOTE426	vs suni = £59,292 - £76,972 vs cabo = £29,835 - £38,346
TA645[46]	2020	1L	3 state PartSA	Ave+axi	Pazo, suni, tivo, cabo (int/poor risk)	JAVELIN Renal 101	Company: vs suni = £26,242 vs pazo = £29,542 vs tivo = £9,220 vs cabo = Dominant
TA542[52]	2018	1L int/poor risk	3 state PartSA	Cabo	Suni, pazo	TA512	vs suni = £37,793 vs pazo= £48,451 vs suni = £31,538
TA512[51]	2018	1L	3 state PartSA	Tivo	Suni, pazo	TIVO-1 trial	Pazo dominates tivo & suni
TA498[56]	2018	1 prior VEGF, ECOG 0-1	3 state PartSA	Lenv+evero	Axi, cabo, evero, nivo	AXIS	Company: vs axi = £32,906 vs cabo = £16,083

TA	Year	Recommendation population	Model type	Intervention	Comparators in final analysis	Source of HRQoL data	Committee ICER
							vs nivo = £17,146 vs evero = £96,403
TA463[55]	2017	Prior VEGF	3 state PartSA	Cabo	Axi, nivo	METEOR and AXIS	Redacted
TA432[57]	2017	Prior VEGF	State transition 4 states: stable disease (no AEs), stable disease (AEs), prog and death	Evero	BSC, axi - exploratory analysis	Swinburn et al., (2010)	vs BSC = £51,700 - £52,261 vs axi = Dominant (list price)

Abbreviations: AE, adverse event; BSC, best supportive care; CDF, Cancer Drugs Fund; DF, disease free; DM, distant metastases; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost effectiveness ratio; int/poor, intermediate / poor risk using IMDC criteria; LR, loco-regional recurrence; MTA, multiple technology appraisal; prog, progression; PartSA, partitioned survival analysis; tx, treatment; VEGF; vascular endothelial growth factor; vs, versus; 1L, 1st line

Notes: he ICERs provided in this table are those described within the Final Appraisal Document where possible. Where this was not possible the EAG or company ICER is provided based upon what was available and which the Final Appraisal Document appeared to most closely align to

Figure 34: Summary of issues from prior NICE appraisals of technologies for RCC



Abbreviations: AE, adverse event; FP NMA, fractional polynomial network meta-analysis; RCC, renal cell carcinoma; RCT, randomised controlled trial; SACT, systematic anti-cancer therapy dataset; TA, technology appraisal; TE, treatment effect

Figure 34 provides a summary of the key issues raised in prior NICE technology appraisals of technologies for RCC. Many of these are interlinked and stem from difficulties with the evidence base available in terms of maturity of information for extrapolation, quality of data for more historic treatments, lack of data in risk status subgroups, lack of data for non-clear cell histologies and methodological disagreements over the most appropriate way to handle violation of proportional hazards within trials.

The importance of subsequent therapy is highlighted in that earlier treatment affects options at later lines, as discussed in Section 2.4.2 and that there is some evidence that type of prior treatment may impact outcomes at later lines. It is clear from a number of prior TAs that Committee preference is for cost and effectiveness to match when considering subsequent treatments and for UK patterns of subsequent therapy to be used above trial data.

It is also clear that there are limitations to the available HRQoL data in RCC, in particular difficulties capturing the full impact of issues with tolerability for certain treatments and uncertainty around post progression utilities (a wide range of estimates are available which is likely influenced by changing practice around subsequent treatment and by collection of post progression utilities being limited to 30 days in a number of the trials).

Lastly, appraisals that have included UK RWE have shown worse outcomes in NHS practice than in trials, based on naïve comparison. There was some suggestion that this may be due to a higher proportion of patients having intermediate / poor risk status in practice than may be included in some trials.

4.1.2.2. Learnings from systematic reviews

Two systematic reviews of the cost-effectiveness of treatments for RCC were identified.[161,162] Both considered only the cost-effectiveness of immune checkpoint inhibitors.

Verma (2018)[161] identified three studies considering the cost-effectiveness of nivolumab versus everolimus for previously treated RCC[163-165]: two PartSA models with considerable differences in results (ICERs of $51,714 per QALY [pharma sponsored] and $146,532 per QALY) and driven by differences in extrapolation techniques, and a state transition model that reported a similar ICER versus everolimus to the more conservative of the PartSA approaches, but concluded that nivolumab was not cost-effective versus placebo. Uncertainties were raised in the review around optimal dosing and duration of immune checkpoint inhibitors and the impact of late presenting toxicities.

Philip (2021)[162] identified 23 studies published between 2008 and 2020, across 9 different countries (1st line treatment (n = 13), 2nd line treatment (n = 8), and 1st line and beyond (n = 2)). The majority, fourteen studies, included the use of novel immune checkpoint inhibitors nivolumab, ipilimumab, pembrolizumab), half of which found that checkpoint inhibitors were more cost-effective when compared to oral systemic therapies (sunitinib, everolimus, axitinib, pazopanib, and cabozantinib). The review did not identify any studies of cabozantinib + nivolumab and did not look in detail at the drivers of results.

4.1.2.3. Learnings from economic evaluations of cabozantinib + nivolumab

Seven publications reported an economic evaluation of cabozantinib + nivolumab (Table 56).[166-173] All of the publications used data from CheckMate 9ER (with the majority using the March

2020 database lock). The four papers not sponsored by industry compared to sunitinib. The other three compared to a variety of treatments including TKIs and combination therapies.

All five publications not sponsored by Ipsen, including the abstract sponsored by Bristol Myers Squibb (BMS), concluded that treatment was not cost-effective based upon the stated prices. BMS concluded that their wholly owned combination (nivolumab + ipilimumab) dominated when compared to cabozantinib. Conversely, Ipsen concluded in their two analyses that when comparing cabozantinib + nivolumab to nivolumab + ipilimumab, that QALY gains were either the same or the opposite direction (i.e. favouring cabozantinib + nivolumab). The rationale for these differences is unclear.

None of the publications were conducted from a UK perspective and none were high quality, with survival extrapolation methods either unclear or driven only by visual and statistical fit. Quality assessment was conducted using the Phillips checklist and is included in Appendix D.

One study explored the difference a state transition vs a PartSA model structure made upon outcomes and concluded that there was little difference. Drug costs, quality of life and effectiveness inputs were key drivers in the majority of models with relative dosing intensity (RDI) also being a key driver in one. The utility sources used by the authors of the papers that were not industry funded were acknowledged as not ideal as EQ-5D data from CheckMate 9ER was not available to them.

Table 56: Summary of published economic evaluations of cabo + nivo (1)

	Li 2021	Liao 2021	Liu 2022	Marciniak 2022
Analysis country	US	US	US	France
Funder	US government	Chinese government	Chinese government	Ipsen
Price year	2021	2021	2021	Unclear
Time horizon	Lifetime	Lifetime	10 years	50 years
Comparators	Suni	Suni	Suni	TKIs+ and combinations¥
Model structure	DES based on PFS, discontinuation & mortality due to AEs, lifetables and OS during BSC Curve selection not justified	3 state PartSA Extrapolation methods unclear	3 state models: state transition & PartSA Curve selection statistical and visual fit only	3 state PartSA Curve selection statistical fit only
Source of efficacy data	CheckMate 9ER (March 2020 DBL), AXIS, TIVO-3, dovitinib vs sora RCT[59,85,99,104]	CheckMate 9ER (March 2020 DBL)[59]	CheckMate 9ER (March 2020 DBL)[59]	CheckMate 9ER[59] (Sept 2020 DBL) NMA for comparators
Price of cabo 60mg / nivo 240mg	$491.30 / $6,849.84 (average CMS sale price)	$866.51 / $8,015.04 (Red Book)	$515 / $7,432 (average CMS sale price)	Not reported
Utilities	By line 0.82, 0.77, 0.66, and 0.494 -0.157 for Grade 3+ AEs	PFS cabo+nivo 0.848, PFS suni 0.73, progressed 0.66	PFS cabo+nivo 0.75, PFS suni 0.73, progressed 0.66	Not reported
Utility sources	Cella 2018 (METEOR)[174] De Groot 2018 (PERCEPTION)[175] Wan 2019 (CheckMate 214)[176] Patel 2021 (myeloma) [177] Wu 2018 (VEG105192 trial)[105]	Wan 2017[165] Wan 2019[176] Wu 2018[178] Data not from CheckMate 9ER. Selection methods unclear	Cabo+nivo estimated from FKSI Wan 2019[176]	CheckMate 9ER

	Li 2021	Liao 2021	Liu 2022	Marciniak 2022
	Selection methods unclear			
Subs therapy	Axi→sora→BSC	Unclear, average cost	CheckMate 9ER	Taken from individual publications for 1L therapies, includes treatments not available in the UK
Perspective	Payer	Payer	Payer	Not reported but appears to be payer
Base case ICER	$508,987/QALY	$863,720/QALY	$555,663/QALY vs $531,748/QALY*	Uses placeholder costs for some inputs 7.4 life years, 5.4 QALYs for both nivo+ipi and cabo+nivo Life-year range, 5.1–6.2; QALY range, 3.8–4.6 for TKIs Life-year range, 6.3–7.1; QALY range, 4.7–5.2 for other combinations
Key drivers	Patients age at treatment, 1L utility, cost of nivo	PF utility, cost of cabo, effectiveness parameters	PF utility, drug costs	Not reported

Notes: * state transition vs PartSA; +TKIs included: cabo, pazo, tem, tivo, sorafenib, suni; ¥ combinations: nivo+ipi, axi+ave, axi+pem, lenv+pem

Abbreviations: AE, adverse event; BRL, Brazilian Real; BSC, best supportive care; CMS, Centers for Medicare and Medicaid Services; DBL, database lock; DES, discrete event simulation; FKSI, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index; ICER, incremental cost effectiveness ratio; OS, overall survival; PF, progression free; PFS, progression-free survival; PartSA, partitioned survival analysis; QALY, quality-adjusted life-year; RDI, relative dosing intensity; US, United States

Table 57: Summary of published economic evaluations of cabo + nivo (2)

	Tempelaar 2022	Wang 2022	Yoshida 2022
Analysis country	France	China	Brazil
Funder	BMS	Chinese government	Ipsen
Price year	2020	2022	Unclear
Time horizon	15 years	20 years	Unclear
Comparators	Nivo+ipi, pem+axi, pazo, suni	Suni	Nivo+ipi, pazo, suni
Model structure	3 state PartSA Extrapolation methods unclear	3 state PartSA Curve selection statistical and visual fit only	3 state PartSA Extrapolation methods unclear
Source of efficacy data	CheckMate 9ER Multi-dimensional treatment effect NMA vs suni	CheckMate 9ER (March 2020 DBL)	CheckMate 9ER[59] (datacut unclear) NMA for comparators
Price of cabo 60mg / nivo 240mg	Not reported	$491.20 / $3,482.57	Not reported
Utilities	Not reported	PFS cabo+nivo 0.848, PFS suni 0.73, progressed 0.66 -0.157 for Grade 3+ AEs	Not reported
Utility sources	CheckMate 9ER French value set	Li 2021, Liao 2021	CheckMate 9ER
Subs therapy	Not reported	CheckMate 9ER	Clinical studies, source and data not reported
Perspective	All payer	Health system	Not reported
Base case ICER	Cost-efficiency frontier was only comprised of two treatments: pazo and nivo+ipi. Nivo+ipi strictly dominated cabo+nivo (incremental Euros / incremental QALYs: 63,792/-0.221)	$292,945/QALY	vs suni BRL 365,591/QALY vs pazo BRL402,944/QALY vs nivo+ipi BRL347,698/QALY (int/high risk)
Key drivers	Multi-dimensional treatment effect NMAs	Drug costs, utilities at progression, subsequent treatment	RDI, discount rate, drug costs

Notes: * state transition vs PartSA; ⁺TKIs included: cabo, pazo, tem, tivo, sorafenib, suni; ¥ combinations: nivo+ipi, axi+ave, axi+pem, pem+lenv

Abbreviations: AE, adverse event; BRL, Brazilian Real; BSC, best supportive care; CMS, Centers for Medicare and Medicaid Services; DBL, database lock; DES, discrete event simulation; FKSI, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index; ICER, incremental cost effectiveness ratio; OS, overall survival; PF, progression free; PFS, progression-free survival; PartSA, partitioned survival analysis; QALY, quality-adjusted life-year; RDI, relative dosing intensity; US, United States

4.1.2.4. Learnings from previous sequencing models

Six publications were identified that provided information on three models considering sequencing within RCC. One model looked specifically at patients assessed as IMDC intermediate / poor risk. Five of the models were discrete event simulation analyses (two papers discussed what appeared to be the same model using the DICE framework[179,180]). One model used a state transition structure.[181] Model structures varied with the more complex manufacturer led models including response, TTD, reason for discontinuation (AE or progression), TTP or next treatment, adverse events and death and the academic-led model considering only treatment line, adverse events and death.

One of the studies used data collected retrospectively from a patient registry,[182] in the Netherlands the others used trial data supplemented by network meta-analysis or trial data alone. None of the studies considered the full network included in this analysis, none report a UK perspective. Only one study considered sequencing after cabozantinib + nivolumab.[181] Key considerations within the publications include:

- **Access to patient-level data**: the majority of the models were produced with industry sponsorship and included analysis of patient-level data from manufacturer sponsored trials. This was necessary to produce the required risk equations accounting for the impact of population characteristics and prior treatments on prognosis. Where data were not available, information from treatments with a similar mechanism of action was generally substituted or additional analyses were required to calibrate the model to account for missing parameters
- **Issues with reporting of time to treatment discontinuation and time to receipt of subsequent treatments** meaning that assumptions were required (e.g. assumption of similar relative effectiveness to PFS or assumption that TTD and TTP are equal)
- **Difficulties in matching observed treatment effects for subsequent treatments** in the CheckMate 214 trial with data observed in clinical trials for subsequent therapies
- Analysis based on CheckMate 025 **assumed that the efficacy of 2nd line treatment was not affected by the 1st line agent** received (due to the 1st line options modelled being only TKI monotherapy). The model which included cabozantinib + nivolumab[181] also appeared to make this assumption although the exact source of effectiveness data was not clear
- The **2nd line treatment** preferred and most frequently observed in the trials following 1st line IO/TKI combinations other than cabozantinib + nivolumab was **cabozantinib**. After cabozantinib + nivolumab this was **lenvatinib + everolimus**
- The need to **include non-RCC mortality separately,** as trial-based mortality hazards were often decreasing at the end of trials
- The **potential for a treatment free interval** for patients receiving immuno-oncology treatments in the 1st line setting (demonstrated in a proportion of participants in CheckMate 214)

- Difficulties using standardly assessed progression to determine treatment failure on immuno-oncology due to the potential for **'pseudo-progression'**; a well-recognised phenomena that has been discussed in multiple NICE TAs, and fitting curves to PFS due to initial **drops in the KM curve linked to scanning protocols**
- Limitation in the number of lines of treatments explicitly modelled (maximum of 2 active treatments)
- **Differences between real-world treatment practice and best practice** as detailed within guidelines. In de Groot 2017[182] only 54% of the patients received a targeted therapy; one in four fulfilling eligibility criteria did not receive targeted therapy

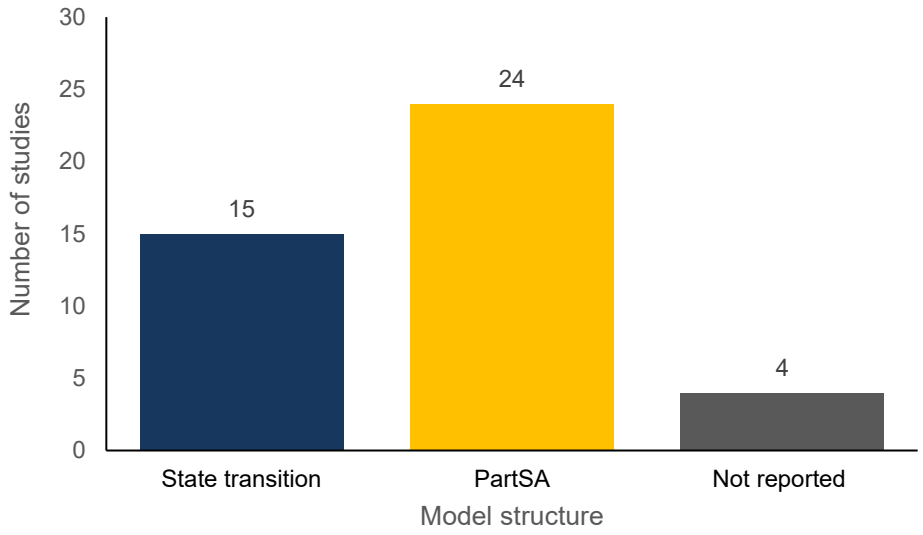
Key prognostic factors identified within a number of analyses included:

- Risk score (MSKCC)
- Age – relatively small impact
- Region (US vs Canada/West Europe/North Europe vs rest of world) – inconsistent direction of effect
- Race – inconsistent direction of effect
- Performance status (KPS, WHO, ECOG) – higher is poorer prognosis
- Histology – non-clear cell poorer prognosis
- Prior nephrectomy – improved prognosis
- Site of metastases – liver and lung metastasis poorer prognosis
- Number of lesions – more is poorer prognosis
- Laboratory values (abnormal values poorer prognosis); LDH, Alkaline phosphatase, haemoglobin, neutrophil count, albumin
- PD-L1 status (poorer prognosis for TKIs, not predictive for immuno-oncology in CheckMate 214)

4.1.2.5. Learnings from other published economic evaluations

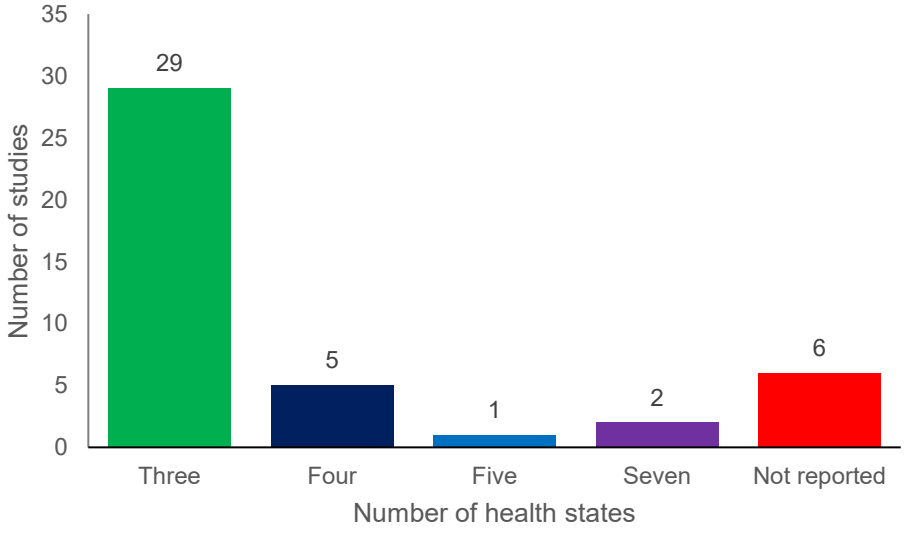
Data were extracted from 43 additional studies. 26/43 (60.5%) of the studies looked at 1st line therapies, 17/43 (39.5%) investigated 2nd line therapies. All of the studies were based in North America, Europe, Australia, or the UK. All studies either evaluated patients with poor/intermediate risk status (IMDC) or did not report the risk status. All the model structures used in these studies have been used by a previous NICE TA, literature review, or a sequencing model. The model structures used have been summarised in Figure 35 and Figure 36. All clinical effectiveness and utility inputs were derived from trials, or from previous NICE TAs.

Figure 35: Model structure used in published economic evaluations.



Abbreviations: PartSA, partitioned survival analysis

Figure 36: Number of health states used in published economic evaluations.



Models that incorporated only three states included pre-progression, post-progression and death. For those with four states, the additional health state was either progression to 2nd line treatment or progression to BSC, or they were not reported in the study. The study including five states included pre and post progression on and off treatments, and death, and the two studies with seven health states included pre-progression (no treatment), pre-progression (treatment), pre-progression (dose reduction), unobserved progression, progression detected by CT scan,

death from RCC. Both of those studies by (Raphael, 2017,2018[183,184]) seem to discuss the same state transition model evaluating the cost effectiveness of from the perspective of the Canadian healthcare system.

Sixteen 1st line studies looked at combination therapies, 14 of those studies contained nivolumab + ipilimumab which resulted in the highest QALYs gain against other comparators in all of them. The study by Zhu et al, 2023[185] evaluated two combinations: lenvatinib + pembrolizumab and lenvatinib + everolimus; both combinations resulted in similar QALY gain. Yfantopoulos et al, 2022[186] evaluated pembrolizumab + axitinib, which is outside of the scope of this appraisal, which resulted in better outcomes compared to sunitinib.

In the comparative analysis of monotherapies, cabozantinib consistently demonstrated a greater gain in quality-adjusted life years than sunitinib across all studies. Pazopanib yielded a slightly higher number of QALYs than sunitinib, albeit by a negligible margin of less than 0.1 in all studies except one which used real-world evidence (Nazha 2018[187]), where sunitinib exhibited better performance. For the 2nd line, cabozantinib came in top place in the evaluations found, followed by nivolumab, which led to a higher QALY gain than everolimus, which then had a higher QALY gain than axitinib.

There were no additional learnings relevant to the specification of the model for the pathways pilot identified in the papers reviewed.

4.2. Structured expert elicitation

4.2.1. Rationale for structured expert elicitation

The maximum follow-up available within the available clinical trials identified is just over seven years (CheckMate 025[188]). A median of 44 months of data are available for CheckMate 9ER, with the median OS only just reached for cabozantinib + nivolumab within published evidence identified so far.[120] Whilst this is relatively long when compared to the length of follow-up usually available within a NICE technology appraisal, this is nevertheless still short when compared to model time horizons of 40 years in the more recent published examples for 1st line treatments. Given this and the fact that recent changes to the treatment pathway are expected to impact on outcomes we plan to conduct a structured expert elicitation exercise to inform expected long-term survival (see Section 4.2.4).

The objective of the elicitation exercise was not to seek a 'single best answer' or point estimate from each expert, but to elicit a probability distribution representing their judgement about the relative likelihood of different values. That is, the distribution represents an expert's uncertainty based upon their existing knowledge. We sought to understand the uncertainty around the average (mean) value and not to understand individual patient heterogeneity.

Materials from the STEER repository[189,190] which was developed in line with the Medical Research Council (MRC) protocol,[189] were used to plan and conduct this exercise. The full protocol can be found in Appendix J.

4.2.2. Expert recruitment

We initially sought to recruit a minimum of five and a maximum of ten oncologists, or urologists who treat RCC, who we would expect to be the experts most likely to be able to provide input on expected survival for given treatment sequences. Following initial conversations with two urologists this criteria was narrowed to oncologists who were considered to be the speciality most able to provide information on systemic treatments.

We sought to include experts from centres from a mix of geographies across England and from a mix of types of centres: e.g. academic vs clinical, urban vs rural populations. Experts were identified by hand searching RCC publications and NHS websites. Recruitment was focussed on substantive skills as recommended within the MRC protocol rather than normative skills. We aimed to minimise conflicts of interest where possible. In particular we did not recruit experts involved in the CheckMate 9ER trial. Experts were required to declare any potential conflicts as consistent with NICE policy.

The inclusion criteria for experts were:

- Willing and able to participate within the required timeframe
- Absence of specific personal and financial conflicts of interest
- Published within the field of advanced RCC or referred by another included expert
- At least five years of experience treating people with advanced RCC

Nine experts were recruited from a total of 38 experts contacted. Expert recruitment was complicated by the junior doctors and nurses strikes which took place during the key recruitment period and the general level of business within the NHS. This led to a much higher number of

contacts being required to find experts able to participate and the timeframe for the expert elicitation exercise needing to be pushed back. In addition, during the training exercises which took place in May the clinicians requested a further delay to allow evidence from ASCO which was held 2-6 June 2023 to be provided in the background information and considered in their responses.

All nine experts completed both the training and the survey. Despite attempts to gather input from a range of geographies the majority of the experts were based in the South of England (3 in London, 2 in the South West, 2 in the East of England, 1 in the South East of England and 1 in Scotland). The mean number of years of experience treating people with advanced RCC was 15 (range 5 – 25) and the mean number of advanced RCC patients treated per year was 190 (range 20 – 600). Five of the nine experts came from a cancer research centre (Glasgow, Belfast, Cambridge, Royal Marsden, Leeds, Manchester, Oxford and Wales); all of the experts stated that their centre either had an academic focus, was a university hospital or a tertiary teaching hospital. Two of the experts stated that their population coverage included rural as well as urban geographies.

4.2.3. Quantities of interest

We sought to understand the expected PFS and OS outcomes for people receiving different subsequent therapies in UK practice, the impact of different types of 1st line treatment on PFS and OS, and the impact on OS of different sequence lengths for subsequent treatments.

There were two potential methods to elicit the required information considered, either:

- landmark survival estimates for treatment sequences; or
- landmark estimates of either PFS or TTNT per line of therapy

Based upon expert input, the latter was expected to be more intuitive and avoids issues with treatment effect being highly dependent upon subsequent therapies. Treatments to include have been selected to reflect both the CheckMate 9ER trial and UK best and current practice as described by the elicitation exercise participants.

Data were elicited for no more than 10 sequences or treatments per expert to keep the exercise manageable. Focus was given when assigning experts to each treatment to the intervention that will be first appraised using the pathways pilot model (cabozantinib + nivolumab) and they key comparators for that treatment.

Table 58: Treatments included within the expert elicitation exercise per clinician

Line	Risk Group	Treatment	Clinician number
1L	Int / poor	Cabo+nivo	1-5,6,7,8,9
1L	Int / poor	Nivo+ipi	1-5,9
1L	Int / poor	Pem+lenv	1-5,9
1L	Int / poor	Pem+axi*	2,3
1L	Int / poor	Cabo	1-5,10
1L	Int / poor	Suni	1-5,6,7,8,9
1L	Favourable	Suni	1-5,9
1L	Favourable	Cabo+nivo	1-5,9
1L	Int / poor	Pem+axi*	2,3
1L	Favourable	Ave+axi	3,6,7
2L	All risk	Cabo (after nivo+ipi)	1,6,8
2L	All risk	Cabo (after an IO / TKI combination)	1,6,8
2L	All risk	Lenv+evero (after an IO / TKI combination)	6,7,8
2L	All risk	Nivo (after 1L TKI monotherapy)	6,7,8
2L	All risk	Cabo (after 1L TKI monotherapy)	6,7,8
2L	All risk	Tivo (after nivo+ipi)	2,7,8
3L	All risk	Lenv+evero (after nivo+ipi and cabo)	4,7,8
3L	All risk	Axi (after an IO/TKI combination and cabo)	4,7,8
4L	All risk	Evero	5,7,9
Last line	All risk	BSC – from the timepoint that the patient and clinician decide that further active treatment is not desired Here we would ask about OS rather than PFS	1,4,9
Adjuvant	Int/poor	Suni	5,6,9
Adjuvant	Int/poor	Cabo+nivo	5,6,9

* This treatment is not within the scope of this pathways pilot and was included at the request of 2 of the experts involved who considered that this should be reappraised when axitinib is available in generic form which they considered would occur in the next few years. It is not in scope of the initial NICE appraisal using this information.

We had planned to provide experts with the demographics of the population to be estimated to reduce the potential for variation driven by patient characteristics. We had planned to match this to the expected UK patient population eligible for 1st line treatment, rather than to the sample in CheckMate 9ER. However, these data were not received in time. We therefore had to consider how to handle this problem:

- Ask experts to estimate for the patient population they see in practice (potential for variation but more observable for participants)
- Ask experts to estimate for the CheckMate 9ER trial population

Given the former option matches more closely to the desired decision problem population and is easier for the experts to observe and therefore comment on we asked experts to provide estimates for the population they see in practice. This was worded within the web tool as: "Please provide your estimates for the advanced RCC patient population in England (including non-clear cell where eligible for the same systemic therapies)." Information was provided on which histologies can be treated with the same treatment options as clear cell.

Experts were asked to estimate landmark PFS at three timepoints for each sequence. These timepoints were selected based upon input from Dr Larkin on the maximum amount of time patients are likely to remain progression free for most treatments and information on the available trial data for each treatment. The timepoints were presented to all of the experts during training and were considered to be reasonable:

- 3 years
- 5 years
- 10 years

For last line (BSC) we asked about OS at six months, one year and two years.

In the preliminary assessment report we specified that additional questions may be added to estimate the expected effect of adjuvant pembrolizumab per NHS guidance on OS in the advanced setting. The level of uptake of adjuvant pembrolizumab in UK practice shown in RWE will drive whether or not these questions will be required. At the time pembrolizumab was appraised uptake was expected to start at 20% of the eligible population rising to 65% in 5 years.[39] This was considered sufficient to warrant questioning.

These questions were asked as a modification of the landmark estimates for two key treatments to account for people who have received prior adjuvant pembrolizumab: nivolumab + cabozantinib (initial intervention of interest) and sunitinib (common comparator in the trials). Experts were asked to provide estimates for the intermediate/poor risk population as this represents the majority of treated patients.

As background information we provided the experts with information extracted from relevant clinical trails. We focussed the information provided on the most recent studies including the treatments considered most relevant within RCC: for 1st line patients we had initially planned to include CheckMate 9ER, CheckMate 214, CLEAR and Javelin Renal 101 and for 2nd line-plus patients CheckMate 025, METEOR and NCT01136733. Following requests from clinicians during training we added KeyNote 426, trials with non-clear cell histology (SWOG1500 and BERAT) and a short summary of the trial for adjuvant pembrolizumab (KeyNote 564). We provided the experts with:

- PFS Kaplan Meier plots for all of the treatments
- OS Kaplan Meier plots for all of the treatments

And summary tables including:

- OS and PFS HRs for all of the trials (including by risk group and 1st line)
- Baseline demographics for all of the trials
- Information on how progression was assessed within the trials

A definition of PFS was provided as follows: "the proportion of patients who have not progressed according to RECIST criteria, received a subsequent treatment or died at a particular timepoint from the start of that line of treatment. "

- Please ignore tumour flare
- We are aware that a small proportion of patients experience oligo site progression which can be treated with radiotherapy (e.g. SABR) without switching treatment. Please count these patients as progressed

This definition was included and discussed with clinical experts during the training sessions with the two clarifying bullets being added based upon recommendations provided by experts.

We included a short narrative on potential differences between assessment of progression in practice and within trials as context. Scan frequencies and definitions of progression can differ substantially between trials and clinical practice. Both Dr Challapalli and Dr Larkin also informed us that in a small number of cases patients continue being treated beyond RECIST-assessed progression on detailed review of the scan if this is considered to be of clinical benefit. This is observed in the dataset supplied by Dr Challapalli. These differences frequently lead to PFS appearing higher in real-world data than in trials whilst OS is lower in real-world data than in

trials. We therefore asked experts to assess PFS in the context of when they think the progression would occur according to RECIST rather than use a definition more aligned with practice which is impacted by less frequent scans and occasional continuation of treatment beyond RECIST-assessed progression. The wording used was: “We are aware that scan schedules and assessment criteria used for progression can differ between trials and practice. Please consider trial-like assessment (RECIST, 6-12 weekly scans) when making judgements.” 6-12 weekly was selected as broadly representative based upon the clinical evidence review (Section 3.3.2.4).

For each sequence we asked the experts:

- *1. “ What proportion of patients will be both alive and progression free at **3 years** for the advanced RCC patient population in England if they received **XXX** at **XXX** line in **XXX** risk group and had **not had previous treatment with adjuvant pembrolizumab**”*
- *2. “ **Of those patients who were alive and progression-free at 3 years**, what proportion would you expect to remain alive and progression free at **5 years** for the* advanced RCC patient population in England *if they received **XXX** at **XXX** line in **XXX** risk group and had **not had previous treatment with adjuvant pembrolizumab**”*
- *3. “ **Of those patients who were alive and progression-free at 5 years**, what proportion would you expect to remain alive and progression free at **10 years** for the* advanced RCC patient population in England *if they received **XXX** at **XXX** line in **XXX** risk group and had **not had previous treatment with adjuvant pembrolizumab**”*

The second and third questions are formatted in such a way as to make them conditional on the answer to the first question in order to account for dependence between the parameters.

For the questions related to use of adjuvant pembrolizumab we asked:

- *4. “*Your previous answer for patients receiving **XXX** at 1st line in the intermediate / poor risk group estimated the number of people who would be alive and progression-free at **3 years** when they had NOT received adjuvant pembrolizumab. How many do you think would be alive *if they **HAD received adjuvant pembrolizumab more than 12 months ago**?”*
- *5.* “Your previous answer for patients receiving **XXX** at 1st line in the intermediate / poor risk group estimated the number of people who would be alive and progression-free at **5 years**, **of those who were alive and progression free at 3 years**, when they had NOT received adjuvant pembrolizumab. How many do you think would be alive if they **HAD received adjuvant pembrolizumab more than 12 months ago**?”
- *6.* “Your previous answer for patients receiving **XXX** at 1st line in the intermediate / poor risk group estimated the number of people who would be alive and progression-free at **10 years**, **of those who were alive and progression free at 5 years**, when they had NOT received adjuvant pembrolizumab. How many do you think would be alive if they **HAD received adjuvant pembrolizumab more than 12 months ago**?”

These questions were piloted with Dr Larkin who suggested three changes:

- Amend the wording around patient population from “English patients” to “patient population in England”
- Remove the qualitative question: “Would you expect the impact of adjuvant pembrolizumab on OS and PFS to be similar across risk groups? Please detail why / why not and if not what you expect the difference would be?” as risk group isn’t assessed until relapse and most relapsers will be by definition favourable risk as they are likely to be picked up earlier due to frequent scanning associated with adjuvant treatment
- Focus questions on adjuvant treatment to the favourable risk group for the reason suggested above

The first two of these suggestions were implemented when sending out the surveys. The final suggestion was not implemented due to space limitations and updates to higher-priority clinical issues in other domains.

For all of the estimates provided we asked the experts to provide the rationale for their answers and any comments.

4.2.4. Approach to elicitation

Given the timeframe available, the following approach was used to seek quantitative expert input:

- One-to-one or group meeting to introduce the exercise and provide training; the training was adapted from the PowerPoint slides provided within the STEER tools and included background materials for each of the trials (see Appendix J)
- Online survey to sent to experts 19.06.2023 for remote individual completion within 2 weeks using the roulette method of the STEER R tool (example https://nice-rcc-clinician-survey.shinyapps.io/rcc_r_code_clinician_1/, dummy unique identifier 0000). The tool includes:
  - Elicitation of plausible upper and lower limits (95% CI) as an initial step
  - Elicitation of values using the roulette method
  - Feedback of values for expert revision and request for provision of rationale and comment
- Check responses and follow-up queries sent if any responses are unclear or inconsistent
- Distributions to be fitted to individual expert elicited judgements – beta distribution given the information provided was expressed as proportions
- Mathematical aggregation via linear opinion pooling

There is a lack of empirical evidence on whether fixed interval methods (such as the roulette method) or variable interval methods work better for healthcare decision making, and both methods have been used in this context.[189] Fixed interval methods are generally preferred by experts and are more intuitive, but there may be a tendency for experts to focus on the shape of the histogram rather than the probabilities they are expressing. Given the timeframe of this work and the number of quantities of interest necessitates conducting the elicitation via remote survey the roulette method was preferred as the benefit of increased intuitiveness was considered to outweigh the potential issues with focus.

There is also a lack of empirical evidence to inform a preferred method to fit distributions,[189] therefore we used the beta distribution which is commonly used where information is in the format of proportions and fitted distributions to each experts responses individually prior to pooling.

The MRC protocol advises the use of linear pooling with equal weights for mathematical aggregation for simplicity and due to a lack of research on how to generate appropriate weights.[189]

4.2.5. Results

All nine recruited oncologists completed the survey. Of the maximum of 270 question responses 256 (95%) were received. Three additional responses were discounted from the analysis as the clinician indicated that they had not understood the question. Three of the clinicians who completed the survey provided probabilities rather than conditional probabilities for the 5- and 10-year timepoints which required data to be reformatted prior to analysis to ensure consistency of results. The results of the exercise were then discussed briefing with Dr Larkin with his commentary provided below.

Clinician estimates from the expert elicitation exercise for sunitinib lay above the CheckMate 9ER KM curves. Contrary to trial data, our clinicians expected a higher proportion of patients to be both alive and progression free at 3 years. Cabozantinib + nivolumab outcomes were expected to be more similar to the trial. The cabozantinib + nivolumab treatment combination is not available for untreated advanced RCC patients in the UK, hence clinicians may have relied more heavily on trial data to make their progression/survival estimates in the elicitation survey. Unlike other therapies, all four clinicians that provided commentary for cabozantinib + nivolumab stated that they relied on trial data alone to make their estimation. The sunitinib estimates being

above the CheckMate 9ER trial data was unexpected. This may be in part due to the CheckMate 9ER Kaplan Meier data being at the lower end of the trial PFS KMs (results were more similar to those reported in CheckMate 9ER) and also in part due to the expectations of the clinicians included in the exercise. It was considered unlikely to be due to the clinicians coming from more academic centres as the majority of aRCC patients are treated in large academic centres. Estimates provided for other combinations lay relatively close to the trial data from the individual trials.

For all treatments where data was available in the UK RWE clinician estimates were above the observed information. Consultation with Dr Larkin suggested that one potential factor behind this could be for the combination therapies in particular clinicians may consider that they can get more out of these treatments now that there is more experience using them in an aRCC setting. In addition clinicians were asked to estimate PFS in a “trial-like” manner.

Interestingly, the type of prior treatment appeared to influence outcomes estimates. For patients receiving cabozantinib 2nd line, there was a lower proportion of patients expected to be alive and progression free at 3 years after receiving prior TKI monotherapy therapy (mean 14%; 95% CI 8% - 23%) than after nivolumab plus ipilimumab therapy (mean 29%; 95% CI 18% - 40%), or IO/TKI combination treatment (mean 31%; 95% CI 22% - 41%). One of the clinicians completing the survey noted that they would expect cabozantinib to perform less well after TKI monotherapy. Two clinicians noted they would expect cabozantinib to behave similarly following IO/IO and IO/TKI combinations. Dr Larkin noted that the activity of cabozantinib would be expected to be lower after receiving treatment with a prior TKI (particularly sunitinib, pazopanib or tivozanib) due to similarities in the mechanism of action and that this would be expected to be particularly evident following TKI monotherapy. This is not something that has been accounted for within the state transition model for this appraisal and may bias results in favour of TKI monotherapy.

The IMDC risk group influenced the outcome estimates of different types of therapies differently. For patients receiving sunitinib 1st line, clinicians estimated that 15% more patients would be alive or progression free at 3 years in the favourable risk group (31%) compared to the intermediate/poor risk group (16%). In contrast, outcome estimates for cabozantinib + nivolumab were broadly similar for patients with favourable risk (36%), and those in the intermediate/poor risk group (33%). Similarly, for pembrolizumab + axitinib the outcome estimates were similar in both favourable (34%) and intermediate/poor risk groups (27%). This

indicates that clinicians did not consider the effect size of IO / TKI combinations to be as large in the favourable risk group as for intermediate/poor risk patients. Dr Larkin considered this to be in line with expectations as patients do similarly well on ICIs regardless of risk group whereas IMDC risk groups are defined in order to be prognostic for TKIs.

There was a difference in clinician responses for patients receiving sunitinib and cabozantinib + nivolumab with or without prior adjuvant therapy. The outcome estimates for patients receiving sunitinib with prior adjuvant therapy (46%) indicated that 30% more patients were expected to be alive and progression free at 3 years compared to patients receiving sunitinib at 1st line without a prior line of adjuvant treatment (16%). Whereas 10% fewer patients were expected to be alive and progression free at 3 years when receiving cabozantinib + nivolumab with prior adjuvant therapy (23%) compared to cabozantinib + nivolumab alone without a prior line of adjuvant treatment (33%). The responses comparing outcomes with and without prior adjuvant therapy were provided by 3 clinicians who had answered both questions. One clinician made an error when completing the survey question for cabozantinib + nivolumab (with prior adjuvant therapy), so their response was excluded from the mean value in this group. Unfortunately, in the comments provided by the clinicians there was no clear rationale for the difference in expected outcomes between patients who receive a prior line of adjuvant therapy and those who do not. Dr Larkin considered the result to be in line with his expectations as for the sunitinib comparison patients will be picked up earlier if they have had a prior adjuvant therapy as they will be scanned more regularly and therefore metastatic spread will be diagnosed at an earlier and more treatable stage; whereas he would expect patients to derive less benefit from a subsequent ICI as by definition patients have demonstrated resistance to pembrolizumab even if there was a gap of at least 12 months between treatments.

Of all the 1st line therapies, the outcome estimates for nivolumab + ipilimumab demonstrated the greatest conditional survival, 67% at 5 years and 59% at 10 years respectively. Clinicians stated that they based their judgement on existing data that indicates that a relatively high proportion of these patients will be long term responders, and the expectation that patients on CTLA4 inhibitors such as ipilimumab will demonstrate a “tail of the curve effect”. Dr Larkin considered this to be in line with his expectation and did not expect a similar effect for IO/TKI combinations.

Table 59: Expert elicitation results

L	Treatment	P	Y	n	Mean	Median (95% CI)	Variance	Commentary
1	Cabo	Int/poor	3	4	17%	16% (11%, 24%)	0.001	Based on existing data (1)
1	Cabo	Int/poor	5	4	32%	32% (22%, 44%)	0.001	Looks to have a low rate of longer-term disease control for patients (1)
1	Cabo	Int/poor	10	4	18%	18% (11%, 28%)	0.001	Expect this group to be small due to progressive downward slope (1)
1	Cabo+nivo	Int/poor	3	9	33%	33% (22%, 43%)	0.004	Based on existing data (4)
1	Cabo+nivo	Int/poor	5	9	51%	50% (34%, 66%)	0.004	Based on existing data (2) There will be a gradual reduction in patients responding but at 3 years many will still be responding at 5 years (2) PFS curve plateaus between 36 and 50months so possibly few events by 60 months
1	Cabo+nivo	Int/poor	10	9	33%	28% (16%, 43%)	0.003	No plateau expected for IO / TKI (1) Uncertain (1) Large range of answers- quite difficult to predict that far ahead but there will definitely be long term responders (1) Based on existing data (3) Estimating that 1/3 to 1/2 would not have progressed between yrs 5 and 10 (1)
1	Nivo+ipi	Int/poor	3	6	32%	32% (23%, 42%)	0.003	Based on existing data (2)
1	Nivo+ipi	Int/poor	5	6	67%	67% (54%, 79%)	0.003	Based on existing data (2) High durability of responses (1)
1	Nivo+ipi	Int/poor	10	6	59%	59% (47%, 70%)	0.003	Based on expected proportion long-term responders (1) Most patients will remain in remission but there will be competing causes for mortality (1) Tail of the curve effect of CTLA4 (1)
1	Pem+axi	Int/poor	3	2	27%	26% (22%, 31%)	0.001	Based on existing data (1)
1	Pem+axi	Int/poor	5	2	60%	60% (48%, 73%)	0.000	Based on existing data (1)
1	Pem+axi	Int/poor	10	2	31%	31% (25%, 39%)	0.000	A few people with favourable disease will get longer-term control (1)
1	Pem+lenv	Int/poor	3	6	33%	33% (23%, 43%)	0.003	Based on existing data (3) Expected outcome worse than clinical trial population (1)
1	Pem+lenv	Int/poor	5	6	49%	49% (34%, 65%)	0.004	Based on existing data (2)
1	Pem+lenv	Int/poor	10	6	30%	30% (21%, 39%)	0.003	Data so far has an almost linear downward trend (1) Do not expect a high rate of longer-term responders (1) Competing causes of mortality (1) There is an expectation of maintenance of PFS with the use of PD1 inhibitors albeit not on the same magnitude as with CTLA 4i (1)

L	Treatment	P	Y	n	Mean	Median (95% CI)	Variance	Commentary
1	Suni	Int/poor	3	8	16%	14% (9%, 21%)	0.002	The KM curve looks poor at 2 years (1) Proportions of longer term non- progressors will be lower in everyday practice than in the trial (1) Unlikely that patients will remain progression free beyond 18 months, as most progress within 1 year (1) Based on existing data (2)
1	Suni	Int/poor	5	8	32%	32% (21%, 43%)	0.001	Would expect a low range to remain progression free which is difficult to predict (2) These will be mostly good prognosis patients that have done w ell with initial therapy (1) Based on existing data (2)
1	Suni	Int/poor	10	8	34%	34% (18%, 48%)	0.001	There are very few patients with longer term disease control in this group (1) It is very likely that after 10 years 2-7% remain progression free (2) Proportion of patients progressing between 60 and 120 months would be slightly higher than those progressing between 36 and 60 months (1) Based on existing data (1)
1	Ave+axi	Fav	3	3	46%	46% (38%, 51%)	0.002	Expect the favourable risk group patients to do very well (1) Based on existing data (1)
1	Ave+axi	Fav	5	3	51%	50% (41%, 60%)	0.002	Expect to see more durable responses in a proportion of patients (1) Based on existing data (1)
1	Ave+axi	Fav	10	3	32%	32% (24%, 43%)	0.002	Small proportion will achieve complete response (1) In favourable risk sunitinib is as efficacious as IO-IO or IO-TKI combination. The rate of progression beyond 60 months would also be expected to be similar between Avelumab-Masitinib and Sunitinib (1)
1	Cabo+nivo	Fav	3	5	36%	36% (29%, 43%)	0.002	Based on existing data (2) Based on trial data, however, would expect to be lower in real life. Would have expected favourable risk group to have done better in the trial (1) There is PFS benefit but not OS benefit with combination of I/O -TKI in favourable risk RCC (1)
1	Cabo+nivo	Fav	5	5	34%	37% (27%, 48%)	0.002	Due to the progressive downward slope without a plateau, I expect this to be further reduced by 30-40% (1) I think that most people will have progressed at this point (1) There is PFS benefit but not OS benefit with combination of I/O -TKI in favourable risk RCC (1)
1	Cabo+nivo	Fav	10	6	38%	51% (28%, 64%)	0.002	Considerable uncertainty but I expect progressive deterioration at 10 years (1)

L	Treatment	P	Y	n	Mean	Median (95% CI)	Variance	Commentary
								Most people will have progressed at this point and will not be o n the therapy (1) Better patients selected out at 5 years, there is reasonable possibility of another 5 years survival (1) There is an expectation of maintenance of PFS with the use of PD1 inhibitors albeit not on the same magnitude as with CTLA 4 (1)
1	Pem+axi	Fav	3	2	34%	34% (29%, 39%)	0.001	Based on existing data (1)
1	Pem+axi	Fav	5	2	56%	55% (44%, 68%)	0.001	Based on existing data (1)
1	Pem+axi	Fav	10	2	28%	28% (23%, 33%)	0.000	There are few patients with longer- term disease control in this group (1)
1	Suni	Fav	3	5	31%	31% (23%, 40%)	0.002	Based on existing data (1) Median PFS of favourable risk RCC patients on sunitinib is 4-5 years (1)
1	Suni	Fav	5	5	45%	45% (32%, 59%)	0.003	Most patient in the favourable risk group won't get longer term disease control (1) The median PFS of favourable risk RCC pts on sunitinib is 5 ye ars (1)
1	Suni	Fav	10	5	27%	27% (18%, 38%)	0.002	With a continued downward slope it is reasonable to assume approx. 40-50% of those progression free at 3 years remain progression free at 5 years (1) There are few patients with longer term disease control in this group (1) This represents the favourable risk group with a very good pro gnosis (1)
1	Cabo+nivo (with prior adjuvant)	All	3	2	23%	23% (14%, 33%)	0.003	Based on existing data (2)
1	Cabo+nivo (with prior adjuvant)	All	5	2	33%	33% (18%, 54%)	0.002	Based on existing data (1)
1	Cabo+nivo (with prior adjuvant)	All	10	2	29%	29% (15%, 51%)	0.000	Based on existing data (1)
1	Suni (with prior adjuvant)	All	3	2	46%	45% (34%, 57%)	0.003	Speculating based on the response to VEGF TKI in TKI naïve patients (1)
1	Suni (with prior adjuvant)	All	5	3	50%	50% (40%, 61%)	0.002	Would expect majority of patients on sunitinib to progress within 18 months (1) Speculating based on the response to VEGF TKI in TKI naïve patients (1)

L	Treatment	P	Y	n	Mean	Median (95% CI)	Variance	Commentary
1	Suni (with prior adjuvant)	All	10	3	33%	33% (26%, 41%)	0.001	Would expect majority of patients on sunitinib to progress within 18 months (1) Speculation based on extrapolation from patients who receive sunitinib without prior adjuvant pembrolizumab (1)
2	Cabo (after IO/TKI)	All	3	3	31%	31% (22%, 41%)	0.002	Even more difficult to predict most will have progressed at 10 years I believe this to be very similar as the situation after IO +IO (1) I would anticipate similar trends with 2L cabozantinib after IO/I O or IO/TKI combination 1L (1)
2	Cabo (after IO/TKI)	All	5	3	29%	28% (14%, 46%)	0.001	patients are less likely to remain progression free at 5 years aft er 2L therapy (1)
2	Cabo (after IO/TKI)	All	10	3	31%	31% (14%, 44%)	0.000	Very similar to cabozantinib after IO+IO Hard to predict but likely to be a small proportion with possibly a broad range (1) patients are less likely to remain progression free at 5 years aft er 2L therapy (1)
2	Cabo (after nivo+ipi)	All	3	3	29%	29% (18%, 40%)	0.004	Poor prognostic group 3 years after starting 2L I do not expect many to remain progression free (1) Not likely that there will be many patients who are progression free on 2L therapy (1) Based on existing data (1)
2	Cabo (after nivo+ipi)	All	5	3	40%	39% (21%, 59%)	0.004	Hard to predict but in the few who had been progression free some long term responders may be hiding (1) Not likely that there will be many patients who are progression free on 2L therapy (1) Based on existing data (1)
2	Cabo (after nivo+ipi)	All	10	3	36%	35% (14%, 51%)	0.001	Very rare to be progression free 10 years after 2L therapy (1) Based on existing data (1)
2	Cabo (after TKI mono)	All	3	3	14%	14% (8%, 23%)	0.002	
2	Cabo (after TKI mono)	All	5	3	34%	33% (18%, 56%)	0.002	Expect proportion will be less than cabozantinib after 1L IO combinations (1) About 20% are progression- free by 20months then the rate of events seems to plateau and would expect 1 in 10 to 1 in 6 patients not to progress (1)
2	Cabo (after TKI mono)	All	10	3	62%	63% (30%, 87%)	0.001	Less durable responses in the long term (1) Approx 15%, bell curve, slight bias to lower end (1)
2	Lenv+evero (after IO/TKI)	All	3	3	21%	20% (13%, 29%)	0.002	Likely to be a low proportion at 5 years as they have already shown TKI resistance by progressing on cabozantinib (1) Would not expect more than 10% to be progression free by 3yr s with a 3L therapy (1)
2	Lenv+evero (after IO/TKI)	All	5	3	27%	23% (10%, 42%)	0.002	Likely to be a low proportion at 5 years as they have already shown TKI resistance by progressing on cabozantinib (1)

L	Treatment	P	Y	n	Mean	Median (95% CI)	Variance	Commentary
								Would estimate at least 50% will progress from yrs 3 to yrs 5 o n a 3L regimen (1) Very low numbers now (1)
2	Lenv+evero (after IO/TKI)	All	10	3	44%	54% (15%, 81%)	0.000	Would expect greater percentage of people to progress from 5 to 10yrs than from 3 to 5yrs on a 3L treatment (1)
2	Nivo (after TKI ono)	All	3	3	25%	25% (17%, 34%)	0.003	Expect durable responses with 2L Nivo (1) Based on existing data (2)
2	Nivo (after TKI mono)	All	5	3	36%	35% (19%, 52%)	0.002	Expect durable responses with 2L Nivo (1) Based on existing data (1) Unlikely >10%, bias toward lower end (1)
2	Nivo (after TKI mono)	All	10	3	37%	37% (13%, 56%)	0.000	Expect patients to survive longer with immunotherapy (1) Likely <10% (under 5 really), skew to lower values (1)
2	Tivo (after nivo+ipi)	All	3	3	14%	9% (6%, 14%)	0.001	Less durable responses in the long term (1) Based on existing data (1) Bias to low values (1)
2	Tivo (after nivo+ipi)	All	5	3	59%	58% (34%, 74%)	0.001	People post progression on IO therapy will do poorly with later lines of therapy (1) Based on existing data (1) <10% (1)
2	Tivo (after nivo+ipi)	All	10	3	54%	56% (33%, 57%)	0.000	There will be few longer-term survivors in this group (1) The percentage not progressing will be comparable to sunitinib and cabozantinib (1)
3	Axi	All	3	2	10%	50% (1%, 52%)	0.001	Expect low proportions as axitinib is less effective than lenv+evero (1)
3	Axi	All	5	3	41%	73% (28%, 73%)	0.000	Would estimate that more than 2/3 will progress from 3 to 5yrs on a 3L therapy (1)
3	Axi	All	10	3	48%	79% (31%, 81%)	0.000	Selecting out a small number of patients (1)
3	Lenv+evero (after nivo+ipi and cabo)	All	3	3	5%	4% (2%, 8%)	0.000	Len-evero has the best PFS among available treatments, so expect a higher proportion of patients to remain progression free (1) Based on existing data (1)
3	Lenv+evero (after nivo+ipi and cabo)	All	5	3	68%	73% (35%, 60%)	0.001	Len-evero has the best PFS among available treatments, so expect a higher proportion of patients to remain progression free (1) Very low, expect <10%, bias toward <5% (1)
3	Lenv+evero (after nivo+ipi and cabo)	All	10	3	65%	65% (29%, 71%)	0.001	Very low, likely <5% (1)
4	BSC	All	0.5	2	13%	53% (2%, 58%)	0.002	Patients usually die fairly quickly particularly if they have been very TKI dependent (1)

L	Treatment	P	Y	n	Mean	Median (95% CI)	Variance	Commentary
4	BSC	All	1	3	14%	40% (6%, 46%)	0.002	Of those who are alive at 6 months a slightly better biology can be expected but it will be short-lived. Great uncertainty therefore broad range. (1) Those with more indolent disease will have survived to 6 mont hs so around 1/5 may get to a year (1)
4	BSC	All	2	3	6%	35% (1%, 37%)	0.001	Similar argumentation as before. It will be a poor prognostic group (1) This will be the indolent patients (1) Based on real world data (1)
4	Evero	All	3	3	6%	6% (3%, 12%)	0.001	Would not expect more than 1 in 10 patients to be progression free by 3yrs using a 4L treatment (1) No data to support use of everolimus in the current era of imm une check point inhibitors (1)
4	Evero	All	5	3	20%	20% (15%, 26%)	0.001	The percentage progression free at 5yrs with a 4L therapy would be lower than with a 3L therapy (1) No data to support use of everolimus in the current era of imm une check point inhibitors (1)
4	Evero	All	10	3	10%	10% (5%, 17%)	0.001	Even less patients would be progression free by 10yrs using a 4L treatment (1)

Abbreviations: IO, immune-oncology; TKI, tyrokinase inhibitor

Notes: 5 and 10 year data are conditional on survival to the prior timepoint

4.3. EAG economic analysis

4.3.1. Model structure

A *de novo* decision model was constructed for this appraisal. Adaptation of previous models, including the model used within the TA858 MTA, was not possible as these were not accessible for such use and also due to differences in the scope of this and previous appraisals.

The following factors were considered when determining the model structure to be used:

- The nature of the disease
- The need to be able to look at multiple decision nodes within the treatment pathway
- The key issues identified within the review of previous economic analysis and NICE technology appraisals
- Methodological guidance
- The available data (type, format and coverage)
- Timelines

4.3.1.1. Nature of the disease

The goal of treatment for RCC is to extend life and delay progression; with long-term survival considered a reasonable goal in the context of many active agents.[191,192]

People may go through rdimultiple lines of treatment. Experts consulted in the scoping meeting for this appraisal recommended that a maximum of four lines of treatment followed by BSC should be incorporated in the model. A previous UK audit found that on progression 69% of patients were able to receive 2nd line therapy, 34% were able to receive 3rd line therapy, 6% were able to receive 4th line therapy and only 1% received a 5th.[193]

Improving HRQoL by relieving symptoms and tumour burden is also an important clinical outcome for people with RCC.[191] Quality of life is impacted by both the stage of the disease and treatment received. Experts consulted indicated that TKI toxicities can have considerable impact on quality of life, particularly as people cannot take prolonged treatment breaks. Within the scoping workshop for this appraisal, experts noted these include chronic fatigue, chronic diarrhoea and hand / foot syndrome. With immuno-oncology treatments, immune-related adverse events are rare but can be serious in nature.

In addition to the impact on the patient, HRQoL is predictive of mortality in RCC; particularly non-RCC-specific mortality,[194] along with other well recognised factors such as age and sex.

Treatment durations vary. Treatment is either given until progression or unacceptable toxicity, or for some immuno-oncology treatments, stopping rules are in place such that treatment is only given for a fixed length of time (typically two years).

4.3.1.2. Surrogacy between PFS, TTD and TTNT

A targeted review was conducted to investigate the plausibility of surrogacy between different endpoints in advanced RCC (see Appendix F for details). The papers identified indicated that:

- RECIST-defined overall response rate and progression-free survival are not reliable surrogate end points for median OS or the treatment effect on OS in trials of PD-(L)1 inhibitor therapy[195-199]
- For targeted agents PFS is a more reliable surrogate for OS; particularly in trials which did not allow cross-over after disease progression and studies published before 2005[200,201]
- PFS may be predictive of PPS for targeted treatments at 1st line (a longer PFS meaning a longer PPS[202]); PPS is then more predictive than PFS of OS[203]
- TTNT may be a more valuable surrogate endpoint for previously untreated patients receiving PD-(L)1 inhibitor therapy[204]
- In a real-world setting prior to the wide-spread availability of IO/TKI combinations (n=171) there was a moderate correlation between PFS, TTNT and TTP with OS. The correlation coefficient for PFS and TTNT was similar (Spearman's correlation coefficients of 0.70 and 0.68)[205]. TTD, was however, less well correlated with OS (Spearman's correlation coefficient of 0.56).

Analysis from the UK real-world evidence dataset indicated a high level of correlation between TTD and PFS endpoints (Spearman's correlation coefficient of 0.83 for TTD vs PFS and 0.91 for PFS vs TTNT). Clinical expert advice to the EAG was that TTNT and PFS are well correlated and similarly TTD and PFS are well correlated for TKIs and that TTNT is a reasonable proxy for PFS. Figure 37 demonstrates that in general TTD and TTNT follow the same shape as PFS with a short lag between treatment discontinuing, progression and starting the next line of treatment (around 1 month between each).

Figure 37: PFS vs TTNT in the UK RWE

Data supplied by BMS in response to the preliminary assessment report indicate that a similar shape can be observed for both PFS and TTD for patients treated with sunitinib as rates decrease at a similar rate over time. In contrast with patients treated with nivolumab + ipilimumab, there is an increasing difference between PFS and TTD over time as a plateau appears to be forming from approximately two years for nivolumab + ipilimumab in terms of PFS whilst TTD continues to decrease.

Kaplan Meier data were requested from Ipsen in the same format for CheckMate 9ER, however, the data supplied had implemented an unexpected censoring rule (the company censored treatment with nivolumab when treatment stopped with cabozantinib and vice versa) and these data cannot therefore be used to investigate the relationship between PFS and TTD for different treatment types. The data we do have which includes TTD for both parts of the combination does not indicate the same sort of relationship (Figure 39).

Figure 38: KM curve of PFS IRRC-assessed, primary definition and TTD by treatment arm: CheckMate 214 intermediate-/poor-risk patients (60-month data cut)

Abbreviations: KM, Kaplan-Meier; PFS, progression free survival; TTD, time to discontinuation

Figure 39: KM curve of PFS versus TTD: CheckMate 9ER all risk population (44-month datacut)

Abbreviations: PFS, progression free survival; TTD, time to discontinuation

4.3.1.3. Conceptualisation of disease model

Given the above, if this model is conceptualised entirely using a disease-oriented approach, as recommended by TSD 13,[160] it would consist of health states based upon:

- Length of life
- Disease status; whether or not the patient has progressed on their current line of treatment and what line of treatment they are receiving (which may be a reasonable proxy for progression)
- Type of treatment received and whether the patient is on or off treatment
- Patient characteristics which are likely to impact upon length, and quality of life, such as age, sex and risk status should also be considered as necessary. In the case of a cohort model, it is necessary to ensure that the patient cohort modelled is reflective of UK practice and that changes in quality of life and mortality risk attributable to the aging process rather than the disease are captured.

4.3.1.4. Available data

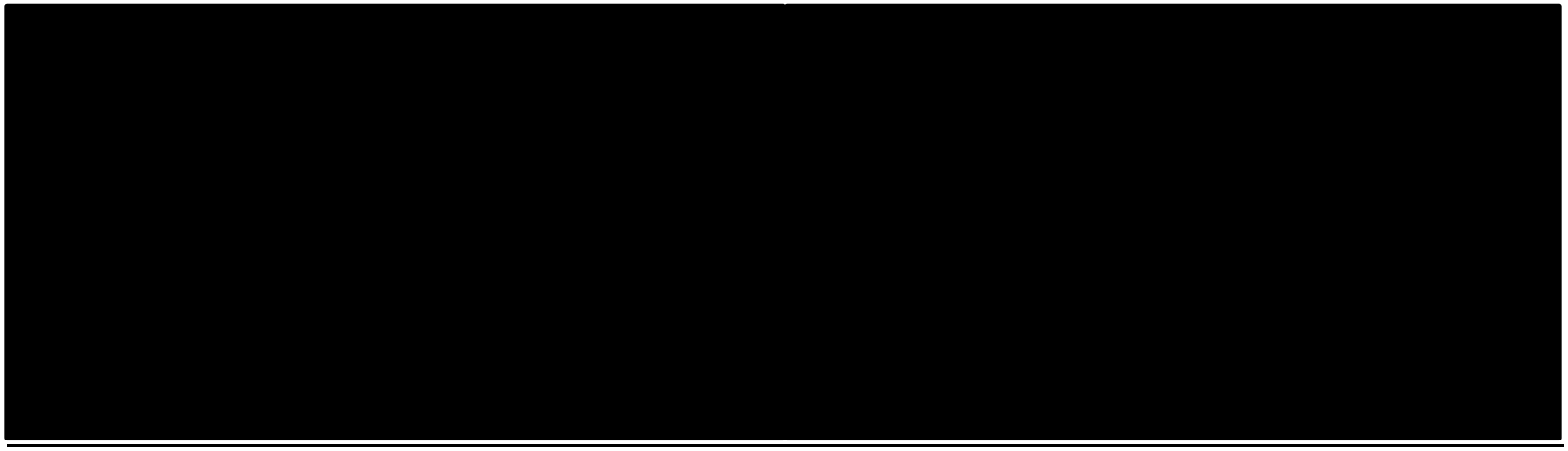
As discussed in Section 3, all identified RCTs provided information on OS and PFS endpoints and 14 of 24 trials reported HRQoL data. Only two trials reported data on TTP and relatively few reported TTD. Data for risk subgroups are less complete than for the overall population, with gaps more of an issue in the favourable risk population. Anonymised IPD was provided to the EAG for CheckMate 9ER for all endpoints except TTD by therapy type. Anonymised IPD was also provided to the EAG for 15 UK centres including OS, PFS, time on treatment (1st line only), line of treatment, risk status and other population characteristics. Data from previous modelling exercises conducted within prior NICE appraisals is not available to the EAG for model input.

It should be noted that PFS as measured within trials and PFS as measured in practice can differ substantially as patients are not routinely scanned as frequently in practice as in trials.[206,207] This can lead to PFS in the real-world appearing longer relative to OS than in trials.

Figure 40 demonstrates that when comparing the sunitinib arm in the UK RWE to that in the CheckMate 9ER trial the PFS outcomes for favourable risk patients are extremely similar whereas OS in the UK RWE is lower than in the trial. For intermediate/poor risk patients after the initial 3 months the curves separate with trial patients having more favourable PFS and for OS the difference is even more pronounced. The difference in OS outcomes between the trial and the UK RWE is expected given the strict inclusion criteria applied to trials and difference in availability of subsequent therapies across markets.

Figure 40: Comparison of UK RWE to CheckMate 9ER for suni

PFS OS



4.3.1.5. Key issues identified within previous economic analysis

The developed model should be able to handle the following additional issues identified in prior economic analyses (Section 4.1.2):

- Matching costs and effectiveness for subsequent lines of treatment
- The potential for treatment effect waning
- Lack of clarity over the most appropriate approach to modelling quality of life (progression status vs time to death).

The first of these is the most relevant to determining the overarching model structure as, although the precedent for prior appraisals has been the use of a partitioned survival approach in most previous TAs, this structure cannot readily handle adjustment for a different subsequent therapy case mix where patient-level data cannot be accessed to implement statistical analyses to adjust for treatment switching.

The latter of these is not possible for us to address as data was not provided by Ipsen for quality of life by time to death and data from prior appraisals is redacted.

4.3.1.6. The need to be able to look at multiple decision points

In order to fulfil all of the objectives, the model needs to be able to start at a user-defined line of treatment for a user-defined population and include a user-defined list of therapies available at each line from then onwards. The type of treatment received in a prior line impacts on options available at later lines and may also impact outcomes.

This sort of problem naturally lends itself to a discrete event simulation (DES) model or a state transition structure. The sequencing models identified within the economic literature review were all discrete event simulation analyses.

TSD15 considers the key benefits of a patient-level simulation to be:

- The ability to model non-linearity with respect to heterogeneous patient characteristics
- The ability to determine patient flow by the time since the last event or history of previous events
- Avoiding limitations associated with using a discrete time interval
- Flexibility for future analyses, particularly when compared to models implemented in Excel
- The ability to model interactions - not relevant to this decision problem

- Potential for efficiency savings within probabilistic sensitivity analysis (PSA)

As anonymised patient-level data in a format where patient characteristics and outcomes are able to be linked by a unique identifier are not available to the EAG for any of the treatments involved in this decision problem, the ability to model non-linearity with respect to heterogeneous patient characteristics is of no additional benefit.

A DES would be more efficient for handling time-to-event outcomes for subsequent lines of treatment where an exponential curve fit is inappropriate, however, alternatives such as the use of tunnel states are available in a state transition structure. The limitations associated with a discrete time interval can be reduced through the use of a smaller time interval.

There are also disadvantages: there can be difficulties in interpretability due to the complex nature of such models and DES models are indeed an investment; they take additional time to build compared to simpler model structures. The timeframes available for this pilot do not lend themselves to the use of a DES. For example, the IVI-NSCLC simulation model took a year and a half to build.[3]

There are a limited number of examples of use of DES within prior oncology NICE technology appraisals[208-210] and only one the authors are aware of where the disease area endpoints were OS and PFS.[208] The drivers for this are likely a mixture of precedent, data availability to gain the benefits from additional flexibilities and issues with interpretability and level of complexity for reviewers.

For example, in the abiraterone appraisal (TA387), the company submitted a DES in order to allow more flexibility to reflect a sequence of treatments and to allow the modelling of response to treatments that depend on previous treatments, both highly relevant to this decision problem. The submitted model also benefited from the availability of patient-level data allowing the modellers to account for patient characteristics that may impact on outcomes. The Committee, however, agreed that using a DES model was not unreasonable, but considered that the company's model was particularly complex.[211] The ERG considered that "an individual patient simulation by means of a DES could have been avoided, since acknowledging patient heterogeneity does not necessarily require patient-level simulation."[212]

4.3.1.7. Methodological guidance

The most relevant TSDs to consider in determining the most suitable model structure(s) for this decision problem are TSD13, TSD15 and TSD19.[160,213,214] The application of TSD13 is discussed in Section 4.3.1.1 and the application of TSD15 is discussed in 4.3.1.6. Given the majority of prior appraisals used a partitioned survival approach and those that did not use this structure were state transition models, the recommendations provided in TSD19 were given careful consideration.

TSD19 recommends consideration is given to both theoretical and practical considerations in determining modelling approach. In this case assuming that PFS and OS are independent of each other, as is the case for a PartSA analysis, would be a considerable stretch to credibility given the nature of the disease and clinical advice received. Given the data identified so far for OS (Section 3), a substantial proportion of the modelled time horizon will use extrapolated data, median OS was only just reached for CheckMate 9ER within the most recently published data-cut for example.[215] As noted in TSD19: "the lack of structural link between endpoints in PartSA models may increase the potential for inappropriate extrapolation."

There are also limitations to the implementation of a state transition structure given the limited data available in the context of this appraisal which need acknowledging. As patient-level data are not available to the EAG, a multi-state modelling approach such as that defined by Williams et al. cannot be implemented.[216] Limited data are available to define the split between progression and death events within PFS and what data are available does not provide information on the timing of events. Only two trials identified within the literature review reported data on TTP. This means that NMA is only possible for PFS as a whole at a given line of treatment rather than for individual transitions.

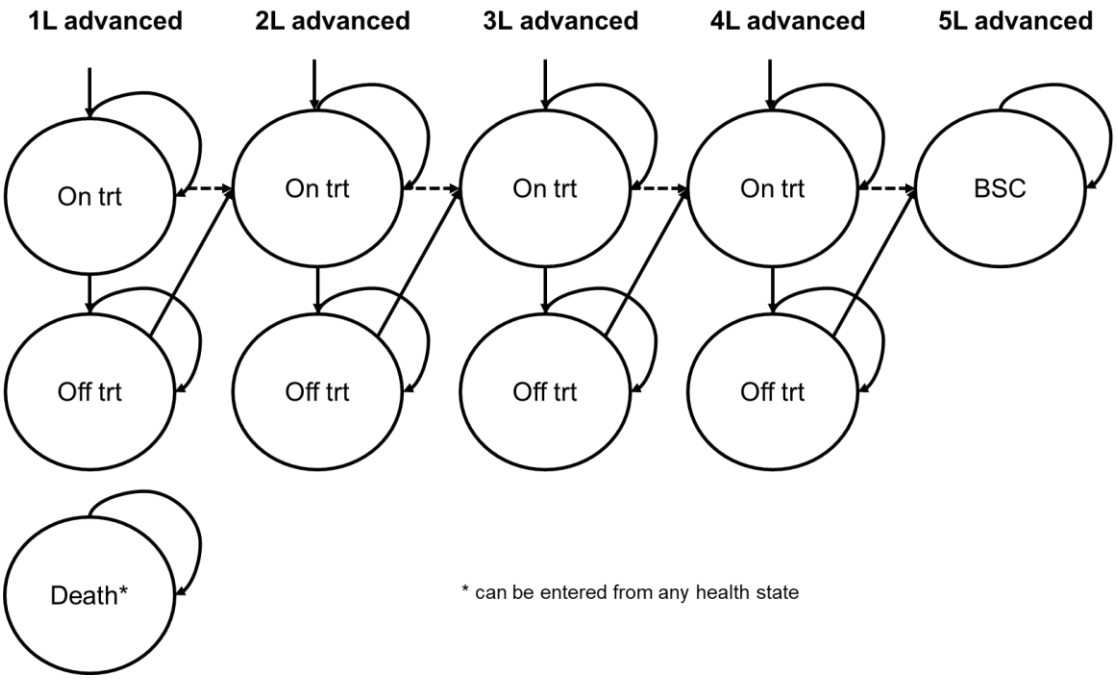
TSD19 recommends the presentation of results based upon a PartSA approach alongside those from a state transition model where a state transition structure is used given the need for further methods research.

4.3.1.8. EAG model structure

Figure 41 demonstrates the planned EAG model structure. The model is expected to allow for up to four active lines of treatment with patients who complete four lines moving to BSC. Patients will be able to receive BSC as a line of treatment at earlier lines, in this case patients will remain on BSC within that line until death.

Transitions between lines are driven by progression status. Transitions between the on and off treatment states are driven by TTD. The option to allow the use of TTNT was originally considered to make best use of data from RWE, however, in eventuality this was not required as the RWE information supplied to the EAG contained PFS.

Figure 41: EAG model structure



Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; 5L, 5th line; BSC, best supportive care; trt, treatment

Given the various considerations detailed above, the base case model structure is a hybrid of a partitioned survival and state transition approach based upon the approach used within TA798.[217] TTP and PFS data from the UK RWE (base case) and CheckMate 9ER (scenario analysis) were extrapolated and the difference between the two used to define pre-progression survival (Pre-PS). Treatment effects for other treatments were applied from the NMA and assume that the treatment effect across TTP and PFS is the same. We refer to this hybrid simply as a state transition model throughout the rest of the report.

Data for time on treatment / time to treatment discontinuation (TTD) were also taken from the UK RWE (base case) and CheckMate 9ER (scenario analysis) and extrapolated. PFS data were used for the relative treatment effect for comparators here as well, given the lack of reported TTD data. Available data from trials which report TTD were used to check that the relationship between TTD and PFS is similar to that within CheckMate 9ER in other trials where treatments

are given until progression or unacceptable toxicity. This was the case for all treatments except nivolumab + ipilimumab where a different relationship was apparent (see Section 4.3.1.2). For fixed duration treatments, the treatment duration was capped to the maximum treatment duration in the SmPC (base case) or included in the model using the mean number of doses received based upon the relevant trial where available (scenario analysis). Relative dosing intensity was taken into account in the base case.

Effectiveness data for subsequent lines following progression on 1st line treatment were taken from available RWE for the majority of treatments with trial data used to model relative effects based upon the NMA. The proportion of patients receiving each type of treatment was modelled to reflect UK practice within the base case analysis. Tunnel states are used to track the time since entry into state for patients receiving 2nd and later lines of treatment.

The structural assumptions made within the base case model are therefore:

- OS is dependent upon progression status and line of treatment; this implies surrogacy between PFS and OS, an assumption which appears to be supported by available literature
- OS is independent of whether or not a patient is on treatment within a particular line
- TTD and PFS are independent; the impact of this is expected to be limited and will be mitigated through selection of the same functional form for fitted curves
- TTP and PFS are independent; the impact of this is expected to be limited and will be mitigated through selection of the same functional form for fitted curves
- The treatment effect from the NMAs for PFS can be applied to TTP, Pre-PS and TTD endpoints
- Patients receive subsequent treatment on progression – this is in line with how PartSA models are implemented and was considered an acceptable simplification as UK RWE showed only a relatively small difference in timing between PFS and TTNT (mean [redacted] days at 1st line)
- Transitions for 1st line are dependent upon risk status, transitions for later line patients are not dependent upon risk status (given that in practice this is only measured at 1st line)

The impact of the type of previous treatment on outcomes at later lines was included where possible, however, the ability to do this is limited based upon data identified. In particular:

- The evidence available looking specifically at the impact of sequencing of different treatments is limited
- There is no trial evidence specific to 3rd or 4th line and the 4th line data available from the UK RWE has a low sample size

- No evidence was available within the UK RWE for sequences following either nivolumab + cabozantinib or pembrolizumab + lenvatinib.

A PartSA is also presented as recommended within TSD19. This model assumes by its nature that OS, PFS and TTD are independent and that any differences between the subsequent therapy mix in practice, CheckMate 9ER and other trials within the NMA do not impact either on relative effectiveness modelled.

Given the proposed primary model structure (state transition), calibration to expected OS estimates was considered as an option. In the end this was not considered necessary as the PartSA analyses were available to cross-check against. This may be further explored in Phase 2.

4.3.1.9. Model implementation

The model was implemented in R given the complexity of the future need to evaluate large numbers of treatment sequences, the need for the model to be reusable for future HTAs and the number of structural options required to be explored.

The use of R has a number of benefits including the integration of the conduct of the core statistical analysis (survival curve extrapolation) within the model.[218,219] Table 60 provides a comparison of the analytical capabilities of R and Excel from a published example using a side-by-side PartSA and state transition structure. The advantages to run time and analytical options are clearly demonstrate for the simpler decision problem addressed by that model (only one line of treatment).

Table 60: Comparative analytical capabilities between R and Excel models in oncology

Functionality	R model	Excel model
Live fitting of parametric models	All parametric models are fitted to the active dataset	Parametric models need to be fitted to the active dataset externally, and results copied into model—a laborious task for updates to data-cut or subgroup exploration
PartSA and StateTM modelling	Model includes PartSA and StateTM modelling strategies. These are informed by the internally calculated parametric fits	Model includes PartSA and StateTM modelling strategies. These are informed by models fit outside of Excel with estimates pasted in

Functionality	R model	Excel model
PSA—time taken for 1000 PSA runs using base-case settings	1.42 min	13.2 min
One-way sensitivity analysis—time taken to run 109 parameter scenarios	0.27 min	2.4 min
Automatic report generation	Report template is set up within R Markdown to automatically populate tables and figures with active modelling analyses when selected	Highly challenging to include; not included
Quality control	Table included with selected diagnostic checks Linear code with vectors and data frames produced by single calculations that need to be checked once. However, tracing an individual calculation from start to finish can take longer than in Excel Packages used are open-source: version to be used needs to be defined to ensure stability over time	Diagnostic checks included in the patient flow sheet Cell-by-cell checks were required across all sheets because of individual calculations, meaning there was potential for drag down error and inconsistency within columns and data frames
Model size	5.1 MB—includes R scripts and Excel input workbooks containing simulated IPD, general population survival statistics and cost inputs	30.9 MB—single workbook
Version control	Managed by the version control software Git to allow tracked changes, code reversions and parallel work streams	Manual change log. Multiple versions required to allow reversions. Difficult to work in parallel

Adapted from Hart et al. R and Shiny for Cost-Effectiveness Analyses: Why and When? A Hypothetical Case Stud[219]y

Abbreviations**:** MB megabytes, MCM mixture-cure modelling, PartSA partitioned survival analysis, IPD individual patient-level data, PSA probabilistic sensitivity analysis, StateTM state transition model

The EAG, however, note that R is less familiar than Excel to many stakeholders within the NICE process. To mitigate the potential impacts of lack of familiarity on model transparency the model input sheet has been designed in Excel and intermediate outputs (patient flow) are provided in Excel. In addition NICE have commissioned the DSU to provide an independent external validation of the model code.

The model is intended to be made open-access using 'GitHub' to improve replicability and collaboration. The model was built broadly aligning with good practice guidelines, for example, the Zorginstituut Nederland National Health Care Institute (ZIN) guidelines for building models in R.[220] Underlying data (model inputs) do not need to be publicly available and can be shared confidentially with NICE abiding to the principles for handling confidential information outlined in the 2022 manual.[74]The publicly available version of the decision model which will be published following conclusion of the nivolumab + cabozantinib appraisal will use dummy data in the correct format as inputs where data are marked as either academic or commercial in confidence within the original data source. The dummy data will be created using the methods used to redact an Excel model as part of a NICE submission.

Data which are expected to need to be marked as confidential and redacted to reduce the potential for back-calculation of confidential prices include:

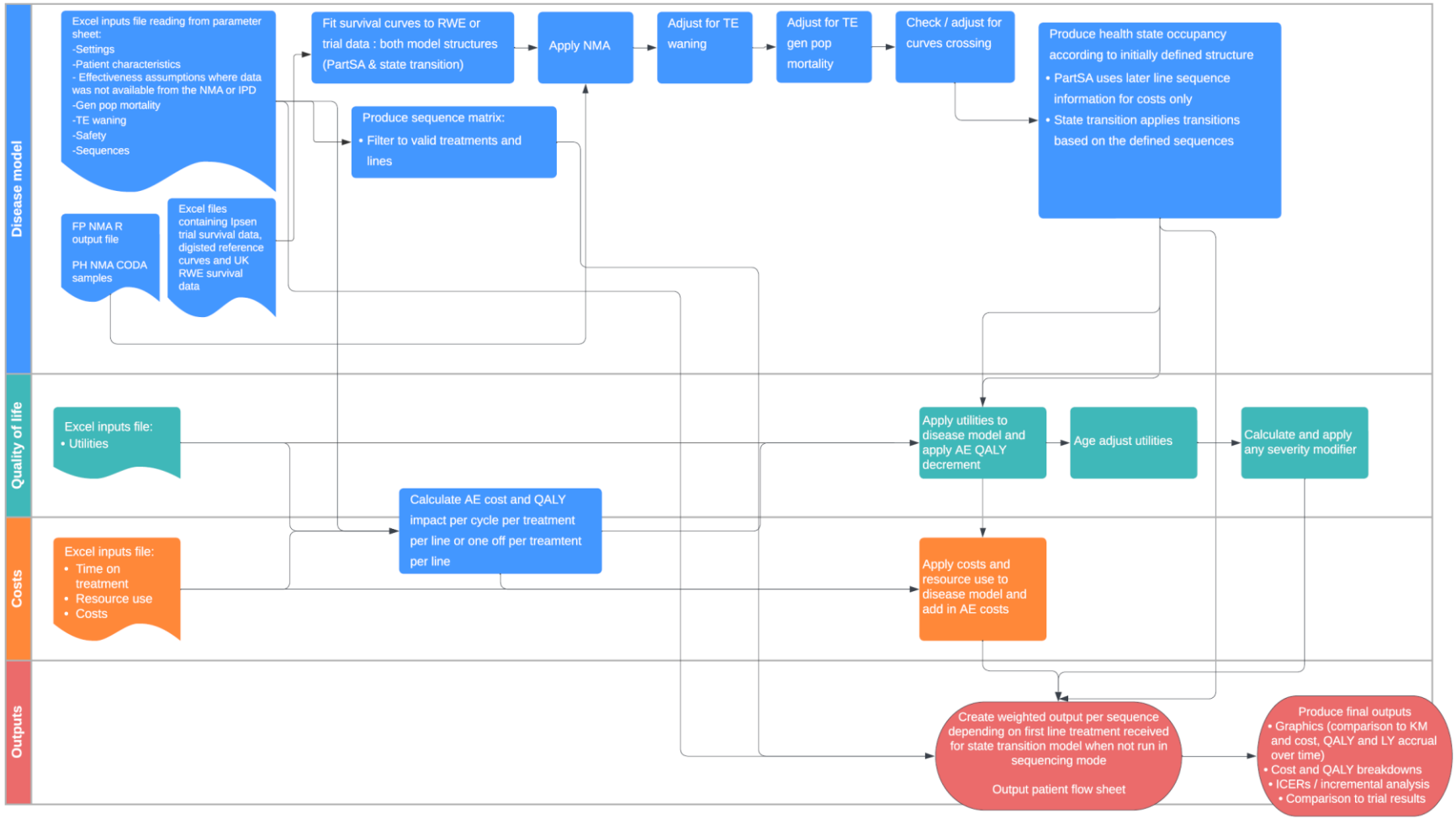
- PAS price discounts
- Any individual patient-level data provided by the company
- Time on treatment input data
- Relative dose intensity input data
- Market share data for subsequent therapies
- Reported ICERs (PAS price and list price).

A later stage of this pilot following the evaluation of cabozantinib + nivolumab will involve the incorporation of a Shiny front-end to the R model. Shiny is an open source R package enables the user to build web applications using R.[221] This will allow model users to interact via an easy-to-understand user-interface operating via their web browser.

Figure 42 demonstrates the model flow for each of the modules incorporated within the R model. Inputs to the decision model come from five sources:

- The main Excel inputs workbook which contains data and settings for the disease model, utilities and resource use and costs
- The R output file from the fractional polynomial NMA
- An Excel output file containing the CODA samples from the proportional hazards NMA
- An Excel file containing pseudo patient-level data for the reference curves for each population, treatment, trial, line and endpoint for the base case and scenario analyses; or
- The RDS output from the survival analysis (available to stakeholders for whom patient-level data access is restricted due to confidentiality)

Figure 42: EAG model flow diagram



Abbreviations: AE, adverse event; NMA, network meta-analysis; RWE, real world evidence; TE, treatment effect

The methods for each of the models required to produce the desired outputs are described in detail in the sections below.

The cost effectiveness of the interventions was estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per life year gained (LYG), net monetary benefit and net health benefit. Base case analyses are probabilistic as this generates expected outcomes and costs and is in line with the NICE manual.[74]

Intermediate outputs including the patient flow sheet and graphical outputs such as fits to KM curves are presented, as well as the final model outputs describing cost-effectiveness and its drivers.

4.3.2. Population

The model population aligns with the decision problem population with results for the appraisal of cabozantinib + nivolumab presented for relevant treatments for untreated advanced or metastatic RCC followed by a subsequent therapy mix reflective of actual or expected UK practice.

Subgroup analysis has been presented for intermediate-/poor-risk and favourable-risk subgroups as defined in the IMDC criteria. The NICE scope requests the presentation of subgroup analysis by prior treatment. Very few patients in CheckMate 9ER received adjuvant treatment. This is not in line with the expectations for uptake of adjuvant pembrolizumab from TA830 which estimates that at full uptake 18% of patients receiving systemic therapy will have had a prior line of adjuvant treatment (see footnote of Table 61 for how this was calculated). Section 4.3.5.8 provides details of exploratory scenario analysis conducted to explore the impact of this mismatch between the available clinical trial data and expected practice.

Population characteristics were taken from the UK RWE data in the base case and CheckMate 9ER in scenario analysis (Table 61). Patients in the UK RWE were on average older than those in the CheckMate 9ER trial, other patient characteristics were similar.

Table 61: Patient characteristics included in the economic analysis

	UK RWE	**CheckMate 9ER**
% IMDC int/poor risk	77.6%	77.3%
Age: mean (SE) All risk	64.4 (0.28)	60.9 (0.41)

	UK RWE	CheckMate 9ER
Int/poor	64.2 (0.33)	61.49 (0.66)
Favourable risk	65.4 (0.56)	61.51 (0.90)
% female		
All risk	29.0%	26.1%
Int/poor	29.5%	25.5%
Favourable risk	26.5%	28.1%
Weight kg (SE)		
All risk	83.38	80.59 (0.76)
Int/poor	81.26	78.55 (0.86)
Favourable risk	90.98	87.94 (1.72)
Prior adjuvant treatment	Scenarios tested: 0%, 5.5%, 18%	

Note: scenarios for % receiving prior adjuvant treatment were calculated as the upper and lower bound of the market shares from TA830 (20 and 65%) based on the proportion of patients eligible in the UK population: 83% clear cell * 55% prior nephrectomy * 60% high risk

4.3.3. Treatments included

The treatments included within the decision model for the 1st line setting align with those specified in the decision problem (Table 3 and Figure 6).

Table 62: Treatments included within the decision model

Treatments	1L population			Administration type and frequency	Treatment duration
	All risk	Fav risk	Poor / int risk		
Cabo+nivo[62]	x	x	x	Cabo: 40mg orally once daily Nivo: 240mg every 2 weeks or 480mg every 4 weeks IV	Until disease progression or unacceptable toxicity Max 24 months for nivo
Pazo[222]	x	x	x	800mg orally once daily	Until disease progression or unacceptable toxicity[50]
Tivo[223]	x	x	x	1340 mcg orally once daily for 21 days, followed by a 7-day rest period	Until loss of clinical benefit or unacceptable toxicity[37]
Suni[224]	x	x	x	50mg orally once daily, for 4 consecutive weeks, followed by a 2-week rest period	Until disease progression or unacceptable toxicity[49]
Cabo[62]			x	60mg orally once daily	Until disease progression or unacceptable toxicity
Nivo+ipi[225]			x	Nivo: 3 mg/kg IV every 3 weeks for the first 4 doses Ipi: 1 mg/kg IV every 3 weeks for the first 4 doses	Maximum 4 cycles of combination treatment

Treatments	1L population			Administration type and frequency	Treatment duration
	All risk	Fav risk	Poor / int risk		
				Nivo maintenance: 240mg every 2 weeks or 480mg every 4 weeks IV starting 3 or 6 weeks after the last dose of combination treatment respectively	Monotherapy until loss of clinical benefit or unacceptable toxicity[37]
Pem+lenv[226,227]			x	Pem: 200mg every 3 weeks of 400mg every 6 weeks IV Lenv: 20mg orally once daily	Until disease progression or unacceptable toxicity Max 35 3 weekly cycles for pem[37] or equivalent number of 6-weekly cycles

Abbreviations: Cabo, cabozantinib; IV, intravenous; ipi, ipilimumab; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab

For subsequent lines of treatment (which may be comprised of either active drug treatment or BSC) the EAG considered the following sources of data to determine what was included within the decision model:

- UK RWE – preferred source
- Trial data from CheckMate 9ER
- Clinical expert input to determine which sequences of treatment are valid for use in practice

Subsequent surgeries and radiotherapy were not considered as a line of treatment and were included only as a cost according to the proportion of patients expected to receive such treatment at each line.

4.3.4. Perspective, time horizon, cycle length, discounting and price year

The model uses an NHS and Personal Social Services perspective in line with the NICE reference case.[74]

The time horizon for the economic analysis was selected to be long enough to reflect any differences in costs or outcomes between the technologies under comparison. This is 40 years in line with the other recent appraisals for untreated advanced RCC TA858, TA780, TA650 and TA645.

A weekly cycle length was applied to account for the difference in dosing regimens across treatments. This is consistent with TA858, TA780, TA650 and TA645. Half cycle correction was not applied given the short cycle length.

Costs and outcomes were discounted at 3.5% per annum after the first year in accordance with the NICE manual.[74] All costs were expressed in UK pounds sterling for the 2022 price year (as the latest NHSCII inflation index was available only until 2022 during the time this report was prepared).

4.3.5. Treatment effectiveness and extrapolation

Modelling of treatment effectiveness requires extrapolation of 4 different curves for the reference treatment at each line in the model base case:

- PFS – progression and death are classed as events
  - Within CheckMate 9ER [redacted] of patients in the nivolumab + cabozantanib arm and [redacted] in the sunitinib arm were censored due to receipt of subsequent treatment (FDA censoring rules), TA858 demonstrated that use of EMA versus FDA censoring rules made little difference in another trial (CLEAR), therefore, given the low proportion and lack of impact in prior appraisals whilst this does not align with the model structure additional analyses were not requested
- TTP – progression is classed as an event and death is classed as a censor variable
- TTD – treatment discontinuation and death are classed as events
- Post progression survival (or post last line survival) for the last line of treatment – time measured starts from progression on the prior line and death is classed as an event.

Within the scenario analysis using PartSA OS, PFS and TTD required extrapolation for the reference curve at the 1st line of treatment only.

The reference treatment extrapolated for the 1st line was sunitinib given this is the comparator in the majority of the available RCTs, a treatment used in UK practice for all risk groups and the most frequently used treatment at 1st line in the UK RWE (n=326). The reference treatment for 2nd and 3rd line when using the UK RWE was as cabozantinib as this treatment was frequently used at both lines (n=245 and n= 103) and the data were mature compared to other treatments. When using trial data the reference treatment for 2nd line-plus was everolimus as this represented the treatment for which the most mature trial data was available (from CheckMate 025).

In line with the NICE manual[74] and discussion from other recent appraisals[228] data for the reference treatment was taken from UK RWE in the base case:

“Quantifying the baseline risk of health outcomes and how the condition would naturally progress with the comparator(s) can be a useful step when estimating absolute health outcomes in the economic analysis. This can be informed by observational studies. Relative treatment effects seen in randomised trials may then be applied to data on the baseline risk of health outcomes for the populations or subgroups of interest.” NICE manual 2022

“Specifically, the committee thought that using randomised data to estimate absolute event rates runs the risk of results that do not reflect NHS practice. It also thought that using observational data to estimate relative effects runs the risk of biased treatment effects because of unadjusted confounding variables. The committee noted that NICE’s technical support document 13 makes this distinction, advocating registry data to estimate absolute baseline event rates and randomised evidence to quantify relative differences. The committee concluded that it still preferred using the real-world evidence to estimate survival for people having cabazitaxel and the network meta- analysis to estimate the relative treatment effect of cabazitaxel compared with lutetium-177” ID3840 ACD2

4.3.5.1. Extrapolation of survival curves

Extrapolation of survival curves was conducted in accordance with NICE TSD 14 and NICE TSD 21. In order to determine if more flexible models were required log-cumulative hazard plots were examined to determine whether or not if they were not approximately straight lines. The company provided log cumulative hazard plots for OS and PFS in response to clarification question A1 for the ITT population and both risk subgroups. The survival analysis output from the R package for the UK RWE, CheckMate 9ER and CheckMate 025 is presented in Appendix K. There was no indication that more flexible models were required.

Standard parametric models were therefore fitted in line with TSD 14: exponential, Weibull, lognormal, log-logistic, Gompertz, gamma and generalised gamma using the flexsurvreg package in R.

The base case survival curve for each endpoint at each line and in each population was selected according to the following criteria which are listed in indicative priority order:

- Clinical validity – both in the biological plausibility of the trends in the hazard function considered via qualitative clinical input and in the absolute survival predicted versus quantitative clinical input from structured expert elicitation
- Consistency with longer term external data
- Consistency and validity across endpoints
  - Extrapolations where curves cross will be ruled out where possible
  - When using the PartSA approach the implications of selected OS and PFS curves on post progression survival and plausibility of this will be carefully considered
  - The overall modelled OS does not exceed the expected OS for the general population
- Statistical goodness of fit within trial (AIC and BIC) – curves with an AIC within 5 points of the best fitting curve are considered to have a similar goodness of fit
- Visual inspection
- Statistical validity versus the NMA type to be applied (the lognormal and loglogistic curves are not consistent with the application for a FP NMA) – this issue is acknowledged but was considered the lowest priority

This approach aligns with the guidance within TSD21: “careful thought should be given to the biological and clinical justification to any statistical approach selected; the approaches detailed herein should not be considered as an extended list of survival methods to “try out” on data. Instead, care should be taken to think through the underlying mechanisms likely to be dictating short and long-term hazard survival functions.”

Input from clinical experts was that the hazard function PFS would be expected to initially rise as those who are not sensitive to treatment progress early (first 1-2 years) followed by a slowing in the hazard function as those patients remaining are those who experienced initial disease control. In the longer term they would expected acquired resistance and general population mortality to take over with the potential for a late increase in hazards beyond the extent of current observed data. Given this curves which experienced continuing increase in hazards were ruled out as implausible.

Two datasets were identified which contained longer term data for sunitinib than CheckMate 9ER: CheckMate 214 and KeyNote 426. These datasets were used to assess consistency with longer term data.

Between one and three curves were selected for each endpoint to be tested in scenario analysis with the number selected based upon how similar the long-term projections were across curves.

In the maximum case a distribution with more pessimistic, more optimistic and similar (clone) projections was selected with attention paid to the same criteria as the base case in selection.

The next sections present the survival curve selections for each of the endpoints used within the state transition and PartSA scenarios for the reference curve for the 1st line all risk population in the model base case (sunitinib in the UK RWE). All other curve selections are presented in Appendix K.

Time to treatment discontinuation

Time on treatment was calculated in the base case using extrapolation of TTD curves where possible. A scenario analysis is included using PFS curves for all trials given the low level of reporting of TTD information across trials.

TTD information was only available for the UK RWE, CheckMate 9ER and CheckMate 214. Given this within the model base case we use TTD information from the reference curve for the UK RWE (base case) or CheckMate 9ER (scenario analysis) and apply the relative effects from the network meta-analysis of PFS. This is expected to provide a reasonable approximation for time on treatment given the close correlation between TTD and PFS observed in CheckMate 9ER and the UK RWE. The two exceptions to this were:

- Within CheckMate 214 the relationship between PFS and TTD differs for nivolumab + ipilimumab with PFS considerably longer than would be expected for the TTD observed – a simple scenario analysis has been carried out reducing TTD in line with the observed data using the estimated hazard ratio between PFS and TTD observed in the trial [redacted] acknowledging that proportional hazards may not hold this at least gives some indication of the expected scale of impact, the EAG does not have access to data on a per patient level which would allow more robust analyses to be carried out)
- Within CheckMate 9ER the observed TTD is slightly longer than the observed PFS for the cabozantinib + nivolumab arm. The impact of using data directly from CheckMate 9ER is tested in scenario analysis

Figure 43 shows that the data for TTD are mature within the UK RWE and that there is little difference in the curve fits. Table 63 shows the results of the curve fitting selection process. The log-logistic curve was selected within the model base case as this provided a good statistical and visual fit and had patients remaining on treatment after 6 years which is consistent with data from CheckMate 214 with the Weibull curve used in scenario analysis as a more pessimistic fit.

Figure 43: Curves fitted to TTD for suni in the UK RWE all risk population

Note: the number at risk is lower for TTD as a number of patients were excluded from the analysis due to invalid or unavailable treatment discontinuation times

Table 63: TTD curve selection for suni in the UK RWE all risk population

	Exp	Wei	Gomp	LogN	Logl	G	GG
Clinical validity hazards	✓	✓	✓	✓	✓	✓	✓
Consistency with CheckMate 214¥	✗	✗	✓	✓	✓	✗	✓
Statistical goodness of fit*	✗	✗	✗	✗	✓	✗	✗
Visual inspection	✗	✗	✓	✓	✓	✗	✓

Abbreviations: Exp, exponential; G, gamma, GG, generalised gamma; Gomp, Gompertz, int, intermediate; LogN, log normal; Logl, log logistic; PFS, progression free survival; RWE, real world evidence; suni, sunitinib; Wei, Weibull

Note: data were only collected for TTD at 1st line in the UK RWE dataset

*AIC within 5 of best fitting curve, underlined curve best statistical fit

¥ Some patients remained on treatment after 6 years

Stopping rules apply for a number of treatments for RCC. Where this is the case, data on the number of doses are used in preference to TTD data; where this has not been reported stopping rules will be applied after production of the expected TTD curve to calculate costs.

Table 64: Mean number of doses for treatments with a fixed duration

	Maximum duration	Mean number of administrations (SE)	Source
Nivo as part of cabo+nivo	2 years	[redacted]	Calculated from mean duration supplied by Ipsen of [redacted] months
Pem as part of pem+lenv	35 x 3 weekly cycles	12.3 (NR)	Calculated from mean duration of 17 months

Abbreviations: SE, standard error; NR, not reported

For combination therapies, in line with standard trial reporting, the TTD curve will only class patients as coming off treatment when both parts of the combination have been discontinued. We account for the reduction in drug cost with early discontinuation of one part of the combination using RDI data for each drug within the combination.

Treatment breaks are often used to allow toxicities to settle. NHSE restricts the length of treatment breaks before therapy is restarted, people who have longer breaks are not able to restart therapy via the normal funding route. Breaks of up to three months are allowed for nivolumab + ipilimumab and nivolumab monotherapy, 12 weeks for pembrolizumab + lenvatinib and avelumab + axitinib and 6 weeks for cabozantinib, tivozanib and lenvatinib + everolimus.[37] Similar restrictions are expected for other TKIs not included in the CDF drugs list. Treatment breaks will be considered within the model using RDI data to account for the impact on cost. The impact on effectiveness is assumed to already be included within the TTD data used to populate the model as people on a break will still be classed as remaining on treatment.

In practice, people are able to discontinue 1st line TKI monotherapy and switch to another TKI. This is only possible when they have had immediate prior treatment with a TKI which has had to be stopped solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.[37] This does not occur frequently (2.8% of patients switched TKI in the UK RWE) therefore these types of switches have been excluded from consideration within the decision model.

Progression free survival

Figure 44 shows that similar to TTD the Kaplan Meier curve for PFS is mature and there is little variation cross curve fits.

Figure 44: Curves fitted to PFS for suni in the UK RWE all risk population

Abbreviations: PFS, progression free survival; KM, Kaplan-Meier; RWE, real world evidence; UK, United Kingdom

The results from the expert elicitation exercise are presented in Appendix K. As noted in Section 4.2.5 for all of the reference curves considered the experts predictions at 3 years were above those in the observed data. The conditional survival probabilities between 3 and 5 years and between 5 and 10 years, were, however, consistent with a number of the potential models fitted to the observed data and these were used within the curve fitting process with a value within the 95% CI of estimates provided viewed as in-keeping with expert views.

Table 65 shows the results of the curve fitting selection process. The loglogistic curve was selected in the base case as this was consistent with available external data and the conditional survival probabilities from the expert elicitation in the individual risk groups. The Weibull curve was used in scenario analysis as a more pessimistic fit.

Table 65: PFS curve selection for suni in the UK RWE all risk population

	Exp	Wei	Gomp	LogN	Logl	G	GG
Clinical validity hazards	✓	✓	✓	✓	✓	✓	✓
Consistency with external data+	✗	✗	✓	✓	✓	✗	✓
Statistical goodness of fit*	✗	✗	✗	✗	✓	✗	✗
Visual inspection	✗	✗	✓	✓	✓	✗	✓

Abbreviations: Exp, exponential; G, gamma, GG, generalised gamma; Gomp, Gompertz, int, intermediate; LogN, log normal; Logl, log logistic; PFS, progression free survival; RWE, real world evidence; suni, sunitinib; Wei, Weibull

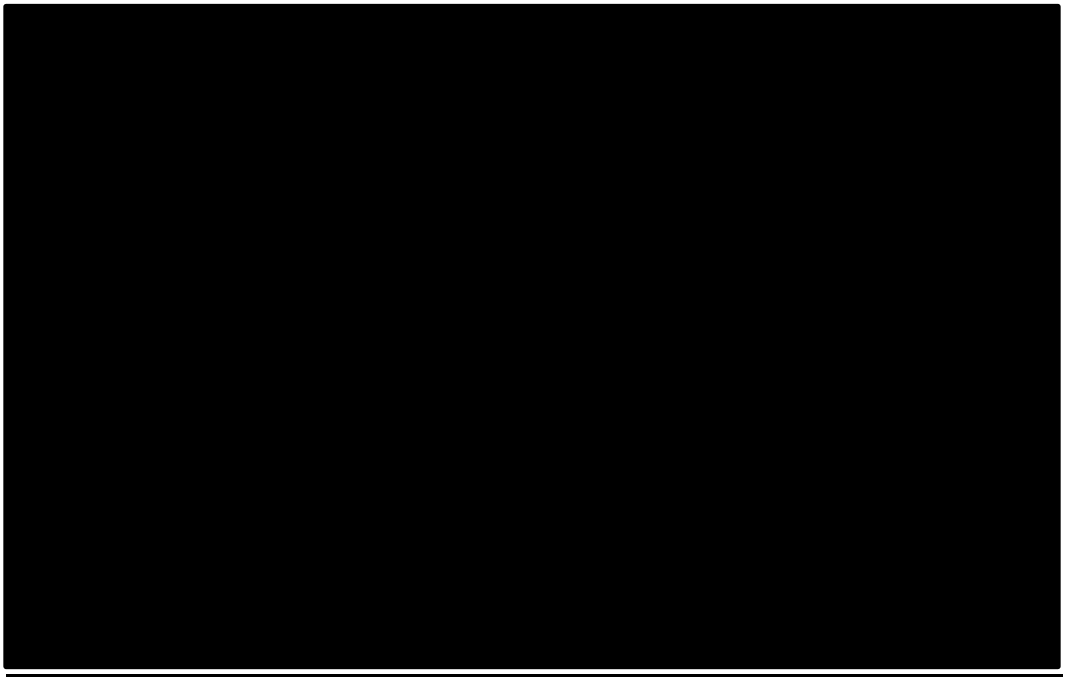
*AIC within 5 of best fitting curve, underlined curve best statistical fit

+ Given differences in populations included (RWE vs trials) curves were only ruled out if no patients remained in PFS at a timepoint clinical trial data (CheckMate 214 and KeyNote 426) indicated there should be patients remaining

Time to progression

Figure 45 shows that the TTP curve also has a high level of maturity. Table 66 shows the results of the curve fitting selection process. Consistent with TTD and PFS, the loglogistic curve was selected in the base case as this was consistent with available external data with the Weibull curve used in scenario analysis as a more pessimistic fit.

Figure 45: Curves fitted to TTP for suni in the UK RWE all risk population



Abbreviations: TTP, time to progression; KM, Kaplan-Meier; RWE, real world evidence; UK, United Kingdom

Table 66: TTP curve selection for suni in the UK RWE all risk population

	Exp	Wei	Gomp	LogN	Logl	G	GG
Clinical validity hazards	✓	✓	✓	✓	✓	✓	✓
Consistency with external data	NA						
Statistical goodness of fit*	✗	✗	✗	✗	✓	✗	✗
Visual inspection	✗	✗	✓	✓	✓	✗	✓

Abbreviations: Exp, exponential; G, gamma, GG, generalised gamma; Gomp, Gompertz, int, intermediate; LogN, log normal; Logl, log logistic; PFS, progression free survival; RWE, real world evidence; suni, sunitinib; Wei, Weibull

*AIC within 5 of best fitting curve, underlined curve best statistical fit

Overall survival (PartSA scenario analysis only)

There is more variation in the predictions using the extrapolated curves for OS than for the other endpoints as the data are less mature (Figure 46).

Figure 46: Curves fitted to OS for suni in the UK RWE all risk population

Abbreviations: OS, overall survival; KM, Kaplan-Meier; RWE, real world evidence; UK, United Kingdom

The loglogistic and lognormal curves both predict a much higher survival with a longer tail than the other curves in line with the nature of their underlying functions. These were not considered reasonable relative to the age of the patient population. All fitted curves except for the lognormal were considered to be of a similarly good statistical fit with all curves except the lognormal and

loglogistic curves also producing a good visual fit. The Gompertz was ruled out as the cumulative hazard function did not behave as expected. Given the similarity of the remaining curves the exponential was selected as the base case as the best statistical fit with the Weibull tested in scenario analysis as another plausible alternative.

Table 67: OS curve selection for suni in the UK RWE all risk population

	Exp	Wei	Gomp	LogN	Logl	G	GG
Clinical validity hazards	✓	✓	✗	✓	✓	✓	✓
Consistency with external data+	✓	✓	✓	✓	✓	✓	✓
Below general population?	✓	✓	✓	✗	✗	✓	✓
Statistical goodness of fit*	✓	✓	✓	✗	✓	✓	✓

Abbreviations: Exp, exponential; G, gamma, GG, generalised gamma; Gomp, Gompertz, int, intermediate; LogN, log normal; Logl, log logistic; PFS, progression free survival; RWE, real world evidence; suni, sunitinib; Wei, Weibull

*AIC within 5 of best fitting curve, underlined curve best statistical fit

+ Given differences in populations included (RWE vs trials) curves were only ruled out if no patients remained in OS at a timepoint clinical trial data indicated there should be patients remaining

Post progression survival

Within the state transition model up to three subsequent lines of treatment were allowed. The reference curve used for 2nd and 3rd line was cabozantinib. Results of curve fits to the endpoints of cabozantinib can be found in Appendix K. For 4th line the sample size was too small for a reference treatment to be selected within the dataset. For simplicity and given clinical expert advice that prognosis worsens as patients move down the lines, a Cox PH analysis was conducted using the UK RWE to determine the difference in outcomes between 3rd and 4th line which was then applied to all treatments equally to down-weight expected outcomes at 4th line relative to 3rd line (Table 68). This was done by 'stacking' 3rd line and 4th line survival times for patients and then estimating a hazard ratio with cluster-robust standard errors.

Table 68: Cox PH analysis comparing 3rd and 4th line outcomes in the UK RWE

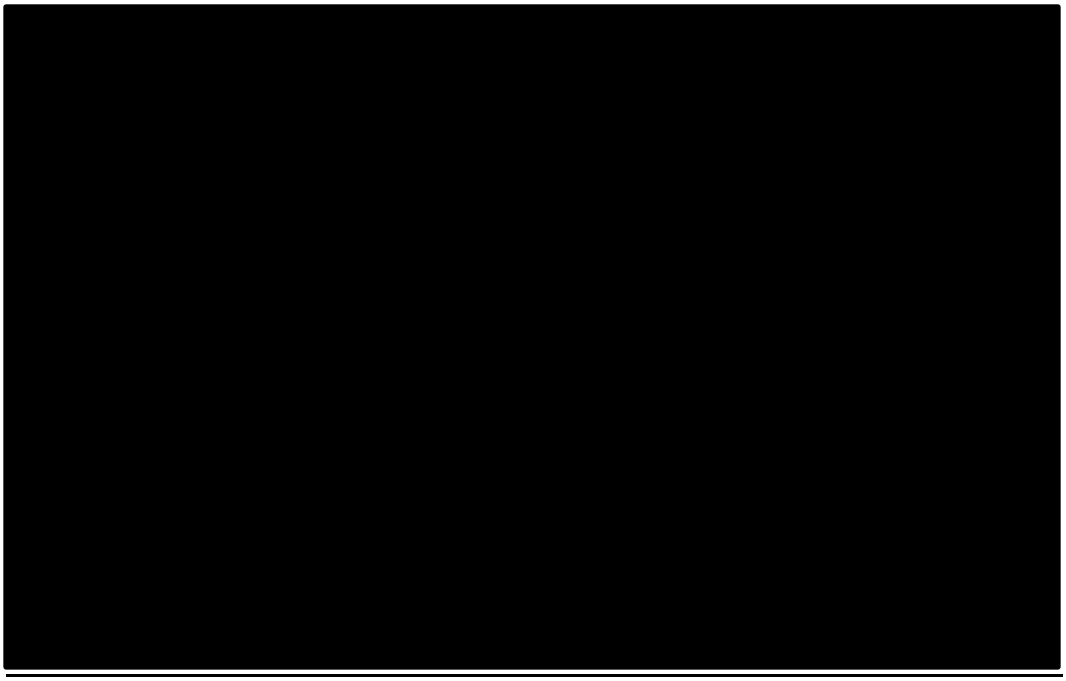
	Number of subjects / number of failures	Hazard ratio (95% CI)
OS	258 / 166	2.01 (1.45, 2.78)
PFS	237 / 176	1.74 (1.21, 2.51)

Abbreviations: OS, overall survival; PFS, progression free survival

For best supportive care pooled PPS outcomes for 4th line were taken for all patients (Figure 47). Outcomes are relatively uncertain as there were only 19 patients in the dataset, however,

the majority of patients experienced outcomes early within the dataset in line with clinical expert advice.

Figure 47: Curves fitted to PPS for 4L patients in the UK RWE all risk population



Abbreviations: RWE, real world evidence; UK, United Kingdom

The lognormal curve was selected as the most appropriate for BSC based on consistency the conditional survival probabilities from the expert elicitation exercise, it should be noted, however, that there is little difference between the fitted curves due to the maturity of the data (Table 69). The exponential curve was tested in scenario analysis as a more pessimistic option and the best statistical fit.

Table 69: BSC curve selection in the UK RWE

	Exp	Wei	Gomp	LogN	Logl	G	GG
Clinical validity hazards	✓	✗	✓	✓	✓	✗	✓
Consistency expert elicitation	✓	✓	~	~	✓	✓	✓
Consistency with external data+	NA						
Statistical goodness of fit*	✓	✓	✓	✓	✓	✓	✓
Visual inspection	✓	✓	✓	✓	✓	✓	✓

Abbreviations: BSC, best supportive care; Exp, exponential; G, gamma; GG, generalised gamma; Gomp, Gompertz; LogN, log normal; Logl, loglogistic; RWE, real world evidence; UK, United Kingdom; Wei, Weibull

*AIC within 5 of best fitting curve, underlined curve best statistical fit

+ Expert elicitation values for evero at 4th line: mean 25.1% at 3 years (17%, 34%) conditional survival between 3 and 5 years 36.3% (19%, 52%) conditional survival between 5 and 10 years 37.2% (13%, 56%)

Final selected curves

Table 70: Final selected curves for suni using the UK RWE

	All risk population		Int/poor risk population		Favourable risk population	
	Curve selection	**Rationale**	**Curve selection**	**Rationale**	**Curve selection**	**Rationale**
TTD	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. Consistent with CheckMate 214 data Consistent with PFS	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Consistent with PFS Consistent with all risk population	Base case: loglogistic Scenarios: generalised gamma	Good statistical and visual fit. All curves provide similar AUC Consistent with PFS Consistent with all risk population
PFS	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. Broadly consistent with external data	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Broadly consistent with external data and expert elicitation Consistent with all risk population	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Broadly consistent with external data and expert elicitation Consistent with all risk population
TTP	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. Consistency with PFS selection	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Consistency with PFS selection Consistent with all risk population	Base case: loglogistic Scenarios: Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Consistency with PFS selection Consistent with all risk population
OS	Base case: exponential Scenarios: Weibull	Good statistical and visual fit Midrange estimate within plausible curves	Base case: exponential Scenarios: Weibull	Good statistical and visual fit Consistent with all risk population	Base case: Exponential Scenarios: Weibull	Good statistical and visual fit Midrange estimate Consistent with all risk population

	All risk population		Int/poor risk population		Favourable risk population	
	Curve selection	**Rationale**	**Curve selection**	**Rationale**	**Curve selection**	**Rationale**
PPS	Base case: lognormal Scenarios: exponential	All curves similar AUC due to completeness of KM Most consistent with expert elicitation Note Kaplan Meier based on 19 patients	NA	NA	NA	NA

Abbreviations: AUC, area under the curve; KM, Kaplan, Meier; NA, not applicable; OS, overall survival; PFS, progression free survival; TA, technology appraisal

4.3.5.2. Calculation of relative treatment effectiveness

Treatment effectiveness for all other therapies has been calculated by applying the results of the NMAs conducted by the EAG in the base case. In scenario analysis we explore the impact of using individually fitted curves to the cabozantinib + nivolumab trial data when using the trial only scenario analysis.

Table 71 provides a summary of where relative effectiveness has been taken from for each of treatments for each endpoint. For first line treatments in the model base case the FP NMA is used where this is available except in the case of pem+lenv where the FP NMA produced implausible results; moreover, PFS curves in intermediate/poor risk are not available for this treatment.. It is acknowledged that use of the PH NMA will bias towards pem+lenv as the CLEAR trial demonstrated non-proportional hazards (curves coming together), the extent of bias is, however, expected to be mitigated by the application of treatment-effectiveness waning in the model base case. For 2nd line and 3rd line treatments we use the PH NMA in preference to the FP NMA due to the sparsity of the available network and extreme results within the fitted models, and our view that the PH NMA likely reflects a more reliable estimate of relative effectiveness. We assume equivalence of sunitinib, pazopanib and tivozanib in the model base case as none of these treatments were available in the FP NMA and tivozanib was not available for OS in the PH NMA. This is in line with prior appraisals which concluded that:

- Pazopanib and sunitinib have similar effectiveness (TA858, TA645)
- Tivozanib is at best similar to pazopanib and sunitinib (TA858, TA645)

In the base case we use the NMA results for everolimus and axitinib, we tested in scenario the assumption that everolimus and axitinib have similar effectiveness (TA432, TA417).

Table 71: Base case application of relative effectiveness in the economic model

	TTD	**PFS**	**TTP**	**OS**
1L				
Cabo+nivo	Rel. effect = PFS	FP NMA	Rel. effect = PFS	FP NMA
Nivo+ipi	Rel. effect = PFS	FP NMA	Rel. effect = PFS	FP NMA
Pem+lenv	Rel. effect = PFS	PH NMA¥	Rel. effect = PFS	PH NMA¥
Ave+axi	Rel. effect = PFS	FP NMA	Rel. effect = PFS	PH NMA
Suni	Reference	Reference	Reference	Reference
Pazo	Equal to suni*	Equal to suni+	Equal to suni*	Equal to suni+

	TTD	**PFS**	**TTP**	**OS**
Tivo	Equal to suni*	Equal to suni+	Equal to suni*	Equal to suni*
Cabo	Rel. effect = PFS	FP NMA	Rel. effect = PFS	FP NMA
2L& 3L				
Nivo	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Pazo	HR to PFS	Equal to tivo*	Rel. effect = PFS	Equal to tivo*
Tivo	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Suni	HR to PFS	Equal to tivo*	Rel. effect = PFS	Equal to tivo*
Cabo	HR to PFS	Reference	Reference	Reference
Lenv+evero	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Evero	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Axi	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA

Abbreviations: HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazards; TTD, time to discontinuation; TTP, time to progression; rel. effect; relative effectiveness

*Data not available in either NMA

+ PH NMA available but not used in base case

¥ FP NMA only available for the all risk population for PFS, PH NMA used due to the FP NMA producing implausible results, this is likely to bias towards pem+lenv

For TTD and TTP where we do not have NMAs conducted due to the sparsity of data in the base case we assume that the PFS hazard ratio for 1st line applies to TTD and TTP as discussed previously. We use the same method for TTP at 2nd and 3rd line. For later lines for TTD as data were not available in the UK RWE we use the hazard ratio between TTD and PFS calculated at 1st line for all treatments:

- TTD HR to PFS: 1.19 (1.15, 1.24)

For 4th line outcomes we apply the hazard ratio between pooled 3rd and 4th line outcomes calculated from the UK RWE to all treatments and then calculate TTP based upon its relationship to PFS at earlier lines.

- 4th line OS HR 2.01 (1.45, 2.78)
- 4th line PFS HR 1.74 (1.21, 2.51)
- TTP HR to PFS: 0.82 (0.80, 0.84)

4.3.5.3. Treatment effectiveness waning

Following application of NMA results we considered the plausibility of the long-term treatment effect predicted for each of the treatments relative to the reference treatment. The application of treatment effect waning assumptions for IO/TKI and IO/IO combinations was considered for each treatment based upon:

- How long the treatment is given for
- The mechanism of action of the treatment and biological plausibility informed by clinical expert advice
- The trends seen within the trials (Figures 30 and 31) and the fitted FP NMA models (see Section 3.7.3)
- Consistency between treatments with similar mechanisms of action
- Precedent in prior appraisals

Precedent was used to guide considerations. Table 72 demonstrates that within RCC, as in many other oncology indications, Committee concerns regarding uncertainty in long-term treatment effects in earlier submissions led to modelling of scenarios around TE waning in later submissions and assumptions becoming part of the base case where stopping rules for treatments were in place, follow-up was particularly short or OS curves crossed. We would note, however, that even in TA858 where follow-up was longer and stopping rules did not apply the Committee considered exclusion of TE waning from the EAG base case to be uncertain.

Looking firstly at cabozantinib + nivolumab the hazard plots supplied by Ipsen in response to clarification questions A21 (44-month datacut) indicate that [redacted]. A similar trend is not seen for PFS.

When looking at the information available across IO / TKI combinations (Figures 30 and 31) the longest-term data available is for pembrolizumab + axitinib (median 67.2 months) which is not recommended in England. Here a clear trend can be seen for OS of increasing hazard ratios (hazard ratios getting closer to 1) with later datacuts and the OS Kaplan Meier appears to be starting to converge with the sunitinib arm at the latest times (acknowledging relatively low numbers at risk). A similar pattern of increasing OS hazard ratios and convergence of Kaplan Meier's can be seen over time for pembrolizumab + lenvatinib for which the latest datacut has a median follow-up of 49.8 months. For PFS the same convergence cannot be seen in the pembrolizumab + axitinib data. In the pembrolizumab + lenvatinib data there is some indicates

of the curves starting to converge and the HR per datacut has seen a small increase over time for cabozantinib + nivolumab (0.51 to 0.59 from first to latest datacut) and pembrolizumab + lenvatinib (0.41 to 0.47).

For nivolumab + ipilimumab there is no clear trend in the HRs by datacut for either OS or PFS and there is no evidence of Kaplan Meier curves coming together for either OS or PFS in the latest datacut (67.7 months).

Input from clinical experts was that IO / TKI combinations would be expected to act similarly in terms of the durability of long-term relative effectiveness compared to TKI monotherapy.

A recent podcast[229] following considerable discussion regarding the latest results released at ASCO summarises well the lack of agreement within the clinical community on the long-term effectiveness of IO/TKI combinations. There are essentially two schools of thought:

- The OS curves coming together is expected and similar to what was observed for IO/BRAF combinations in melanoma. This could be due to initial responses being TKI driven, benefit being lost when TKIs are stopped and/or combining IOs and TKIs being unhelpful in terms of getting the best immune response due to the toxicity of the TKI component precenting the best results being achieved by the IO component
- The OS curves coming together is an artefact of low numbers at risk.

One thing is clear, the most recent datacuts have added to, rather than reduced, uncertainty regarding the long-term effectiveness of IO / TKI combinations.

Our FP NMA shows that with the models selected for the base case there is an upward trend in the hazard ratios for the IO / TKI combinations for OS. This is not the case for PFS with the exception of pembrolizumab + lenvatinib.

All of the IO / TKI combinations in the decision problem for cabozantinib + nivolumab have a stopping rule in place for the IO component, whereas there is no stopping rule in place for nivolumab maintenance within the nivolumab + ipilimumab component.

Given that stopping rules are in place and more mature datacuts have added uncertainty to the durability of the long -term effect for IO / TKIs the EAG base case applies treatment effect waning at 5 years to all IO / TKI combinations based on hazards, all endpoints. Five years was selected as the longest timepoint at which data is available for 1st line combinations with a

reasonable number at risk remaining. IO / TKI combinations are assumed to wane towards the reference curve (sunitinib).

The following scenarios are tested within the EAG analysis:

- Waning applied at 10 years to all IO / TKI combinations based on hazards, all endpoints
- Waning applied at 10 years to all IO combinations based on hazards, all endpoints
- Waning applied between five and 20 years to all IO / TKI combinations based on hazards, all endpoints
- Waning applied between five and 20 years to all IO combinations based on hazards, all endpoints
- No treatment effect waning

These scenarios are all more optimistic than the base case due to the maturity of the available data and difficulties modelling a direct impact on OS in a state transition framework where OS is driven instead by the mix of subsequent therapies.

The following additional scenarios are applied when presenting the PartSA:

- Waning applied to OS only at five years to all IO / TKI combinations based on hazards
- Pessimistic scenario: waning applied between four and six years to all IO/TKI combinations based on absolute survival for OS only, this is based on the timing of convergence of the OS curves for pembrolizumab + lenvatinib and pembrolizumab + axitinib.

The latter scenario represents the worst-case scenario if the fears around IO/TKI lack of long-term durability of effect discussed at ASCO 2023 play out.

Treatment effect waning has not been applied for 2nd line and later treatments as mature data exists for CheckMate 025 (median 87.7 months) where there is no indication of convergence of the Kaplan Meier curves and the majority of other treatments included in the network have the same mechanism of action as the reference treatment.

In order to avoid implausible results in cases where the hazards were higher with the intervention prior to the application of treatment effect waning we retain the original hazards rather than lowering them to match the reference curve.

Table 72: Precedent from prior appraisals on treatment effect waning

TA	Treatment type	Stopping rule prior to progression?	OS follow-up	Committee considerations on TE waning
TA858	IO+TKI	No	Median 33 months	Excluded from EAG base case, Committee considered uncertain
TA780	IO+IO	Ipi only given during first 4 cycles	Min 60 months	Death hazards between arms would be likely to equalise, probably between 4.5 and 21 years
TA650	IO+TKI	Yes	Median 13 months	5 year TE waning (also looked at 3 and 10 years) regardless of response
TA645	IO+TKI	No	Min 13 months	Excluded after removal of stopping rule, Committee request presented TE over time
TA542	TKI	No	Median 29 months OS curves crossed	Modelling should assume that there is no treatment effect beyond the observed survival data, which covered a duration of less than 4 years. EAG base case 5 year TE waning accepted
TA498	TKI+mTOR	No	> Median 25 months*	Lifetime treatment effect in EAG base case. Committee would have liked to have seen more conservative assumptions explored
TA463	TKI	No	Median 21 months	Assuming the effect of cabo continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain
TA417	IO	No	Median 17 – 18 months	Committee remained concerned that the company assumed a continual post-treatment benefit of nivo and had not presented to the Committee analyses that excluded this benefit

Abbreviations: EAG, external assessment group; IO, immunotherapy; OS, overall survival; mTOR, mammalian target of rapamycin inhibitor; TE, treatment effect; TKI, tyrosine kinase inhibitor

Notes:
*Follow-up only reported for Dec 2014 data-cut, July 2015 data-cut used in model

4.3.5.4. Accounting for general population mortality

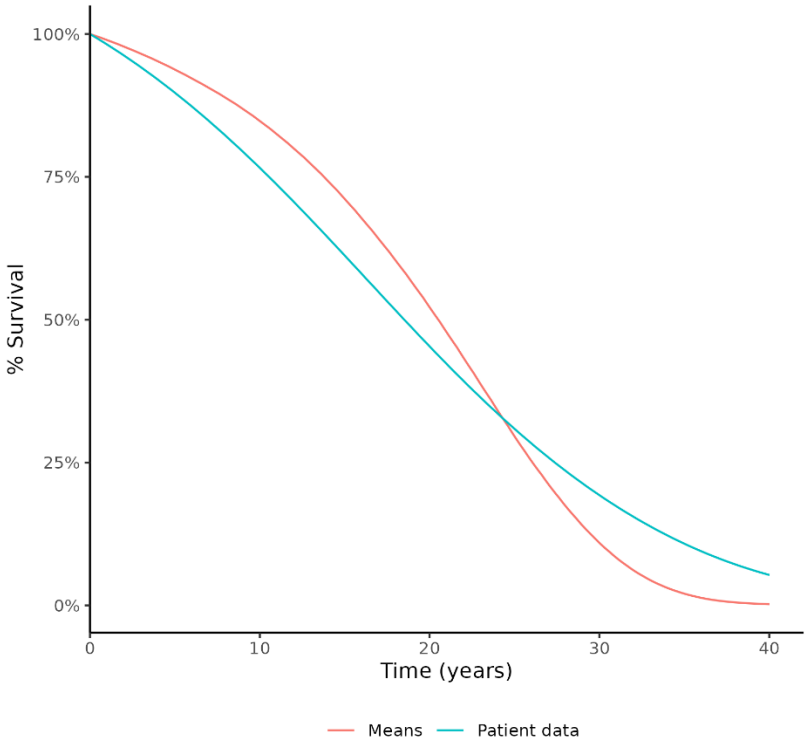
In addition to the base check that the predicted survivor function for OS does not exceed that of the general population we ensure that the hazard function for OS does not fall below that of the general population for any of the modelled cycles.

As the EAG does not have access to cause-specific death data survival curves we have used a simple method (selection of the maximum hazard function for any time period) to account for any issue of patients with RCC being projected to live longer than those in the general population with the same age and sex mix at baseline. Other alternatives such as the relative survival models described in TSD21 require cause specific mortality data.

ONS life tables[230] were used to calculate mortality for the general population with age and sex data for patients at the start of treatment taken from UK RWE if possible. Data were used from 2017-2019 as 2018-2020 values were affected by COVID. We model mortality separately by sex accounting for the differences in life expectancy by gender.

Figure 48 shows the expected general population mortality for people with an age and sex profile matching the 1st line all risk population in the UK RWE. This demonstrates that a maximum time horizon of 40 years is appropriate and the difference that the method for calculation of general population mortality makes. Using the full age and sex demographics produces a steeper drop at the beginning of the curve and a longer tail than assuming all patients have the same mean age.

Figure 48: Expected general population survival: age and sex matched to the UK RWE



4.3.5.5. Adjustment for curves crossing

Whilst every effort has been made to ensure that curves do not cross during survival curve selection this may be unavoidable for outcomes where curves are close together (e.g. TTP and PFS). In these cases, we adjust curves such that PFS <= TTP and PFS <= OS to remove any logical inconsistency. We had initially considered applying a restriction that TTD <= PFS, however, as some patients in the dataset continued to receive treatment beyond progression this was not considered appropriate.

4.3.5.6. Calculation of final outcomes by first line treatment

Within the state transition analysis first the survival curves are calculated for each treatment available in practice at each line included within the model. Health state occupancy is then calculated for each possible treatment sequence. Possible treatment sequences were defined by the following rules which were tested with clinical experts (see Appendix M):

- Ave+axi1L in any risk
- Cabo+nivo 1L in any risk

- Suni 1L in any risk
- Pazo 1L in any risk
- Tivo 1L in any risk
- Nivo+ipi 1L in intermediate/poor risk only
- Pem+lenv1L in intermediate/poor risk only
- Cabo 1L in intermediate/poor risk only
- Nivo+ipi, pem+lenv, ave+axi, cabo+nivo and nivo cannot be used if an IO was used in the last 12 months in the adjuvant setting
- Only one of nivo+ipi, pem+lenv, ave+axi, cabo+nivo and nivo within the treatment pathway
- Axi, cabo, lenv+evero, suni, tivo, evero, pazo, nivo can all be used 2nd and 3rd line
- Axi and evero can be used 4th line
- Lenv+evero can only be used after one prior anti-VEGF (ave+axi, axi, cabo cabo+nivo, pazo, pem+lenv, suni, tivo)
- Suni, tivo and pazo when 2L+ can only be used after nivo+ipi, pem+lenv, ave+axi and cabo+nivo
- The same treatment cannot be used twice (either as monotherapy or as part of a combination)

Once health state occupancy was calculated for each treatment sequence the expected outcomes given the first-line treatment were calculated by weighting each possible sequence by the percentage of patients expected to receive that sequence (see Section 4.3.8.6). In the base case this was informed by the UK RWE, in scenario analysis use of trial data is tested.

4.3.5.7. Validation

Within the model results and validation addendum which will follow this report we will present the final modelled curves vs Kaplan Meier data and compare outcomes for the restricted mean survival time, including for OS, based upon the aggregation of outcomes for each line of treatment to determine whether the model fit is appropriate. The model curve will then be compared to the projections from other models previously used for NICE STAs in the same decision point.

4.3.5.8. Exploratory analysis looking at the impact of prior adjuvant therapy

Based upon the information provided during expert elicitation the impact of prior adjuvant therapy is expected to be different according to the type of treatment with prior adjuvant therapy expected to negatively impact on outcomes for cabozantinib + nivolumab even after a wait of at

least a year in line with NHS criteria and expected to positively impact on outcomes with sunitinib (as patients who receive adjuvant therapy are scanned more frequently and therefore disease progression is expected to be picked up at an earlier stage). The EAG conducted an exploratory analysis looking at the impact of prior adjuvant treatment based upon the outcomes of the expert elicitation exercise, acknowledging that the number of experts who answered these questions was low (n=2 or 3). This analysis compared the expected survival at the 3-, 5- and 10-year timepoints for each treatment using information from the experts who answered the questions related to adjuvant treatment only. The average hazard ratio across the 3 timepoints available for sunitinib was 0.51 and for cabozantinib plus nivolumab was 1.36 accounting for the conditional survival format of the 5- and 10-year timepoints.

4.3.6. Adverse events

The impact of toxicity on both costs and quality of life has been included within the economic analysis. The impact of toxicity on discontinuation has been addressed through the TTD endpoint and not separately of other types of discontinuation given the data available.

Adverse events rates were taken from data supplied by Ipsen for CheckMate 9ER. The initial data request asked for these to account for cases where there are multiple events rather than just being the number of people experiences a specific type of adverse event. This was not supplied and adverse events were instead presented as is commonly the base according to the number of patients experiencing each type of event. This is not considered to be a major limitation.

The model included G3+ AEs which occur in more than 5% of patients in any trial arm in the model. This aligns with TA858.[38] In addition the following three adverse events were included at any grade on the advice of clinical experts that these were the AEs with most impact on patient quality of life and NHS resources at lower grades:

- Hand foot syndrome
- Diarrhoea
- Fatigue

All three of these were noted as common chronic VEGF toxicities with a large impact on patients.

Reporting of specific adverse events was inconsistent across the literature and producing NMAs per specific AE, given the number of interest, was not considered feasible therefore the following options are presented to capture the impact of toxicity within the model:

5. Base case: NMA relative effects applied to reference treatment (sunitinib (1st line) and everolimus (2nd line-plus)) and trial (CheckMate 9ER[59] and CheckMate025[89]) using EAG NMA for grade 3+ AEs and all grade NMA from the cochrane review[150] for the 3 specified Grade 1-2 AEs namely diarrhoea, fatigue and palmar-plantar erythrodysaesthesia syndrome
6. Scenario analysis: treatment related naïve AE rates for Grade 3+ (in ≥5% of patients) AEs (absolute estimates) from CheckMate 9ER or comparator pivotal trials – this is standard practice in the majority of oncology TAs

No data was available for adverse events from UK RWE for RCC specifically. One publication was identified focussing on safety outcomes for IOs which showed that from 2,125 patient records one third of patients experienced a clinically significant (Grade 3+) immune-related AE.[131] Real-world data from Germany indicated that 32/67 (48%) of patients receiving nivolumab + cabozantinib experienced Grade 3+ AEs.

AE rates per patient per cycle was calculated as: number of patients experiencing any grade or grade 3+ AEs/patient weeks observed (number of patients in the trial multiplied by the treatment duration in the trial). This is likely to underestimate the impact, however, data on the number of events experienced was not available.

AEs may either be applied as a per cycle event rate or as a one-off cost and utility impact at the start of each treatment. Given clinical advice that the majority of AEs occur within the first 6 months the model base case applies impact as a one-off. This is consistent with TA858.

In scenario analysis events were applied per cycle which assumes they are equally likely to occur for the entire duration of treatment as data was not available for the majority of treatments on when AEs occurred. Clinical expert advice was that IO-related toxicities are usually experienced within the first 6 months although late events can occur (but are rarely of major impact) and that TKI-related toxicities are also usually first experienced within the first six months but that cumulative fatigue is a major issue which continues into the longer-term.

These approaches are considered to give a reasonable approximation given that adverse events were not found to be a key model driver in any of the published literature.

The final costs and quality of life impacts for each treatment will be checked with clinical experts to ensure they hold face validity, if the experts indicate issues then scenarios provided by the experts will be considered.

Table 74 presents the rate per patient per week for the reference treatment (sunitinib) and Table 75 presents the relative risk estimates for comparators from the EAG NMA and Cochrane review.

Based on clinical expert advice that the impacts of diarrhoea are different dependent on whether it is IO or TKI induced the rates were split up for this specific adverse event. The rates were split up into IO or TKI induced based on the CheckMate 9ER data (Table 11 of the company evidence submission v2.0 dated 13042023[110]) which indicated 8 G3+ diarrhoea events were considered to be immune-mediated out of 28 events in total and 10 G1/2 diarrhoea events were considered to be immune-mediated related out of 182 events in total. It was assumed that same proportions apply to all IO/TKI combinations, for nivo+ipi and nivo monotherapy all diarrhoea events were 100% IO related and for all other treatments 100% TKI related, as mentioned in the Table 73 below.

Table 73. Diarrhoea events that are IO or TKI related for all treatments

Treatments	Diarrhoea (G3+)		Diarrhoea (G1/2)		Source/Assumption
	IO related (%)	TKI related (%)	IO related (%)	TKI related (%)	
Nivo	100%	0%	100%	0%	Assumed IO related
Cabo+nivo	[redacted]	[redacted]	[redacted]	[redacted]	CheckMate 9ER (company submitted data[110])
Nivo+ipi	100%	0%	100%	0%	Assumed IO related
Lenv+pem	29%	71%	5%	95%	Assumed same as cabo+nivo
Ave+axi	29%	71%	5%	95%	
Pazo	0%	100%	0%	100%	Assumed TKI related
Tivo	0%	100%	0%	100%	Assumed TKI related
Suni	0%	100%	0%	100%	Assumed TKI related
Cabo	0%	100%	0%	100%	Assumed TKI related
Lenv+evero	0%	100%	0%	100%	Assumed TKI related
Evero	0%	100%	0%	100%	Assumed TKI related
Axi	0%	100%	0%	100%	Assumed TKI related

Table 74: Adverse event rates per patient per week (reference treatment)

Adverse events	Suni 1L reference treatment	Evero 2L reference treatment
Grade 3+		
ALT increased	0.0000	0.0000
Anaemia	0.0000	0.0049
Decreased appetite	0.0000	0.0000
Diarrhoea	0.0023	0.0008
Fatigue	0.0009	0.0017
HFS or palmar-plantar syndrome	0.0021	0.0000
Hypertension	0.0031	0.0000
Hypertriglyceridemia	0.0000	0.0031
Hyponatraemia	0.0010	0.0000
Hypophosphatemia	0.0010	0.0000
Increase in lipase	0.0000	0.0000
Increased AST	0.0000	0.0000
Leukopenia	0.0000	0.0000
Lymphopenia	0.0000	0.0000
Nausea	0.0000	0.0000
Neutropenia	0.0000	0.0000
Platelets count decreased	0.0000	0.0000
Proteinuria	0.0000	0.0000
Stomatitis	0.0000	0.0000
Vomiting	0.0000	0.0000
Weight loss	0.0000	0.0000
Specified grade 1/2		
Diarrhoea	0.0107	0.0022
Fatigue	0.0083	0.0345
HFS or palmar-plantar syndrome	0.0087	0.0000

Abbreviations: HFS, Hand-foot syndrome

Table 75. Relative risk estimates (for AEs) from NMA

Treatments	Grade 3+	Source	Specified grade 1/2			
			Diarrhoea	Fatigue	HFS	Source
Sora	0.944	EAG NMA (1L)	1.95	0.62	4.80	Cochrane review (for nivo+ipi within trial relative risk from CheckMate 214 has been used as it is not available in the Cochrane review)
Cabo+nivo	1.238		1.57	0.73	1.00	
Nivo+ipi	0.808		0.52	0.86	0.03	
Lenv+pem	1.316		1.82	0.97	1.04	
Ave+axi	1.082		2.44	0.95	1.33	
Pazo	1.034		1.14	0.63	0.48	
Tivo	0.77		0.60	1.36	0.66	
Cabo	1.134 (1L)		0.92	0.38	1.85	
	1.367 (2L+)	EAG NMA (2L+)				
Lenv+evero	1.601		2.18	1.72	0.74	
Evero	1 (2L+)		0.18	1.79	0.10	
Axi	2.303		3.76	3.76	2.27	
Nivo	0.582		1	0.5	0	

Abbreviations: HFS, Hand-foot syndrome; NMA, network meta-analysis

Note: the Cochrane review assumes that the impact of cabozantinib on AEs is the same across lines of treatment

4.3.7. Utility values

4.3.7.1. Utility values from CheckMate 9ER

HRQoL data were collected in the CheckMate 9ER study using patient-reported outcome (PRO) instruments, including the EQ-5D-3L, EQ-VAS and the National Comprehensive Cancer Network (NCCN) Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19). The company provided the EAG with updated CheckMate 9ER HRQoL data on the 9th of May 2023. Based on this analysis, HRQoL data were available up to week 223, reflecting a longer timeframe than that reported by Cella et al.[122] (2022; median follow-up 23.5 months), which reported change in patient HRQoL from baseline to week 115. The number of patients included in the cabozantinib + nivolumab arm was reported to be n=320 and the number of patients in the sunitinib arm was n=319. EQ-5D data were not published for the most recent datacut at the time of writing.

For patients in the cabozantinib + nivolumab arm EQ-5D-3L data were collected on Day 1 of Week 1 of each 2-week study cycle and at the first two safety follow up visits (approximately 30 days and 100 days after the last nivolumab dose). For sunitinib patients EQ-5D-3L data were collected on Day 1 of Week 1 of each 6-week study cycle and at the first two safety follow up visits (approximately 30 days and 100 days after the last sunitinib dose). The EAG note that the estimation of utility values based on two data points, after stopping treatment with nivolumab (in the cabozantinib + nivolumab arm) and sunitinib introduces uncertainty into the analysis. This uncertainty is further compounded in the cabozantinib + nivolumab arm due to the 24-month stopping rule in place for nivolumab.

Overall, the EQ-5D-3L completion rate within the trial was considered reasonably high (88%). At baseline, 94% and 97% of patients in the cabozantinib + nivolumab arm and the sunitinib arm had completed the EQ-5D-3L respectively. Completion rates across treatment arms (and according to progression status) varied over time. The EAG noted that in the cabozantinib + nivolumab arm there was a marked increase in missing/not completed EQ-5D-3L data from week 179 to week 221, particularly for progressed disease patients. Further information regarding number of patients completing the EQ-5D-3L by health state can be found in Appendix G.

In their analysis of HRQoL data, the company used a mixed model repeated measures (MMRM) approach which included fixed-effect variables i.e. baseline EQ-5D-3L, week number of the visit

and adverse events. Random effects variables included, week number of the visit, adverse events, progression status, and prognostic status. The company's mixed model equation is outlined in Table 76 (for Visit i under patient j).

The company justified the use of a MMRM approach as the same patient needed to complete the questionnaire multiple times throughout the study period and a MMRM accounted for the hierarchical nesting of the data, which allowed for consideration of evolving intra-individual values, longitudinally, thus leading to more robust utility estimates. Whilst the EAG considered the use of a MMRM model to be reasonable, there was some uncertainty surrounding the company's approach to imputing missing values. During clarification the company was asked to comment on why the imputation was used and the exact methods applied. Based on their clarification response, imputation was conducted as some patients did not complete EQ-5D-3L questionnaires at follow up visits, which could introduce statistical bias, exaggerated type 1 error or reduced power. A single mean imputation was not undertaken as this would ignore the nature of hierarchically organised data. Furthermore, the company provided utility values based on a model without imputed estimates. The EAG noted that the utility values estimated without imputed estimates broadly aligned with the utilities based on modelled imputed estimates. The EAG considered the company's approach to be reasonable and noted that the use of imputed estimates did not appear to bias the analysis.

The estimates from the final model predicting EQ-5D-3L change from baseline are outlined in Table 76. The EAG noted several concerns surrounding the company's MMRM approach which include the following.

- Validity of the stepwise backward elimination method for model selection is unclear. Based on the EQ-5D-3L data provided to the EAG on the 9th of May, the company generated 12 models used to predict change in EQ-5D-3L from baseline, each with different fixed and random effects parameters. Based on the company's response to EAG clarification questions, the final model (used to estimate health state utilities) was selected based on the lowest Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The initial model contained a relatively large number of covariates including age, sex, race, first measurement of EQ-5D utility value, treatment group, adverse events, weeks of visit, progression status and prognostic score group. As part of the stepwise backward elimination approach, covariates were removed one by one. Once a covariate was removed, the model was compared to the previous best fitting model. If the model had a lower AIC/BIC than the previous best fitting model, the poorer fitting model was eliminated. Based on this method, the final model selected by the company did not include age, sex, race or treatment as covariates. Based on 'Model 6' provided by the company, age and treatment did not appear to be key determinants in the variability of EQ-5D-3L, suggesting that their exclusion may be reasonable.

- The EAG noted that cross/external validation of the stepwise backward elimination method was not discussed by the company. Other potential limitations including the sensitivity to the order in which the variables were removed were not highlighted. Overall, the EAG considered the methodological rigour of the approach as a means of model selection is associated with uncertainty and the level of uncertainty was not adequately categorised by the company. Furthermore, based on AIC/BIC statistics presented, several models could be considered broadly similar i.e. with less than five deviations in AIC/BIC between them. The company's decision to therefore select the model with the lowest AIC/BIC, whilst rational, is associated with uncertainty as other models could be considered reasonable. Ultimately, for each model generated, the company did not present health state utilities (based on progression status). Therefore, it was not possible to comment on the comparative validity of each model with respect to their generated health state utility values.
- The company provided detail on the MMRM approach used to estimate change in EQ-5D-3L from baseline and also provided summary statistic tables outlining utility by progression status and prognostic status, however the interim step detailing the calculations used to estimate the precise mean utilities was not provided. The company's clarification response to the EAG provided a description of the approach undertaken, however the granular calculations for utility estimation were not provided. This remains an area of uncertainty. The EAGs interpretation of the response provided is that the company use only the week numbers observed within the trial within the prediction of utilities. This is likely to overestimate the utility associated with the entire modelled horizon.

Table 76: Mixed model equation used by the company

Full mixed model equation	Yij = 0.008971 + 0.000003703*Week number of the visit ij+0.01065* AE ij+0.007209* Progression status ij+ 0.002978 * Prognostic status ij+ 0.3884+ (-0.49670) * First measurement of EQ5D-3L index value ij+ (-0.03339) * AE ij + (-0.00021) * Week number of the visit ij + 0.01276
Random effects	0.008971 + 0.000003703*Week number of the visit ij+0.01065* AE ij+0.007209* Progression status ij+ 0.002978 * Prognostic status ij+ 0.3884+
Fixed effects	(-0.49670) * First measurement of EQ5D-3L index value ij+ (-0.03339) * AE ij + (-0.00021) * Week number of the visit ij
Level-1 error variance	+ 0.01276

Utility values estimated by the company from CheckMate 9ER using the MMRM approach are outlined in Table 77. The values are reported according to progression status (progression free or progressed disease) and are based on pooled HRQoL data from the cabozantinib + nivolumab arm and the sunitinib arm of CheckMate 9ER (using the latest data cut provided to the EAG). The EAG noted that utility values for the progression free health state remained relatively high for most subgroups (with the exception of the poor prognostic subgroup) and that for each prognostic subgroup the difference in utility from moving from progression free to progressed disease was relatively minor. Furthermore, utilities for the progression free and progressed disease health states were high relative to those values used in published NICE TAs i.e. 1st line treatments in previously untreated patients (see Section 4.3.7.2).

The company was asked to comment on the face validity of the CheckMate 9ER values relative to those reported within the NICE TAs in Table 24 of the company submission (TA512, TA542, TA581 and TA645). Based on the response provided to the EAG the company were unable to adequately provide a satisfactory explanation, however noted that high utility values were reported in published literature, including Ambavane et al. (2020)[231], Bensimon et al. (2020)[232], McCrea et al. (2018)[164], Haddad et al. (2020)[233] and NICE TA630.[234] The EAG noted these studies to be associated with limitations which prevent the generalisability of values including differences in patient population baseline characteristics, differences in utility estimation methods and lack of robust HRQoL methodology and reporting. Ambavane (2020) report a higher utility than the CheckMate 214 publication despite the authors saying the values are from CheckMate 214, Bensimon (2020) use a time to death approach, McCrea (2018) reports a lack of HRQoL data collection as a limitation of the analysis, Haddad (2020) is in head and neck cancer and TA630 is in NTRK fusion positive tumours.

To further justify the face validity of the CheckMate 9ER utility values study, the company stated that utilities from CheckMate 9ER were supported by the *'rapid and sustained improvement in clinical an HRQoL outcomes'* associated with the mechanism of action of cabozantinib + nivolumab (reference to the MMRM analysis using the median 32.9 month follow up data cut were provided to support this statement). The company also presented time to definitive deterioration data from CheckMate 9ER to support the thesis that cabozantinib + nivolumab reduced the risk of deterioration relative to sunitinib. The EAG noted that whilst cabozantinib + nivolumab resulted in a significant reduction in the risk of deterioration compared to sunitinib using the EQ-5D-3L VAS [HR 0.74 (0.59-0.92)], when the EQ-5D-3L UK utility index was used the difference was non-significant [HR 0.86 (0.70-1.06)]. Additionally, treatment was not selected in the MMRM as a covariate, suggesting that treatment may not meaningfully contribute to the variability of EQ-5D-3L.

The EAG acknowledged the HRQoL data collected and presented in CheckMate 9ER, however, the company's response did not sufficiently postulate why values from the pivotal study were higher than those reported in the majority of other NICE TAs for 1st line treatment of aRCC. Furthermore, based on clinical opinion provided to the EAG, the values from CheckMate 9ER were considered to lack face validity when compared to those reported in other trials including CheckMate 214 and JAVELIN Renal 101. Clinical opinion noted that values from JAVELIN Renal 101 may better reflect patients HRQoL in clinical practice (see Table 78). Additionally, the EAG noted that the utility values estimated from CheckMate 9ER were broadly similar to the

age and sex adjusted EQ-5D-3L values reported by Hernandez Alva et al. (2022), which estimated expected EQ-5D-3L values for UK males and females using the Health Survey England (HSE) 2014 dataset. Baseline utility for males and females aged 61 were estimated to be 0.8476 and 0.8206 respectively, and for males and females aged 62, baseline utility was estimated to be 0.8444 and 0.8165 respectively. Due to the lack of clinical plausibility (and concerns surrounding the MMRM approach), the EAG did not use the company's trial derived utilities in the base case model. However, to test uncertainty, values from CheckMate 9ER have been used in a scenario analysis (see Section 4.3.7.3 for further detail).

Table 77: Utility values from CheckMate 9ER

Risk group	Progression free (mean)	Progressed disease (mean)
ITT	[redacted]	[redacted]
Favourable	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]
Poor	[redacted]	[redacted]
Intermediate and Poor	[redacted]	[redacted]

Abbreviations: ITT, Intention to treat. Utilities were derived from Table 3 in the 'utility and disutility' tab within the company's excel model provided 9th of May 2023. Note: utility values have been marked academic in confidence (AIC) as per the marking within the company submission

4.3.7.2. Literature search and data extraction

A total of 82 studies were identified in the literature containing utility values for people with advanced RCC (1st, 2nd and subsequent lines of therapy). To identify relevant and generalisable utility values for inclusion within the model, a set of prioritisation criteria was established. Based on this criteria, UK and NICE technology appraisals, European and Western (non-European) studies containing utility values (published from 2017 onwards) were considered most relevant for consideration. Using the prioritisation criteria, 34 studies were identified. For the complete list of prioritised studies including rationale for inclusion/exclusion, see the utilities data extraction grid in Appendix D.

- UK studies from 2017 including NICE TAs (n=12)
- Europe (non-UK) studies from 2017 (n=8)
- Western studies from 2017 (non-European) (n=14)

Studies considered for data extraction and inclusion within the decision model were those by Meng et al. (2018)[235], Amdahl et al (2017)[236], Porta et al (2021)[237], Henegan et al. (2022)[238],

Motzer et al (2021)[239], Mouillet et al (2017)[240], Cella et al (2019)[122], Cella et al (2021)[241], Cella et al (2022), Cella et al. (2022)[242], Bedke (2022)[243], Buckley (2019).[244] A summary of results can be found Appendix H). However, these studies were ultimately excluded from consideration due to values not being reported in a manner suitable for model input, the lack of face validity, use of secondary data sources for utility estimates, no direct elicitation from patients and lack of EQ-5D-5L mapping.

Ten published NICE TA's were identified that met the prioritisation criteria (Table 78. The EAG noted that some utility data were not available in the public domain as these were marked as confidential. There was some variability in progression free and progressed utilities across NICE TAs for 1st line treatments (and amongst 2nd line treatments), this appeared to be due to heterogeneity across clinical trials with respect to patient characteristics including risk score. Utilities within these appraisals were presented primarily according to health state/progression status, however in TA650 a time to death (TTD) approach was used. Treatment specific utility values were not commonly used within NICE aRCC appraisals, though this approach was adopted in TA780. In order to be congruent with aRCC TAs submitted to NICE, our model estimates utility based on health state/progression status. Furthermore, NICE TAs were considered as the primary source for utility data for 1st and 2nd line treatments, specifically TA645 and TA498 respectively (see Section 4.3.7.3 for more detail).

Table 78: Utility values in published NICE TAs

TA	Year	Recommendation Population	Intervention	Source of utilities	Utilities
TA858	2023	1L	Pem+lenv	CLEAR trial (EQ-5D-3L)	Redacted
TA830	2022	Adjuvant: increased risk of recurrence after nephrectomy	Pem	KEYNOTE 564 (EQ-5D-5L mapped to EQ-5D-3L)	Disease free: 0.868 PFS (distant metastases): 0.803 PD (distant metastases): 0.772
TA780 (CDF review of TA581)	2022	1L int/poor risk	Nivo+ipi	CheckMate 214 (EQ-5D-3L)	PFS on/off nivo+ipi: 0.793 on and 0.749 off PFS on/off suni: 0.754 on and 0.707 off PPS on/off nivo+ipi: 0.794 on and 0.702 off PPS on/off suni: 0.763 on and 0.707
TA650	2020	1L	Pem+axi	Manufacturer derived utility values from KEYNOTE 426 (EQ-5D-3L). A time to death approach was used in the company's base case.	Redacted NICE noted that use of utilities from KEYNOTE 426 and published literature were acceptable for decision making.
TA645	2020	1L	Ave+axi	JAVELIN Renal 101 (EQ-5D-5L mapped to EQ-5D-3L)	PFS: 0.753 PD: 0.683
TA542	2018	1L int/poor risk	Cabo	TIVO-1(EQ-5D-3L)	PFS: 0.726 PD: 0.649
TA512	2018	1L	Tivo	TIVO-1 (EQ-5D-3L)	PFS: 0.726 PD: 0.649
TA498	2018	2L (1 prior VEGF, ECOG PS 0-1)	Lenv+evero	AXIS (EQ-5D, version unclear)	PFS: 0.69 PD: 0.61
TA463	2017	2L/3L (Prior VEGF)	Cabo	METEOR (EQ-5D-5L)	PFS: 0.817 PD: 0.777
TA432	2017	2L	Evero	Swinburn et al (2010)[245]	SD: 0.795 PD: 0.36

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group Performance Status; EQ-5D-3L, EuroQol five dimension three level; EQ-5D-5L, EuroQol five dimension five level; NICE, National Institute for Health and Care Excellence; PFS, progression free survival; PD, progressed disease; SD, stable disease; TA, technology appraisal; VEGF, vascular endothelial growth factor

4.3.7.3. Utilities used in the model

As noted previously, the most appropriate sources identified for the base case analyses were TA645 for patients treated at 1st line and TA498 for patients treated at 2nd line. We opted to derive utilities from these NICE TAs on the basis that the utilities for 1st and 2nd line demonstrated face validity, were elicited directly from patients using the EQ-5D and were previously assessed and accepted by NICE. In TA645, quality of life data were collected directly from patients in the JAVELIN Renal 101 study using the EQ-5D-5L. Values were then appropriately mapped to the EQ-5D-3L using the Van Hout crosswalk algorithm,[246] resulting in a PFS utility of 0.753 and a PD value of 0.683. These utilities are in broad alignment with the utilities used in TA512 for tivozanib, the off-treatment values in TA780 for nivolumab + ipilimumab (which derived values from CheckMate 214) and TA542 for cabozantinib. Utilities also reflect clinical opinion to the EAG (which noted that JAVELIN Renal 101 appeared to better reflect patient HRQoL in clinical practice). We noted that in TA498, utilities were not collected in the pivotal trial HOPE 205 and that the values used within that appraisal were taken from the AXIS trial (for axitinib), however the EAG and NICE concluded that utilities from AXIS were appropriate for use in the analysis. We noted that PFS utility in TA498 for 2nd line treatment (0.69) was slightly higher than the PD utility reported in TA645 for 1st line treatment (0.683), thus presenting a logical inconsistency. To mitigate this, our analysis therefore assumes that progression free patients at 2nd line will have a utility of 0.683, reflective of progressed 1st line patients.

To estimate the PD utility in 2nd line and subsequent lines, we used the approach outlined in NICE DSU12 guidance,[247] which states that when utility values from cohorts with combined health states are not available*, 'the multiplicative method should be used to combine the data from subgroups with the single health conditions (p.22)'*. In our analysis, the % reduction in utility (from moving from PFS to PD) in TA498 was used applied i.e. 2nd line utility was estimated as follows 0.69/0.683*0.61=0.616. Due to a lack of robust, published utility values for people receiving 3rd line treatment (or later), the same approach was used to estimate PD utility in later lines. Overall, the decision to apply the percentage reduction in utility (in moving from PFS to progressed disease) from TA498 to estimate utility values for progressed disease at 2nd, 3rd and 4th line, was to ensure logical consistency based upon clinical feedback, that is, to ensure patient utility decreases with disease progression.

For 3rd line, the PFS utility value was assumed to be reflective of the progressed disease value for 2nd line patients, that is 0.616. As described previously, to estimate the progressed disease value, we applied the percentage reduction in moving from PFS to progressed in TA498, to the PFS utility value, which resulted in a 3rd line progressed disease utility value of 0.545. For 4th line, the PFS utility value was assumed to be reflective of the progressed disease value for 3rd line patients, that is 0.545. To estimate the progressed disease value we applied the percentage reduction in moving from PFS to progressed disease in TA498, to the PFS utility value, which resulted in a 4th line progressed disease utility value of 0.482. This value is consistent with palliative care utility estimates within oncology submissions to NICE.

For completeness, the EAG sought clinical input on the validity of this approach. Based on clinician input, the application of a similar proportional decrease in quality of life for each later line of treatment (to that between PFS and PD in 2nd line) may be considered somewhat conservative, as there is likely to be a higher proportional decrease on progression after each line of therapy. In order to explore uncertainty surrounding utility values in later lines (3rd and 4th line), the EAG has conducted scenario analysis assuming a higher proportional decrease in quality of life (see below).

Table 79: Utility values used in the model

Line of treatment	Utility	Source
1L	PFS: 0.753 PD: 0.683	JAVELIN Renal 101(TA645[46])
2L	PFS: 0.683 PD: 0.616	PFS utility assumed to reflect PD in 1L. PD value estimated based on % reduction from the AXIS trial (TA498[56])
3L	PFS: 0.616 PD: 0.545	Estimated based on % reduction from the AXIS trial (TA498).Approach follows NICE DSU12 guidance[247])
4L	PFS: 0.545 PD:0.482	Estimated based on % reduction from the AXIS trial (TA498).Approach follows NICE DSU12 guidance[247])

Abbreviations: PFS, Progression free survival; PD, Progressed disease

Due to a lack of published HRQoL data for carers and to be consistent with previous NICE appraisals for advanced RCC, our analysis did not include carer disutility.

Utility values were adjusted for age and sex using the published equation by Ara and Brazier et al (2010)[248] and the Health Survey England (HSE) 2014 dataset, as per Hernandez Alava et al (2022).[249]

Disutility associated with adverse events has been included in the EAG's model. These were derived from HRQoL data collected in the CheckMate 9ER study (received by the EAG on the 9th of May 2023). Adverse events were included as a variable in the company's MMRM model, which was used to estimate the disutility associated with any grade 3-4 adverse event. The mean disutilities associated with Grade 3-4 adverse events are outlined in Table 80. The EAG noted that several adverse events had a positive impact on patient utility which lacked face validity i.e. neutropenia and hypophosphatemia. Data were not available for specific adverse events within TA858 and given the results of the analysis of CheckMate 9ER these events were expected to be of limited impact, therefore we did not include these adverse events in the model.

The EAG noted that several specific adverse events resulted in relatively high disutility, including anaemia, palmar-plantar erythrodysesthesia (hand/foot) syndrome and fatigue. Based on clinical expert opinion to the EAG, treatment related toxicities accumulate over time, particularly fatigue. Patients can experience fatigue either on an immunotherapy (IO) or TKI, however TKI toxicities are chronic and will impact most patients. For completeness, the EAG has conducted two scenario analyses surrounding adverse event disutilities (see Section 4.3.7.4)

The impact for of the 3 key adverse events was presented to Dr Larkin to check its validity. He stated that the information presented showed impact in the wrong ordering which is likely due to sicker patients being unable to complete the relevant questionnaires. He considered that in fact diarrhoea has the greatest impact, followed by HFS and then fatigue. Given this the utility values for fatigue and diarrhoea from CheckMate 9ER were switched around.

Table 80: Modelled disutility associated with adverse events from CheckMate 9ER

	Disutility (Mean)	**Duration (days)**	**Source**
General Grade 3-4 adverse event disutility	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Specific adverse event (Grade 3-4)			
ALT increased	[redacted]	[redacted]	Assumed same as increased lipase (in line with TA858[38])
Anaemia	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
AST increased	[redacted]	[redacted]	Assumed same as increased lipase (in line with TA858[38])
Decreased appetite	[redacted]	[redacted]	Assumed same as fatigue

	Disutility (Mean)	Duration (days)	Source
Diarrhoea	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9 input for fatigue used based on expert advice. IO-induced diarrhoea was assumed to last longer based on clinical expert advice
Fatigue	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9 input for diarrhoea used based on expert advice
Hypertension	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Hypertriglyceridemia	[redacted]	[redacted]	Assumed same as increased lipase (in line with TA858[38])
Hyponatraemia	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Hypophosphatemia	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Lipase increased	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Leukopenia	[redacted]	[redacted]	Assumed same as platelet count decreased (in line with TA858[38])
Lymphopenia	[redacted]	[redacted]	Assumed same as platelet count decreased (in line with TA858[38])
Nausea	[redacted]	[redacted]	Assumed same as fatigue
Neutropenia	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Palmar-plantar erythrodysesthesia syndrome	[redacted]	[redacted]	CheckMate 9ER[59]; clarification response document A9
Platelet count decreased	[redacted]	[redacted]	Assumed same as neutrophil count decreased from CheckMate 9ER[59]; clarification response document A9
Proteinuria	[redacted]	[redacted]	Assumed same as increased lipase (in line with TA858[38])
Stomatitis	[redacted]	[redacted]	Assumed same as fatigue
Vomiting	[redacted]	[redacted]	Assumed same as diarrhoea
Weight loss	[redacted]	[redacted]	Assumed same as fatigue
Grade 1-2			
Diarrhoea	[redacted]	[redacted]	Assumed to have 50% of the impact as at Grade 3-4 based on clinical expert advice
Fatigue	[redacted]	[redacted]	
Palmar-plantar erythrodysesthesia syndrome	[redacted]	[redacted]	

*No disutility (i.e., zero disutility) considered in the EAG model

4.3.7.4. Scenario analyses conducted

Due to uncertainty surrounding health state utilities (particularly for later treatment lines), the EAG plan to conduct the following scenario analyses;

- 1st line: Use utility values from CheckMate 9ER. These values reflect direct trial data.
- All lines: Use CheckMate 9ER utility values for all lines i.e. CheckMate 9ER data used for 1st and 2nd line utility values (and no decrement is applied for 3rd and 4th lines).
- 2nd line onwards: Assume the same PFS and PD utility for 2nd, 3rd and 4th line i.e. PFS utility of 0.68 and PD utility of 0.616. This is a simplifying assumption, however it is useful to see the impact on the ICER when assuming there is no reduction in HRQoL after 2nd line.
- 3rd and 4th line: Assume a higher proportional decrease in HRQoL on progression from 2nd to 3rd line and from 3rd line to 4th line. This is consistent with clinical advice to the EAG. In this scenario, for 3rd line it will be assumed that the decrease in HRQoL associated with moving from PFS to PD will be 10% more than observed in 2nd line. For 4th line, it will be assumed that the decrease in HRQoL associated with moving from PFS to PD will be 20% more than observed in 3rd line.
- Removing the impact of adverse events: Applied to test the impact of adverse events on the ICERs given that there is the potential for some double counting as utility data comes from trials where a proportion of patients will have experienced adverse events.
- Increase adverse event disutilities by 10%. Applied to test the impact of increasing adverse event disutilities on the ICER. Based on clinical input to the EAG patients are likely to experience disutility due to adverse events. This analysis assumes the impact of these disutilities increases by 10%.

4.3.8. Resource use and costs

4.3.8.1. Results from literature search and data extraction

A total of 13 studies were identified in the literature containing cost and resource use data (Section 4.1.1.3, Figure 35) for people with advanced RCC across different lines of therapy (namely 1st, 2nd and subsequent lines), of which there were ten NICE TAs and three published studies. Subsequent data extraction from these studies was performed. All of the identified studies were found to be UK based and adopted an NHS and PSS perspective. The costs included comprised of drug and administration costs, disease management or health state costs based on the healthcare resource utilised and terminal care costs. Some studies also reported adverse event costs and subsequent therapy costs. Resource use frequency was sourced from one of the following sources: clinical trial or its post-hoc analysis, previous NICE technology appraisals or feedback from clinical experts. Unit costs associated with the healthcare resource use were derived from NHS reference costs and Unit costs of Health and Social Care from

PSSRU etc. Summary of cost and resource use information from published studies has been provided in Table 81 and from previous NICE technology appraisals has been provided in Table 82. Detailed data extraction tables are provided in Appendix D.

It can be noted that the source of unit costs, medicine costs and terminal costs were consistent across the published studies as well as the previous NICE technology appraisals. However, the source of resource use frequency was quite varied across the studies. Table 83 in Section 4.3.8.2, therefore compares the different sources for resource use inputs and provides rationale for selecting specific inputs.

Further, in the following sections, the selection of appropriate sources and specific inputs for each type of costs used in the model has also been discussed briefly.

Table 81: Summary of cost and resource use information from published studies

	Amdahl 2017	**Edwards 2018 [NICE TA463]**	**Meng 2018**
Setting/country	UK	UK	England, UK
Intervention	Pazo	For patients who have received previous cytokine therapy (aldesleukin or interferon alfa): axi, sora, suni, BSC For people who have received previous VEGF-targeted therapy: axi, cabo, evero, nivo, suni	Cabo
Comparator	Suni	The interventions listed above compared with each other and BSC	Axi Evero Nivo
Patient population	Treatment-naïve patients with mRCC consistent with that of the COMPARZ trial	Patients with previously treated aRCC who received previous VEGFR-targeted therapy	Adult patients with aRCC following prior VEGFR-targeted therapy
Cohort/Sample size	1,100 (COMPARZ)	Sample size of the included studies ranged from 14 to 362	1,096
Perspective	NHS and PSS	NHS and PSS	NHS and PSS
Price year	2014	2015	2017 (not explicitly stated but assumed, as prices were inflated to 2017)
Currency	GBP	GBP	GBP
Discount rate	3.5%	3.5%	3.5%
Type of costs included	Costs of treatment initiation, medication, and dispensing for pazo and suni Pre-progression follow-up and monitoring, other mRCC-related care associated with pazo and suni treatment during PFS, post-progression supportive care, and in a sensitivity analysis, post-treatment anti-cancer therapy	Drug and administration costs Disease management costs Terminal care costs Adverse events costs and Subsequent therapy costs	Drug and administration costs Disease management/health state costs Terminal care costs and Adverse events costs

	Amdahl 2017	**Edwards 2018 [NICE TA463]**	**Meng 2018**
Source of resource use estimates	HCRU data sourced from post-hoc analysis of COMPARZ trial.[250] Data collected included medical office visits, laboratory visits and tests, home healthcare, hospitalization, urgent care, and medical/surgical procedures.	Previous NICE TAs complemented by expert clinical opinion sought by AG	Source of resource use frequency not reported
Source of unit costs	National Schedule of Reference Costs for 2011–2012,[251] adjusted to 2014 prices using the Consumer Price Index (CPI) for health.[252]	NHS reference costs 2014-15,[253] PSSRU 2015[254]	NHS reference costs 2014-15,[253] PSSRU 2015[254]
Source of medicine costs	List prices of pazo and suni from BNF. For pazo, the list price was adjusted to reflect 12.5% PAS discount[50] and for suni the first treatment cycle (i.e., 28 days of treatment in first 6 weeks) was provided at no cost.[49]	BNF	BNF Dosing and administration schedules from relevant trials, publications, or NICE TAs[58,85,255]
Source of terminal care costs	Terminal care costs not considered	Based on Nuffield Trust report 2014[256]	Based on Nuffield Trust report 2014

Abbreviations: AG, Assessment Group; aRCC, advanced Renal Cell Carcinoma; BNF, British National Formulary; BSC, Best supportive care; GBP, British Pounds; HCRU, Medical Resource Use; NHS, National Health Services; PAS, Patient Access Scheme; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; TA, Technology appraisal; UK, United Kingdom; VEGFR, Vascular Endothelial Growth Factor Receptor;

Table 82: Summary of cost and resource use information from previous NICE technology appraisals

NICE TA #	Year	Patient population	Type of costs included	Source of resource use estimates	Source of unit costs	Source of medicine costs	Source of terminal care costs
TA858	2023	1L int/poor risk, where nivo + ipi would otherwise be offered	Drug costs, Admin and health state costs, AE costs, End of life costs	TA650	PSSRU 2020, NHS reference costs 2019-20	BNF	Based on Nuffield Trust report 2014 inflated to 2019/20 costs
TA830	2022	Adjuvant: increased risk of recurrence after nephrectomy	Drug acquisition costs, administration costs, disease management costs, costs for managing adverse events, subsequent treatment costs and terminal care costs incurred at the end of life	KEYNOTE 564, TA650, clinical expert opinion	PSSRU 2020, NHS reference costs 2019-20	BNF, Dosing from SmPC	Based on Nuffield Trust report 2014 inflated to 2019/20 costs
TA780	2022	1L int/poor risk	Drug costs, Admin and health state costs, AE costs, End of life costs	TA581	Not reported	BNF	Not reported
TA650	2020	1L (not recommended)	Drug acquisition and administration of 1L and subsequent treatments, with adjustment for dose intensity; monitoring and disease management in PF and PD states; treatment of included TEAEs for 1L treatments; and terminal care costs in the last cycle before death	TA542 and clinical expert opinion	PSSRU 2018 and NHS reference costs 2017-18	BNF, dosing from SmPC	Based on Nuffield Trust report 2014 inflated to 2019/20 costs
TA645	2020	1L	Drug costs, Admin and health state costs, AE costs, End of life costs	Aligned with TA581	PSSRU 2018, NHS reference costs 2017-18	BNF	Addicott et al. 2008
TA581	2019	1L int/poor risk	Drug and admin costs, health state costs, subsequent treatment costs and AE costs	TA333 and TA417	PSSRU 2015 and 2017, NHS reference costs 2015-16 and 2016-17	BNF	Based on Nuffield Trust report 2014, inflated to 2016/2017
TA542	2018	1L int/poor risk	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent	Estimated by UK clinicians, aligned with	PSSRU 2016, NHS reference costs 2016-17	BNF	Based on Nuffield Trust report 2014, inflated to 2017

NICE TA #	Year	Patient population	Type of costs included	Source of resource use estimates	Source of unit costs	Source of medicine costs	Source of terminal care costs
			treatment costs and Terminal care costs	TA512 and TA215			
TA512	2018	1L	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs	TA333	PSSRU 2015, NHS reference costs 2015-16	BNF	Not reported
TA498	2018	1 prior VEGF, ECOG 0-1	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs and Terminal care costs	TA333	PSSRU 2015, NHS reference costs 2015-16	BNF	Based on Nuffield Trust report 2014, inflated to 2016
TA463	2017	Prior VEGF	Drug and treatment costs, health state unit costs and resource use, AE costs and resource use, Subsequent treatment costs and Terminal care costs	Estimated by UK clinicians	PSSRU 2015, NHS reference costs 2015-16	BNF	Based on Nuffield Trust report 2014, inflated to 2016
TA432	2017	Prior VEGF	Drug and treatment costs, health state unit costs and resource use, AE costs and Terminal care costs	SLR and economic evaluation, 2008[257]	PSSRU 2015, NHS reference costs 2014-15	BNF	Guest et al. and Coyle et al.

Abbreviations: AE, Adverse events; BNF, British National Formulary; NHS, National Health Services; PSSRU, Personal Social Services Research Unit, SmPC, Summary of Product Characteristics; TA, Technology appraisal.

4.3.8.2. Disease management or health state costs

The quantum of health state resource use (i.e., medical oncologist outpatient consultations, CT scans, blood tests etc.) was found to differ across the included studies. A comparison especially of the consultant outpatient follow-up and CT scans pre- and post-progression between the estimates from previous NICE TAs[38,52,55] which had detailed description of the health care resource use with the individual components broken down and the BMJ and ESMO published RCC guidelines,[42,43] has been presented below in Table 83. As can be seen, a noticeable variation was observed in the resource use frequency within the NICE TAs and when compared to the published guidelines as well. For instance, while the ESMO RCC guideline recommended a consultant follow up visit every 2-4 months, BMJ RCC guideline indicated that it could be best judged by the treating clinician and in the previous NICE TAs the observed frequency of follow up visit ranged from every month to every three months.

Table 83: Comparison of long term follow up frequency across key published studies/NICE TAs and RCC guidelines

Heath state	Resource type	Resource use frequency				
		NICE TA463[55]	**NICE TA542[52] & TA858[38]**	**Edwards 2018[258]**	**BMJ RCC guideline[42]**	**ESMO RCC guideline[43]**
Pre-progression (on and off treatment	Consultant outpatient follow up	0.67 per 4-week cycle (~every 6 weeks)	0.25 per week (~every month)	Every 3 months	Left to judgement of treating clinician	Every 2 to 4 months
	CT scan	0.33 per 4-week cycle (~every 3 months)	0.08 per week (~every 3 months)	Every 3 months	Few monthly intervals	Every 2 to 4 months
Post-progression (off treatment)	Consultant outpatient follow up	Not included*	0.25 per week (~every month)	Not included	Left to judgement of treating clinician	Every 2 to 4 months
	CT scan	Not included*	0.08 per week (~every 3 months)	Not included	Few monthly intervals	Every 2 to 4 months
	GP and specialist nurse visit	1 per 4-week cycle (every month)	Not applicable	20 visits per year (only specialist nurse visit)	Not discussed	Not discussed

Abbreviations: BMJ, British Medical Journal; ESMO, European Society for Medical Oncology; NICE, National Institute of Health and Care Excellence; RCC, Renal Cell Carcinoma, TA, Technology appraisal;

*TA463 was conducted in previously-treated patients at a time where few options were available, therefore post-progression here essentially represents BSC and patients were assumed to be discharged from the oncology.

Note: There was no clear reason reported for why there is a difference in resource use frequency between NICE TA463 and Edwards 2018 (the related EAG monograph), however, it looks likely that the clinical expert opinion to EAG matured over time as Edwards 2018 indicated that estimates based on TA333 and TA417 were complemented by clinical expert opinion to AG (however such a statement was not explicitly available in NICE TA463)

The health state costs and resource use estimates used in the model (Table 84) were based on NICE TA542[52], TA858[38] and Edwards 2018,[258] also complemented by the clinical expert opinion to EAG.

When initiating a new line of treatment patients would have an initial visit with the medical oncologist (including a blood test) and a specialist nurse visit happening alongside. Then a subsequent visit where tolerability to the new treatment would also be assessed (in line with standard practice of a formal medical review to determine tolerability[37]), followed by successive follow up visits. It is to be noted that given the advanced stage of the disease and acknowledging some patients might need to be seen more or less frequently, a monthly follow up until 12 weeks and every 2.5 months beyond 12 weeks based on clinical opinion to EAG was deemed appropriate.

Patients would also receive CT scans every 3 months (which was found to be almost consistent across the included studies) to check for the signs of progression and a routine blood test aligned with the consultant visits. The frequency of consultant follow-up visits, CT scans and blood tests was assumed to be the same across all lines of treatment, as monitoring would broadly remain the same irrespective of the treatment received (consistent with NICE TA858[38]). In addition, patients were assumed to have daily pain medication and regular specialist nurse visits in line with Edwards 2018,[258] however, only during the last line of treatment prior to death. These assumptions were also checked with the clinical experts.

Table 84: Health states resource use and unit costs

Health state	Resource type	Frequency of use (per week)	Unit cost (2022 costs)	Source
Treatment initiation	Consultant outpatient visit (first visit)	1	£206.47	Frequency: NICE TA858 Unit cost: NHS reference costs 2021-22; HRG code WF01B, Clinical oncology - Non-Admitted Face-to-Face Attendance, First
	Specialist nurse visit	1	£53	Frequency: assumed same as consultant visit per clinical opinion to EAG Unit cost: PSSRU 2022,[259] Section 11.2.2 Nurse specialist (Band 6), cost per working hour
	Blood test	1	£2.39	Frequency: NICE TA 858 Unit cost: NHS reference costs 2021-22; HRG code DAPS 03 - Integrated blood services
All lines of treatment, on and off treatment (until 12 weeks)	Consultant outpatient follow up	0.25 (until 12 weeks) 0.1 (beyond 12 weeks)	£164.19	Frequency: NICE TA542, NICE TA858 until 12 weeks; every 2.5 months beyond 12 weeks based on clinical opinion to EAG Unit cost: NHS reference costs 2021-22; HRG code WF01A, Clinical oncology - Non-Admitted Face-to-Face Attendance, Follow up
	CT scan	0.083	£99.88	Frequency: NICE TA542, NICE TA858 Unit cost: NHS reference costs 2021-22; HRG code Outpatient - RD27Z – CT scan of more than three areas
	Specialist nurse visit	0.25	£53	Frequency: assumed to happen in conjunction with consultant visit per clinical opinion to EAG Unit cost: PSSRU 2022,[259] Section 11.2.2 Nurse specialist (Band 6), cost per working hour
	Blood test	0.25	£2.39	Frequency: NICE TA542, NICE TA858 Unit cost: NHS ref costs 2021-22 DAPS03 Integrated blood services
BSC	Consultant outpatient follow up	0.25	£164.19	Frequency: assumed to happen in conjunction with specialist nurse visit based on clinical opinion to EAG Unit cost: NHS reference costs 2021-22; HRG code WF01A, Clinical oncology - Non-Admitted Face-to-Face Attendance, Follow up
	Specialist nurse visit	0.25	£53	Frequency: Based on Edwards 2018 but assumed to be twice as frequent as consultant follow up

Health state	Resource type	Frequency of use (per week)	Unit cost (2022 costs)	Source
				Unit cost: PSSRU 2022,[259] Section 11.2.2 Nurse specialist (Band 6), cost per working hour
	Pain medication	7 (1 mg/ml vial morphine sulphate daily)	£5.78	Frequency: Based on Edwards 2018 Unit cost: BNF; 50mg/50ml vial morphine sulphate solution for infusion

Abbreviations: BNF, British National Formulary; NICE, National Institute of Health and Care Excellence; NHS, National Health Services; PSSRU, Personal Social Services Research Unit; TA, Technology appraisal;

4.3.8.3. End of life costs

End of life or terminal care costs are incurred by all patients dying in the model based on the Nuffield Trust report exploring the cost of care at the end of life.[256] All the previous published studies and the NICE TAs (except TA645) derived terminal care cost from this report (as seen in Table 82).

The cost components of terminal care per the Nuffield Trust report have been given below in Table 85. All costs are presented from an NHS / PSS perspective and were inflated to 2022 costs using the NHS cost inflation indices (NHSCII) from PSSRU.[259] The total estimated cost of terminal care (inflated to 2022) was found to be £8,714.

Table 85: Summary of costs related to end of life or terminal care

Resource type	Resource use frequency*, Mean (SD)	Unit cost per patient (SD, where available)	Source	Total costs (adjusted for inflation)
GP consultation	11.4 (6.2) visits	£42	Resource use frequency: Nuffield Trust report, 2014.[256] [Table 1, Group: Cancer diagnosis] Unit cost: PSSRU 2022,[259] Section 9.4 GP unit costs – patient contact lasting 9.22 minutes, including direct care staff and with qualification costs	£479
District nursing care	7.53 (19.57) hours	£53	Resource use frequency: Nuffield Trust report, 2014. [Table 2, Group: Cancer diagnosis] Unit cost: PSSRU 2022,[259] Section 11.2.2 Nurse specialist (Band 6), cost per working hour	£399
Local authority funded social care	Not available	£444 (£1,484)	Cost: Nuffield Trust report, 2014. [Table 3, Group: Cancer diagnosis; 2010 costs]	£549
Hospital care	Not available	£5,890 (£5,264)	Cost: Nuffield Trust report, 2014. [Table 4, Group: Cancer diagnosis; 2010 costs]	£7,287
Total				£8,714

Abbreviations: GP, General Practitioner; PSSRU, Personal Social Services Research Unit; SD, standard deviation

* number of visits or cost of care in the last 90 days before death

Note: 2010 costs were inflated to 2022 by applying year on year annual % increase on the 2014/15 HCHS index = 293.1 from PSSRU 2017[260] (which resulted in 2022 index = 332.3)

4.3.8.4. Drug and administration costs

A summary of acquisition costs of the treatments considered in the 1st line setting and their respective dosing schedules (as provided in detail in Section 4.3.3), along with the treatments in subsequent lines has been presented in Table 86 below. Please note that the unit costs for each drug were extracted from either the drugs and pharmaceutical electronic market information tool (eMIT) or the British National Formulary (BNF) and the cheapest unit price was used where multiple formulations existed for the same drug. Except for everolimus and sunitinib (for which the costs were derived from eMIT), all other drug costs were sourced from BNF.

The per cycle costs for each drug component were calculated based on the respective dosing regimen/intensities and were applied to proportion of patients remaining on treatment in each model cycle within the modelled time horizon (informed by the TTD curve in the base case and mean number of administrations in the scenario analysis). The dosing regimens are the same across the favourable and intermediate/poor risk subgroups and RDIs are assumed equivalent across subgroups.

Wastage is calculated for IV administered drugs dosed by patient weight with the average number of vials calculated using the method of moments based upon the subset of patients for whom individual patient weights were available within the UK RWE (patients who received nivolumab + ipilimumab). The model base case considers wastage with the assumption of no wastage explored in scenario analysis. Considering wastage increased the cost of nivolumab by 4% and the cost of ipilimumab by 30%. Further, for IV drugs given at a fixed dose missed doses were assumed not to be wasted in the base case based upon expert clinical input that steps are taken to minimise wastage and that either the shelf life is so short that treatments are only prepared when a patient has confirmed attendance (ipilimumab) or remaining vials are reused (other products). For oral treatments, no additional wastage costs were included as costing was done based on packs used.

The model will include confidential PAS and commercial access arrangement discounts (where applicable) as received from NICE with the ICER containing all discounted prices presented in a confidential appendix.

Table 86: Acquisition costs of treatments considered in the economic model

Treatment	Formulation	Size of pack	Dose per unit	Pack price (list price)[261,262]	Confidential discount price (discount %)
Ave	Bavencio® 200 mg/10 ml infusion vials	1 vial	20 mg per ml	£768	See cPAS appendix
Axi	Inlyta® 5 mg tablets	56 tablets	5 mg	£3,517	
Cabo	Cabometyx® 40 mg	30 tablets	20, 40 and 60 mg	£5,143	[redacted]
Evero	Evero 10 mg tablets (generic)	30 tablets	10 mg	£373.48	See cPAS appendix
Ipi	Yervoy® 50mg/10 ml infusion vials	1 vial	5 mg per ml	£3,750	
Lenv	Lenvima® 10 mg capsules	30 capsules	10 mg	£1,437	
Nivo	Opdivo® 100mg/10 ml infusion vials	1 vial	10mg per ml	£1,097	
	Opdivo® 40mg/4 ml infusion vials	1 vial	10 mg per ml	£439	
Pazo	Votrient® 400 mg tablets	30 tablets	400 mg	£1,121	
Pem	Keytruda® 100mg/4 ml infusion vials	1 vial	25 mg per ml	£2,630	
Suni	Suni 50 mg capsules (generic)	28 capsules	50 mg	£1,388.77	
Tivo	Fotivda® 1340 µg capsules	21 capsules	1.34 mg	£2,052	

Abbreviations: mg, milligrams; ml, millilitres; NHS, National Health Service; UK, United Kingdom.

Relative dose intensities from trials and RWE (with RWE considered in base case and trial estimates in scenario) are applied to calculate the actual cost of the treatments consistent with the previous NICE technology appraisals, as provided in Table 87. RWE data was not available for cabozantinib + nivolumab, pembrolizumab + lenvatinib or the IO component within combination therapies; in the scenario using RWE we assume these are the same as the trial information available.

Table 87: Relative dose intensities of treatments considered (trial and RWE)

Drug	Treatment line	Relative dose intensity, % (SE where available)		Trial source/assumption
		Trial	RWE	
Ave+axi	1L advanced	Ave: 91.5 Axi: 89.4	[redacted]	Motzer et al 2019[95]

Drug	Treatment line	Relative dose intensity, % (SE where available)		Trial source/assumption
		Trial	RWE	
Axi	Prior TKI or cytokine (2L)	99	[redacted]	AXIS trial: Rini et al. 2011[85]
Axi	3L	99	[redacted]	Assumed same as 2L
Axi	4L		[redacted]	
Cabo	1L advanced	93.3	[redacted]	CABOSUN Clinical study report (as reported in TA542[52])
Cabo	2L	93.3	[redacted]	Assumed same as 1L
Cabo	3L+	93.3	[redacted]	Assumed same as 1L
Evero	Prior VEGF (2L)	84 (1.1)	[redacted]	METEOR clinical study report (as reported in TA542[52])
Evero	3L	84 (1.1)	[redacted]	Assumed same as 2L
Evero	4L		[redacted]	
Lenv+ evero	Prior VEGF (2L)	Lenv: 70.4 Evero: 89.3	[redacted]	CLEAR trial: Motzer et al 2021[45]
Lenv+ evero	3L	Lenv: 70.4 Evero: 89.3	[redacted]	Assumed same as 2L
Lenv+ pem	1L advanced	Lenv: 69.6 Pem: 62.9 – median number of infusions reported as 22	[redacted]	CLEAR trial: Motzer et al 2021[45]
Nivo	Previously treated (2L)	97.5	[redacted]	CheckMate 025 company submission (as reported in NICE TA463[55])
Nivo	3L	97.5	[redacted]	Assumed same as 2L
Nivo+ cabo	1L advanced	Nivo: [redacted] Cabo: [redacted]	[redacted]	CheckMate 9ER (clarification response; A10a)
Nivo+ ipi	1L advanced	Nivo induction: 79*; Nivo maintenance: [redacted] Ipi: 79*	[redacted]	Motzer et al 2018[90] For nivo, same RDI as cabo+nivo to be assumed for nivo mono maintenance as data not available
Pazo	1L advanced	86	[redacted]	VEG105192 trial (as reported in NICE TA215[50] and TA512[51])
Pazo	2L	86	[redacted]	Assumed same as 1L
Pazo	3L		[redacted]	
Suni	1L	[redacted]	[redacted]	CheckMate 9ER (clarification response; A10a)
Suni	2L	[redacted]	[redacted]	Assumed same as 1L
Suni	3L		[redacted]	

Drug	Treatment line	Relative dose intensity, % (SE where available)		Trial source/assumption
		Trial	RWE	
Tivo	1L advanced	94	[redacted]	TIVO-1 study (as reported in NICE TA512[51])
Tivo	2L	94	[redacted]	Assumed same as 1L
Tivo	3L		[redacted]	

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; NICE, National Institute for Health and Care Excellence; NR, not reported; RDI, relative dose intensity; SE, standard error; TA, technology appraisal; TKI, tyrosine kinas inhibitor

*79% reported to receive all 4 doses of nivolumab and ipilimumab within the induction phase

Different administration modes were used for different drugs depending on route of administration and whether or not the drug is administered jointly based on NICE TA858/TA645, which has been provided below in Table 88, along with the unit costs extracted from NHS reference costs 2021-22.[259]

Table 88: Unit cost of drug administration

Treatments	Administration mode	Unit cost (2022)	Source
Pem, nivo, ave	Simple parenteral Chemotherapy at First Attendance - Outpatient	£207.59	NHS reference costs 2021-22; HRG code: SB12Z
Ipi (for first 4 cycles when nivo is delivered jointly with ipi)	Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance - Outpatient	£440.71	NHS reference costs 2021-22; HRG code: SB14Z
Lenv, suni, pazo, tivo, axi and cabo	Exclusively Oral Chemotherapy (first cycle) + Pharmacist (Band 6) assuming 12 minutes (subsequent cycles)	First cycle: £197.25 + Subsequent cycles: £11	First Cycle: NHS reference costs 2021-22; HRG code: SB11Z – Deliver exclusively oral chemotherapy. Subsequent cycles: PSSRU 2022. Pharmacist time based on NICE TA645.

Abbreviations: HRG, Healthcare resource group; IV, intravenous; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TA, technology appraisal
Note: 2020-21 costs were inflated to 2022 using NHSCII annual % increase on previous year index (2.72%) from PSSRU 2022[259]

4.3.8.5. Adverse event costs

AE management costs have been calculated using the unit costs per event and the rate of AEs for each treatment under consideration (for the two options explained in Section 4.3.6).

Table 89 presents the costs per event of all the adverse events considered per the two options/data sources mentioned in Section 4.3.6, incorporating the clinical opinion to EAG, in line with NICE TA858[38] and the unit costs derived from NHS reference costs 2021-22[263].

Table 90 presents the average cost and QALY decrement of Grade 3+ and specified grade 1/2 AEs for each treatment considered in the base case based on RWE. Please note that the similar table for the trial scenario has been presented along with the AE rates from trials in Appendix O. The disutilities associated with the AEs considered have been provided and described in Section 4.3.7.3.

Table 90 was presented to Dr Larkin for comment. He noted that he would have expected tivozanib and axitinib to be more similar given their similar mechanism of action. The ordering of the TKI monotherapies was as expected. Given this a scenario analysis has been included setting the impact of axitinib on adverse events to the same as tivozanib. Dr Larkin also noted that he would have expected similar treatments to be more closely grouped together particularly TKI monotherapy and lenvatinib + everolimus with more AEs than monotherapy and the IO+TKIs with nivolumab monotherapy and nivolumab + ipilimumab expected to be different. This does appear to be the case when looking at the total cost of managing AEs but and QALY impact, but this sensible grouping is not seen when looking at per cycle impacts which validates the choice to use one-off cost and QALY impacts in the base case.

Noting previous clinical advice that the impact of AEs has often been underestimated in previous appraisals, scenario analysis is also presented doubling this impact.

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Table 89: Adverse event costs per event

AEs	Cost per event (2022 costs)[263]	Assumptions
Grade 3+		
Anaemia	£655.75	Weighted average SA04G-L. Iron Deficiency Anaemia, Non-elective stay + nurse (GP practice) cost per hour
Decreased appetite	£0.00	Assumption
Diarrhoea (TKI induced)	£827.18	Based on clinical opinion to EAG: Weighted average FD10E-H Non-Malignant Gastrointestinal Tract Disorders without Interventions, non-elective short-stay
Diarrhoea (IO induced)	£4,321.12	Based on clinical opinion to EAG: Weighted average FD10E-H Non-Malignant Gastrointestinal Tract Disorders without Interventions, non-elective long-stay
Fatigue	£662.61	Based on clinical opinion to EAG: 3*Consultant led medical oncology service: service code 370 (blood test cost not included as it is already included in resource use)
Hypertension	£424.60	EB04Z. Non-elective short stay.
Hypertriglyceridemia	£0.00	Assumed to be zero as regular blood test already considered in health state costs; in line with TA542[52]
Hyponatraemia	£574.71	Weighted average KC05G-N, Fluid or electrolyte disorders, non-elective short stay
Hypophosphatemia	£0.00	Assumed to be zero as regular blood test already considered in health state costs; in line with TA542[52]
Increased ALT	£0.00	Assumed to be zero as regular blood test already considered in health state costs; in line with TA542[52]
Increased AST	£0.00	Assumed to be zero as regular blood test already considered in health state costs; in line with TA542[52]
Increased lipase	£655.75	Assumed to be the same as anaemia (per TA645)[46]
Leukopenia	£0.00	Assumed to be zero as regular blood test already considered in health state costs; in line with TA542[52]
Lymphopenia or lymphocytopenia	£679.97	Weighted average of SA35A-E Agranulocytosis. Non-elective short stay + nurse (GP practice) cost per hour
Nausea/vomiting	£801.11	Non-elective short stay unit cost assumed.
Neutropenia	£655.75	Assumed same cost as anaemia (as per TA645)[46]
HFS or Palmar-plantar syndrome	£621.43	Based on clinical opinion to EAG: 50% of patients are admitted to a general medical word for a short stay, the other 50% see their oncologist (~2 x appointments)
Platelet count decreased	£801.11	Non-elective short stay unit cost assumed (as per TA498)[56]
Proteinuria	£220.87	Consultant led medical oncology service: service code 370 (as per TA542[52])
Stomatitis	£801.11	Assumed same as weight decreased cost
Weight decreased	£801.11	Non-elective short stay unit cost (as per TA645)

AEs	Cost per event (2022 costs)[263]	Assumptions
Grade 1/2		
Diarrhoea	£220.87	Based on clinical opinion to EAG: Outpatient appointment + blood test to rule out infection (blood test cost not included as it is already included in resource use)
Fatigue	£441.74	Based on clinical opinion to EAG: 2*Consultant led medical oncology service: service code 370 + blood test (blood test cost not included as it is already included in resource use)
HFS or palmar-plantar syndrome	£441.74	Based on clinical opinion to EAG: 2*Consultant led medical oncology service: service code 370

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFS, Hand-foot syndrome; TA, technology appraisal

Table 90: Total AE (grade 3+ and grade 1/2) costs (base case)

Treatment	AE costs (per cycle)	AE costs (one-off)	QALY decrement (one-off)
Cabo+nivo	£11.89	£1,126.81	-0.003
Nivo+ipi	£9.75	£334.76	-0.029
Nivo	£6.74	£161.13	-0.006
Lenv+pem	£14.36	£1,061.75	-0.027
Ave + axi	£17.91	£1,035.51	-0.028
Pazo	£14.71	£511.61	-0.013
Tivo	£14.50	£407.94	-0.007
Suni	£15.60	£603.81	-0.013
Cabo (1L)	£20.28	£731.83	-0.017
Cabo (2L)	£20.61	£743.65	-0.025
Lenv+evero	£28.53	£942.87	-0.004
Evero	£20.69	£332.88	-0.038
Axi	£58.72	£1,634.23	-0.017

Abbreviations: AE, Adverse events

4.3.8.6. Subsequent treatment costs

Given different pathways are possible following and conditional upon 1st line treatments received in aRCC treatment landscape, relevant subsequent treatment costs need to be considered upon progression and subsequent treatment discontinuation. Within the state transition analysis subsequent treatment costs are applied to patients on treatment per line of therapy dependent upon the sequence being calculated. Within the PartSA analysis subsequent treatments are applied as a one-off cost on progression based on the mean duration of subsequent treatment.

Two relevant data sources were considered for calculating the subsequent treatment costs:

1. Costs based on subsequent treatments as observed in RWE (see Section 3.5) and
2. Costs based on subsequent treatments from CheckMate 9ER or other relevant comparator pivotal trials (Appendix N)

The UK RWE is used for subsequent systemic therapies in the model base case (Table 92) to better reflect clinical practice with the distribution of subsequent treatments observed in the trials will be explored as a scenario analysis. When analysing the UK RWE treatments which are not available via routine commissioning as illustrated in the treatment pathway diagram (Figure 6) were not included. It is to be noted that the subsequent radiotherapy and surgery costs were also considered (as given in Table 91 below) following progression and added as a one-off cost with frequencies based on data from CheckMate 9ER as data was not available from the UK RWE. Pooled rates from both arms were used as the proportion of patients receiving subsequent radiotherapy and subsequent surgery was similar.

The following assumptions were made to inform the subsequent treatment proportions and durations. The same drug and administration costs were used as described in Section 4.3.8.4.

Assumptions common to both RWE and trial:

- The type of subsequent treatment was assumed to be independent of the 1st line risk group and only dependent on the prior treatments received. Analysis of real-world evidence stratifying the contingency table of treatment types at first and second line (excluding types only available for intermediate/poor risk groups at first line, i.e. IO/IO combination) suggested that this was a reasonable assumption, with no evidence of

interaction between risk group and type of second-line treatment conditional on first-line treatment (p=0.88).

- Subsequent treatment proportions were set to zero for nivolumab after an IO had already been used in line with UK clinical practice for all subsequent lines
- Subsequent treatments after pazopanib and sunitinib were assumed to be the same as tivozanib for 3rd line as data was too sparse to estimate separately
- All subsequent treatment proportions were adjusted based on BSC proportions sourced from RWE and CheckMate 9ER (as it was otherwise unavailable in the trial-based scenario).
- Where the final percentages calculated did not sum to 100% either due to rounding errors, patients receiving sequences that did not follow UK practice or data indicating patients received the same treatment twice patients were reallocated equally between all sequences that involved an active 2nd line systemic treatment.
- Where data were not available for the duration of subsequent treatments from one source data from the alternative source was used (for instance where mean treatment duration was not available from trials, mean duration from the RWE was used instead) – this only impacts scenario analysis using the PartSA model

Table 91: Subsequent radiotherapy and surgery costs following progression

	Unit Cost (£)	Number of sessions	Proportion of patients receiving (all risk)*	Source/Assumptions
Subsequent radiotherapy	£255.51	2	[redacted]	Based on clinical input to the EAG the main uses are palliation for painful mets (particularly bone mets), gamma knife for brain mets or SBRT for oligometastatic disease to postpone resistance to therapy with the last two uses being more expensive but rarer. Most patients require 2 treatments for palliative radiotherapy with SBRT requiring 5 treatments. BMJ guidance[264] states that palliative radiotherapy is inexpensive and generally given at a low dose using a linear accelerator and that it takes around 15 minutes. The cost code selected was aligned to this guidance. SC31Z - Deliver a Fraction of Adaptive Radiotherapy on a Megavoltage Machine; NHS reference costs 2021-22; outpatient
Subsequent surgery	£5,393.26	1	[redacted]	Clinical expert advice was that there are a large number of types of surgery possible. The key types which occur following start of systemic treatment are lobectomy or pneumonectomy if single / two sites in lung nodules, fixation for symptoms for bone fracture in bones or for excisions for single site for bone mets (radical approach), stents to optimise kidneys and occasionally resection for brain metastases, In some cases nephrectomy is deferred until after the patient has started systemic therapy and is used in patients who respond well to systemic therapy to gain better disease free survival figures. Average of weighted costs of HRG codes selected as broadly representative: LB06J-M and DA17P-R (based on clinical opinion to EAG); NHS reference costs 2021-22; elective inpatient

***** Denominator is the number of patients receiving a 2nd line treatment

Table 92: Subsequent treatment proportions from the UK RWE

1L treatments	Subsequent 2L treatments, %							
	Axi	**Cabo**	Lenv+evero	**Nivo**	**Pazo**	**Suni**	**Tivo**	**BSC**
Ave+axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1L treatments	Subsequent 2L treatments, %							
	Axi	Cabo	Lenv+evero	Nivo	Pazo	Suni	Tivo	BSC
Cabo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivo+ipi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabo+nivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenv+pem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suni	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2L treatments	Subsequent 3L treatments, %								
	Axi	Cabo	Lenv+evero	Evero	Nivo	Pazo	Suni	Tivo	BSC
Axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenv+evero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suni	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tivo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3L treatments	Subsequent 4L treatments, %		
	Axi	Evero	BSC
Axi	[redacted]	[redacted]	[redacted]
Cabo	[redacted]	[redacted]	[redacted]
Lenv+evero	[redacted]	[redacted]	[redacted]
Nivo	[redacted]	[redacted]	[redacted]
Suni	[redacted]	[redacted]	[redacted]
Tivo*	[redacted]	[redacted]	[redacted]
Pazo*	[redacted]	[redacted]	[redacted]

Abbreviations: Axi, axitinib; Cabo, cabozantinib; Evero, everolimus; Len, Lenvatinib; Nivo, nivolumab; Pazo, pazopanib; RWE, real world evidence; Suni, sunitinib; Tivo, tivozanib; UK, United Kingdom

*Assumed equal to sunitinib as no 4th line treatments were observed after tivozanib in the dataset

Table 93. Subsequent treatment costs (base case using RWE at list price)

Population	1L treatment	Average one-off drug cost weighted by sub txt prop and mean duration of treatments (PartSA scenario only)	Average one-off admin cost weighted by sub txt prop and mean duration of treatments (PartSA scenario only)
All/fav risk	**Cabo+nivo***	£29,506.35	£650.95
	Ave+axi	£34,024.80	£647.70
	Pazo	£51,823.32	£4,310.21
	Tivo	£54,225.21	£5,122.24
	Suni	£51,333.18	£4,409.59
Int/poor risk	**Cabo+nivo***	£29,506.35	£650.95
	Nivo+ipi	£26,619.16	£750.26
	Pem+lenv	£33,784.61	£663.48
	Ave+axi	£34,024.80	£647.70
	Pazo	£51,823.32	£4,310.21
	Tivo	£54,225.21	£5,122.24
	Suni	£51,333.18	£4,409.59
	Cabo	£47,280.42	£5,836.59

Abbreviations: Axi, axitinib; Cabo, cabozantinib; Evero, everolimus; Len, Lenvatinib; Nivo, nivolumab; Pazo, pazopanib; Suni, sunitinib; Tivo, tivozanib; fav, favourable; int, intermediate

*Cabo+nivo subsequent treatment costs were found to be lower as none of the treatment sequences starting with cabo+nivo in 1L, included nivo or cabo in the subsequent lines for which the drug costs and the treatment duration in subsequent lines were relatively higher

4.3.9. Severity

The NICE manual is unclear as to how current practice should be defined in a multi-comparator decision space such as is present here for calculation of the severity modifier. There are three clear options to define current practice in these circumstances:

- Define a common reference treatment to calculate severity modifiers for all other treatments compared to this
- Calculate the severity modifier based upon the market shares of all the comparators
- Calculate severity modifiers separately for pairwise comparisons

Use of pairwise comparisons, whilst being the simplest option, is inconsistent with the principle of fully incremental analysis. Use of market shares would also be inconsistent with the principle of fully incremental analysis. Therefore, in the EAG base case absolute and proportional shortfall are calculated using a common reference treatment for the overall population and each risk subgroup with QALY weightings assigned based upon NICE's severity modifiers (Table 94). The reference treatment to which cabozantinib + nivolumab is compared is the treatment with the largest absolute QALYs which is not ruled out via the rules of dominance / extended dominance within incremental analysis. The EAG consider this to represent current best practice in the absence for formal NICE guidance. Pairwise analysis will be presented in addition.

Table 94: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Abbreviations: QALY, quality-adjusted life-year

The future health lost by people living with RCC was calculated using age and sex data taken from the UK RWE on an individual patient level to preserve correlations. ONS life tables (2018 – 2020)[230] were used to calculate future life expectancy for the general population and the HSE 2014 dataset to calculate future quality of life for the general population.[249] QALYs for the general population were discounted at a rate of 3.5%, consistent with modelled QALYs for RCC treatments.

Modelled discounted QALYs for the reference treatment were then be used to calculate absolute and proportional QALY shortfall amounts and the relevant QALY modifier to apply.

4.3.10. Uncertainty

Base case analyses will be probabilistic as this generates expected outcomes and costs and is in line with the NICE manual.[74] Additional scenario and one-way sensitivity analyses have been conducted where they add value and clarity.

Table 95: List of scenario analyses conducted

Parameter	Base case	Scenario	Justification
Model structure			
Overall structure	State transition 4 lines	PartSA	Most frequently used structure in prior submissions
		State transition 3 lines	Last line at which there is good sample size in the UK RWE
		State transition 2 lines	Matches number of lines available from CheckMate 9ER
Discount rate	3.5%	0%	NICE manual 2022
		6%	NICE manual 2022
Primary data source			
Data source for baseline risk and patient characteristics	UK RWE, state transition model	Trial-based analyses, state transition model	Testing impact of use of trial data rather than RWE for patient characteristics, baseline risk and subs therapy
	UK RWE, state transition model	Trial-based analyses, PartSA	Testing interaction with model structure
Population characteristics			
Data source	UK RWE	CheckMate 9ER	Testing impact of patient characteristics alone
Use means or IPD	IPD	Mean	Testing impact of use of individual patient characteristics preserving correlation between age and sex vs means
Effectiveness			
Baseline risk	UK RWE	CheckMate 9ER	Testing impact of baseline risk
Preferred 1st line NMA	FP NMA	PH NMA	Testing impact of NMA used
Preferred 2nd line NMA	PH NMA	FP NMA	Testing impact of NMA used
Preferred NMA for pem+lenv	PH NMA	FP NMA	Testing impact of NMA used
Method used to adjust crossing curves	Hazards	Survivor function	No guidance available for preferred method
Assume pazo equal to suni	Yes	No	

Parameter	Base case	Scenario	Justification
Assume tivo equal to suni	Yes	No	Testing impact of relaxing equivalency assumptions from prior TAs
Assume evero equal to axi	No	Yes	
Time on treatment data taken from	TTD	PFS	TTD data are sparse, testing use of PFS which is available for all treatments but less accurate
	Relative effectiveness for nivo + ipi from PFS consistent with other treatments	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	TTD Kaplan Meier supplied by the company indicates a different relationship between TTD and PFS than for other treatments
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints, based on hazards	10 years for IO/TKIs, all endpoints, based on hazards	Considerable uncertainty around long-term relative effectiveness
		10 years all IO combinations, all endpoints, based on hazards	
		Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	
		Between 5 and 20 years all IO combinations, all endpoints, based on hazards	
		No treatment effect waning	
		PartSA: 5 years for IO/TKIs, OS only, based on hazards	
		Between 4 and 6 years for IO/TKIs, OS only, based on absolute survival	
Survival curve selections			
All risk population			
Sunitinib RWE 1L			
PFS	Log-logistic	Weibull	Good statistical and visual fit. Broadly consistent with external data.
TTD	Log-logistic	Weibull	Good statistical and visual fit. Consistent with CheckMate 214 data Consistent with PFS
TTP	Log-logistic	Weibull	Good statistical and visual fit. Consistency with PFS selection.
OS	Exponential	Weibull	Good statistical and visual fit.

Parameter	Base case	Scenario	Justification
			Midrange estimates within plausible curves.
Cabozantinib RWE 2L			
PFS	Log-logistic	Generalised gamma, Weibull	Good statistical and visual fit. Consistent across lines.
TTP	Log-normal	Weibull	Best statistical and clear best visual fit. Consistent across lines.
OS	Log-logistic	Weibull	Good statistical and visual fit. Consistent across lines.
Cabozantinib RWE 3L			
PFS	Log-logistic	Generalised gamma, Weibull	Good statistical and visual fit. Consistent across lines.
TTP	Log-normal	Log-logistic, Generalised gamma	Good statistical and visual fit. Consistent across lines
OS	Log-logistic	Weibull	Good statistical and visual fit. Consistent across lines.
BSC			
4th line PPS pooled	Log-normal	Exponential	All curves provide similar AUC due to completeness of KM data. Consistency with expert elicitation Note Kaplan Meier based on 19 patients
Intermediate/poor risk population			
PFS	Log-logistic	Weibull, Log-normal	Good statistical and visual fit. All feasible curves provide similar AUC Broadly consistent with external data and expert elicitation Consistent with all risk population
TTD	Log-logistic	Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Consistent with PFS Consistent with all risk population
TTP	Log-logistic	Weibull	Good statistical and visual fit. All feasible curves provide similar AUC. Consistency with PFS selection. Consistent with all risk population.
OS	Exponential	Weibull	Good statistical and visual fit. Consistent with all risk population.
Favourable risk population			

Parameter	Base case	Scenario	Justification
PFS	Log-logistic	Weibull	Good statistical and visual fit. All feasible curves provide similar AUC Broadly consistent with external data and expert elicitation Consistent with all risk population
TTD	Log-logistic	Generalised gamma	Good statistical and visual fit. All curves provide similar AUC. Consistent with PFS. Consistent with all risk population
TTP	Log-logistic	Weibull	Good statistical and visual fit. All feasible curves provide similar AUC. Consistency with PFS selection. Consistent with all risk population.
OS	Exponential	Weibull	Good statistical and visual fit. Midrange estimate. Consistent with all risk population.
Costs			
Number of administrations for fixed duration treatments based on	TTD	Mean number of administrations	Testing impact of using trial data on mean duration where available
RDI	Applied	Not applied	Data taken from numerous sources and uncertain whether or not IV therapies missed still incur a cost
Utilities			
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	CheckMate 9ER for 1L	CheckMate 9ER utilities higher than literature
		CheckMate 9ER for all lines	Fully aligned to trial utilities but these are higher than literature
		Same PFS and PD from 2L onwards	Data uncertain after 2L
		Higher proportional decrease for 3L and 4L	Decrease after 3L unclear
Utilities for BSC	Assumed same as progressed: current line	Assumed same as progression free: current line	Testing impact of alternative utilities for BSC
		Assume same as final health state	
Adverse events			

Parameter	Base case	Scenario	Justification
Data source used for AEs	NMA	Individual trials	Exploring impact of assuming same relative effectiveness for all G3+ AEs
AEs applied	One off	Per cycle	Exploring impact on how AE rates change over time
AE disutilities not considered	Yes	No	Potential for double counting in trial data sources
Scale of impact	Per analysis	Doubled	Clinical advice that AE impacts were underestimated in prior appraisals
Axitinib	Per NMA	Set the same as tivozanib	The NMA is based upon a small low-quality trial and clinical advice was that tivozanib and axitinib would be expected to have a similar safety profile given their similar MoA
Subsequent treatments			
Data source	RWE	Trial	Testing impact of subs therapy assumptions

Abbreviations: FP, fractional polynomial; MoA, mechanism of action; NMA, network meta-analysis; PARTSA, partitioned survival analysis; PH, proportional hazards; PFS, progression free survival; RDI, relative dosing intensity; RWE, real world evidence; TA, technology appraisal; TTD, time to discontinuation; UK, United Kingdom

5. COST-EFFECTIVENESS RESULTS

5.1. Model validation and face validity check

Within the model results and validation addendum which will follow this report, model outputs will be compared to the data used as model inputs (for example visual comparison to Kaplan Meier data) to ensure the appropriateness of model structure and data derivation. The model will then be compared to the projections from other models previously used for NICE STAs in the same decision point. Clinical expert input will be used to ensure that the model retains clinical face validity.

5.2. Benefits not captured in the QALY calculation

The only potential benefit identified that could not be included within the QALY calculation, is the potential benefit of cabozantinib within the combination for patients with bone metastases which was raised by one of the experts consulted. Literature, however, is conflicting as to whether or not there may be additional benefit in this subgroup.[265-267]

6. DISCUSSION AND CONCLUSIONS

6.1. Discussion

The major considerations identified for this appraisal include:

- Modelling methods, and outcomes of the cost-effectiveness analyses of various combinations, vary across the available literature including within prior NICE TAs. This underlines the benefit of a common modelling framework as far as practicable to enable consistency of decision making using the best available data at the time.
- Comparators for cabozantinib + nivolumab differ by risk status (combination therapies are only available outside of the CDF for intermediate / poor risk), which necessitates comparison by risk status; data for favourable risk patients is less well reported but what is available demonstrates that risk group is a potential treatment-effect modifier for IO/TKI combinations.
- Earlier treatment options affect what is available at later lines and may also impact on outcomes at later lines; data to be able to model the latter impact appears to be limited and prior appraisals have failed to meet Committee preferences to use UK data for the type of subsequent therapy received and to match costs and effectiveness.
- The outcomes demonstrated with RCTs showed greater absolute benefit than those demonstrated in SACT in a previous appraisal, indicating that use of RCT data for baseline risk may lead to an overestimate of benefit for treatments. This was also the case when comparing the RWE identified by the EAG in this pilot to the trials.
- The assumption of proportional hazards may not hold within RCC, but fractional polynomial NMAs pose additional challenges relating to estimability.
- Relatedly, the duration of treatment effect for newer combination treatments is uncertain, and evidence from a range of trials suggests ‘slippage’ in OS and PFS estimates with longer follow-up, particularly for IO/TKI combinations.
- NMAs broadly suggest that cabozantinib and nivolumab is an effective treatment in first line, but for intermediate and poor risk patients specific, long-term benefits against other treatments (including cabozantinib monotherapy) are less clear.
- NMAs at second line are challenged by difficulties linking networks to include all treatments.
- Sparseness of networks precluded exploration of key effect modifiers, though the EAG regarded that NMAs were feasible.
- There remain outstanding questions about the relevance of evidence across histologies, and the role of adjuvant pembrolizumab in impacting first-line treatment effectiveness.
- Our general modelling approach represents a shift from partitioned survival models to state transition models, though we preserve functionality for partitioned survival models. This ‘return’ to state transition models is necessary in order to have the flexibility to meet NICE’s objective to create a model capable of looking at the entire treatment pathway, though it also adds additional challenges in obtaining appropriate data and ensuring the plausibility of predictions of OS.

6.2. Conclusions for the cabozantinib + nivolumab appraisal

- In relation to the decision problem, the EAG disagreed on the full range of appropriate comparators, the relevance of time to next treatment, and the importance of risk group-specific analyses.
- The EAG noted a number of potential issues with respect to generalisability of the trial, including high rates of treatment after progression, over-optimistic estimates of OS and PFS compared to real-world evidence, low numbers of UK patients and low use of nivolumab after sunitinib, but was satisfied that the trial presented evidence of effectiveness of cabozantinib plus nivolumab as compared to sunitinib across key outcomes.
- Within the trial, there is evidence of modification by risk group for key outcomes, with systematically lower benefits for OS and PFS seen with more favourable risk.

6.3. Planned further work

- Model results will be provided in a separate addendum following this report
- The following additional work is planned to occur during the technical engagement phase of the cabozantinib + nivolumab appraisal:
  - Internal and external QC of the economic model
- The following additional work is planned to occur during final phases of the pilot after the appraisal of cabozantinib + nivolumab:
  - Review of clinical effectiveness information focussing specifically on sequencing and the impact of previous treatment on effectiveness.
  - Tidy up and genericise the model code for public release.
  - Addition of a Shiny user interface phase prior to public release.
  - Programming and analysis of model outputs related specifically to sequencing.
  - Consideration of how the platform model could be used for alternative decision making frameworks.
  - Release of the open source version of the economic model.

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Appendices

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Treatments for renal cell carcinoma [ID6186]: A Pathways Pilot Appraisal

Appendix Q: List price economic results

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All CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all AIC (academic in confidence) data is highlighted in yellow and underlined

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List of key issues

List of abbreviations

Abs	absolute
AE	Adverse Event
ASCO	American Society Of Clinical Oncology
AUC	Area Under The Curve
BSC	Best Supportive Care
cabo	cabozantinib
CDF	Cancer Drugs Fund
CE	Cost Effectiveness
DSU	Decision Support Unit
EAG	External Assessment Group
EOL	End Of Life
evero	everolimus
fav	favourable
FP	Fractional Polynomial
Gen	general
HFS	Hand Foot Syndrome
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
int	intermediate
IO	Immune-Oncology
IPD	Individual Patient Data
ipi	ipilimumab
IV	Intravenous
KM	Kaplan-Meier
lenv	lenvatinib
LY	Life Year(s)
LYG	Life Year(s) Gained
MRU	Medical Resource Use
NICE	National Institute For Health And Care Excellence
nivo	nivolumab
NMA	Network Meta-Analysis
OS	Overall Survival
PAS	Patient Access Scheme
pazo	pazopanib
PD	Progressed Disease

pem	pembrolizumab
PFS	Progression Free Survival
PH	Proportional Hazards
Pop	population
PPS	Post Progression Survival
Prop	proportional
QALY	Qualiy Adjusted Life Year(s)
QC	Quality check
RCC	Renal cell carcinoma
RDI	Relative Dosing Intensity
RWE	Real World Evidence
SF	shortfall
SOC	Standard of care
suni	sunitinib
TA	Technology appraisal
tivo	tivozanib
TKI	Tyrosine Kinase Inhibitor
TTD	Time To Discontinuation
TTP	Time To Progression
UK	United Kingdom
vs	versus

Appendix Q. Economic evidence

Q.1. Economic evidence key issues

Key Issue 1: Inconsistency between prior appraisals

Report sections	
Description of issue and why the EAG has identified it as important	Previous NICE appraisals for RCC have used a range of modelling methods, leading to challenges in comparing across prior appraisals. This exacerbates decision risk for any one appraisal and has led to some possible inconsistencies in prior decision-making. For example, in TA858, the EAG concluded that the combination of pembrolizumab and lenvatinib was not cost-effective as compared to cabozantinib in the population of patients with intermediate or poor risk; however, a similar conclusion would have been reached for the combination of nivolumab and ipilimumab if it had been appraised at that time. As a result, pembrolizumab and lenvatinib combination therapy is only recommended for patients eligible for nivolumab and ipilimumab combination therapy.
What alternative approach has the EAG suggested?	The EAG has proposed a common modelling framework for RCC based on a state transition model, with additional functionality to explore partitioned survival analysis-based results. This unified modelling framework also permits the exploration of treatment sequences and subsequent treatments given the NICE treatment pathway now includes multiple options and first, second and third lines.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on cost-effectiveness estimates is not with respect to their direction of travel but with respect to decision risk and corresponding uncertainties arising from inconsistencies in modelling methods.

Abbreviations: cabo, cabozantinib; CDF, Cancer Drugs Fund; EAG, External Assessment Group; ipi, ipilimumab; lenv, lenvatinib; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; pem, pembrolizumab; RCC, renal cell carcinoma; TA, technology appraisal

Key Issue 2: Economic implications of trial generalisability to real-world evidence

Report sections	
Description of issue and why the EAG has identified it as important	As a result of access to a robust RWE dataset, the EAG has been able to compare estimates for OS and PFS between trials and data from a UK cohort. Linked to Key Issue 6 in the clinical effectiveness analysis, it is generally the case across most treatments that RWE reflects lower survival than the corresponding trial evidence, though RDIs are also lower in RWE than the corresponding trials. This raises important questions about the generalisability of the trial evidence base as a whole as a suitable basis for understanding expected impacts in the UK population. For example, pembrolizumab + lenvatinib is cost-effective against cabozantinib using the state transition model when trial data is used for effectiveness, patient characteristics and subsequent treatment distribution together. An additional benefit arising from the use of RWE is it is considerably more mature than the corresponding trials, reducing extrapolation uncertainty.
What alternative approach has the EAG suggested?	The EAG has used RWE to parameterize curves for reference treatments in its base case, while maintaining relative treatment effects from corresponding NMAs at each line.
What is the expected effect on the cost-	The expected effect on the cost-effectiveness estimates is that LYs and QALYs will be decreased for most treatments compared to analyses

Report sections	
effectiveness estimates?	using trial baselines. It may also be the case that a different pattern of cost-effectiveness results, possibly suggesting different decisions, would be in evidence using RWE instead of trial evidence.

Abbreviations: EAG, External Assessment Group; LYs, life years; NMA, network meta-analysis; QALYs, quality adjusted life years; RWE, real world evidence; UK, United Kingdom

Key Issue 3: Maturing data relating to IO/TKI combinations have magnified uncertainties relating to their long-term effectiveness

Report sections	
Description of issue and why the EAG has identified it as important	Clinical effectiveness Key Issue 10 highlighted the evolution over time in survival outcomes, particularly for IO/TKI combinations, as well as some evidence of 'slippage' on OS and PFS outcomes. Indeed, there is [redacted] for cabozantinib + nivolumab combination therapy. In the context of the cost-effective analysis, this exacerbates decision risk due to differential follow-up between IO/TKI combinations and generates additional extrapolation uncertainty. The longest-term available data for an IO/TKI combination relate to pembrolizumab + axitinib combination therapy, which is not recommended in England. Slippage in estimated HRs for OS is reflected in a Kaplan-Meier curve that converges with sunitinib at later timepoints. A similar pattern is apparent for pembrolizumab + lenvatinib combination therapy with a data cut at 49.8 months median follow-up, but not for nivolumab + ipilimumab combination therapy. Clinical input suggested that IO/TKI combinations would be expected to reflect similar long-term relative effectiveness as TKI monotherapy. As a result, the long-term effect of IO/TKI combinations remains unclear. Converging survival curves may be due to low numbers at risk, initial response driven by TKIs, loss of benefit when TKIs are stopped, or antagonistic impacts of TKI-related toxicity precluding optimal IO effectiveness.
What alternative approach has the EAG suggested?	The EAG undertook extensive scenario analyses to understand the impact of different long-term effectiveness scenarios.
What is the expected effect on the cost-effectiveness estimates?	As highlighted in clinical effectiveness Key Issue 10, it is likely that cost-effectiveness estimates for novel treatments drawing on comparatively less mature trials may be unduly optimistic. From an economic perspective, additional extrapolation uncertainty may increase decision risk.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; IO, immuno-oncology; OS, overall survival; pem, pembrolizumab; PFS, progression free survival; TA, technology appraisal; TKI, tyrosine kinase inhibitor

Key Issue 4: Impact of RDI and toxicity on economic case

Report sections	
Description of issue and why the EAG has	Toxicity was quantified using standard methods, but the extent and impact of toxicity remains highly uncertain. HRQoL information from company estimates did not pass face validity when scrutinised by clinical

Report sections	
identified it as important	experts, including as relates hand and foot syndrome, diarrhoea, and fatigue; in addition, the EAG implemented a number of adjustments to capture the relative impacts of these three key AEs. Due to selection bias (i.e. the worst off patients being the least able to report impacts), the impact of key AEs is likely to be underestimated. The EAG could not obtain any relevant RWE to inform AE rates or impact. In addition, RDIs appear lower in clinical practice (i.e. based on the RWE) as compared to trials, though these data are not of high quality. The RDI for pembrolizumab plus lenvatinib may be less reliable than for other treatments given it was estimated based on the median number of infusions.
What alternative approach has the EAG suggested?	The EAG explored scenarios relating to doubling AE impacts and examining RDIs from RWE instead of from relevant trials, as well as setting RDI to 100%. All RDI scenarios should be considered to understand the impact of differential quality of estimation and generalizability on cost-effectiveness estimates.
What is the expected effect on the cost-effectiveness estimates?	Increasing AE impacts reduces estimated QALYs from included treatments, whereas lower RDIs reduce treatment costs. Increased impact would be expected to reduce the cost-effectiveness of combination therapies relative to monotherapies. We would welcome additional input from the company during technical engagement on whether the differences in RDI between the different IO/TKIs calculated are realistic and if not alternative suggested inputs. The EAG will also seek additional clinical input on this point during technical engagement.

Abbreviations: AE, adverse event; EAG, External Assessment Group; HFS, hand foot syndrome; HRQoL, health related quality of life; KM, Kaplan-Meier; RDI, relative dosing intensity; RWE, real world evidence

Key Issue 5: Problems with the HRQoL data supplied by the company

Report sections	
Description of issue and why the EAG has identified it as important	HRQoL data supplied by the company did not have face validity with respect to the general population. In addition, HRQoL estimates were higher across health states than for most other appraisals. The EAG also noted a range of methodological problems with the HRQoL estimates, including the justification for model selection approach; a lack of cross-validation or external validation; and a lack of transparency relating to calculation steps between model estimation and mean utilities.
What alternative approach has the EAG suggested?	The EAG base case uses an alternative source considered to have greater face validity. Company estimates were tested in scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	The EAG's base case generates lower QALYs, leading to higher ICERs. However, the impact is relatively limited.

Abbreviations: EAG, External Assessment Group; HRQL, health related quality of life; KM, Kaplan-Meier; QALYs, quality adjusted life years; TA, technology appraisal

Key Issue 6: Outstanding uncertainties in application of severity modifiers

Report sections	
Description of issue and why the EAG has identified it as important	Application of the severity modifier remains unclear for multi-comparator decisions, such as in the current appraisal. The EAG has found that the relevance of the severity modifier depends on whether the comparator is current best practice or pairwise differences are calculated against every other treatment. In addition, the availability of different comparators will impact the estimated QALY shortfall in different risk groups. Comparison to current best practice suggests a proportional shortfall of 0.85 in the all-risk group but not in any of the risk-specific groups, which is counterintuitive. This finding is primarily because of the availability of high-effectiveness comparators in intermediate/poor risk patients, whereas in favourable risk patients, older treatments generate better prognoses; moreover, in all-risk populations, only TKI monotherapies are available via routine commissioning.
What alternative approach has the EAG suggested?	The EAG discusses application of the severity modifier as compared to current best practice as opposed to pairwise, but has not applied the severity modifier. Until more detailed guidance is produced, the method of application of the severity modifier is a key uncertainty.
What is the expected effect on the cost-effectiveness estimates?	Application of a severity modifier will impact the cost-effectiveness threshold in different risk populations and to different degrees.

Abbreviations: EAG, External Assessment Group

Key Issue 7: Impact of model structure on results

Report sections	
Description of issue and why the EAG has identified it as important	The EAG incorporated flexibility to undertake modelling in a state transition framework (EAG base case) or a partitioned survival analysis framework (scenario analysis). Predicted life years and QALYs were generally higher when using a partitioned survival analysis. In particular, differences in the all risk group were between 0.5 and 0.7 life years, with differences more pronounced for TKI monotherapies than for cabozantinib + nivolumab; but differences were even greater (0.9-2.0 life years) in the favourable group, again with more substantial impacts for TKI monotherapies. In the intermediate/poor risk group, differences ranged from -0.03 to 1.3 life years; in this risk group, estimates were similar between modelling approaches with the exception of nivolumab plus ipilimumab due to the use of fractional polynomial NMA results. The fractional polynomial NMA predicted a larger plateau for OS than for PFS; this is consistent with clinical advice received that there may be issues with the assessment of PFS for this particular combination and observation of higher than might be expected post-progression survival in nivolumab plus ipilimumab arm of the CheckMate 214 trial.
What alternative approach has the EAG suggested?	The EAG maintains that while both strategies are appropriate, it is for the committee to prefer one approach to the other. The EAG will explore drivers and plausibility of the two results during technical engagement.
What is the expected effect on the cost-effectiveness estimates?	While differences did not impact the overall result for cabozantinib + nivolumab in the favourable or intermediate/poor risk groups, the EAG notes that this is a point for committee discussion.

Abbreviations: EAG, External Assessment Group; NMA, network meta-analysis; TKI, tyrosine kinase inhibitors

Key Issue 8: Subgroups in the context of changing comparators

Report sections	
Description of issue and why the EAG has identified it as important	Previous NICE recommendations in RCC have been optimized on the basis of risk status, and indeed only TKI monotherapies are available in routine commissioning for patients in the favourable risk group. As noted in clinical effectiveness Key Issues 7 and 9, there is evidence of effect modification by risk group in both CheckMate 9ER and the broader evidence base; however, as regards cabozantinib plus nivolumab, the company's perspective is that this treatment should be principally considered in an all-risk group. The NICE manual notes that there should be clear justification and plausibility for patient subgroup definition; the EAG has received clinical advice that subgroups based on risk are indeed salient for clinical decision-making.
What alternative approach has the EAG suggested?	The EAG has explored the impact of risk groups on cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	The EAG notes that risk group-specific cost-effectiveness results rely on different combinations of comparators than all-risk cost-effectiveness results, and thus may lead to different conclusions about the cost-effectiveness of cabozantinib plus nivolumab by risk group. The all-risk results whilst providing more certainty in the comparison to TKI monotherapies are less relevant for decision making than the favourable risk results as according to best practice guidance TKI monotherapies should not be used in patients who are able to receive combination therapies in the intermediate / poor risk group.

Abbreviations: EAG, External Assessment Group; NMA, network meta-analysis; QALYs, quality adjusted life years; TKI, tyrosine kinase inhibitors

Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population

Report sections	
Description of issue and why the EAG has identified it as important	In cost-effectiveness results for the intermediate/poor risk population, cabozantinib dominates cabozantinib plus nivolumab (and other novel combinations). However, the EAG notes that the underpinning trial for cabozantinib, CABOSUN, included a high dose as part of a monotherapy; and clinical advice to the EAG noted that CABOSUN showed an unusually large effect, a discrepancy noted in previous appraisals (e.g. TA858).
What alternative approach has the EAG suggested?	The EAG notes that this is an area for committee scrutiny.
What is the expected effect on the cost-effectiveness estimates?	The EAG notes that the clinical validity of this specific finding is a point for committee discussion.

Abbreviations: EAG, External Assessment Group; NMA, network meta-analysis; QALYs, quality adjusted life years; TKI, tyrosine kinase inhibitors

Q.2. Economic evidence results

Economic results have been presented deterministically. Probabilistic results will be produced following model QC by the Decision Support Unit (DSU). All results are presented at list price. A cPAS appendix containing results with all PAS's applied has been supplied separately.

Q.2.1. Deterministic base-case results

Table 1 provides the base case results, both as fully incremental analysis and as pairwise analysis.

As would be expected the LYs and QALYs for the three TKI monotherapies are similar (these are set to have the same 1st line effectiveness in the model base case). The results differ slightly as the types of 2nd line therapies used differ across the treatments in line with the UK RWE and the adverse event impacts also differ across treatments. In all three groups pazopanib was associated with the highest QALYs accrued of the three TKI monotherapies with tivozanib accruing the least.

In the favourable risk group cabozantinib + nivolumab has an ICER of £408,449 when compared to the next best non-dominated comparator (pazopanib). Results have a similar structure in the all-risk group (ICER £289,554) which is expected given that this has the same comparator set. As would be expected all three TKI monotherapies had similar costs and QALYs.

In the intermediate / poor risk group cabozantinib + nivolumab is dominated by pembrolizumab + lenvatinib. This is driven both by the higher effectiveness of pembrolizumab + lenvatinib predicted from the proportional hazards NMA (HR = 0.767 (0.562,1.049) vs cabozantinib + nivolumab) and the high drug cost associated with cabozantinib + nivolumab relative to other combination therapies (note analyses presented at list price). In the comparison of pembrolizumab + lenvatinib this is driven primarily by the difference in RDI, the data for which are potentially less reliable than for other treatments, this was flagged as a key issue for consideration during technical engagement and scenario analyses are presented using alternative data supplied by the company in response to technical engagement. Pembrolizumab + lenvatinib is itself not cost-effective in comparison to cabozantinib monotherapy (ICER £130,387.50, pairwise comparison not shown in Table 1), which aligns with the conclusion of TA858. Pazopanib or sunitinib are the most cost-effective treatments given the upper (£30,000) and lower (£20,000) bounds of NICE's threshold respectively.

Table 1: Base-case results (ordered in increasing cost)

	Total			Incremental				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER cabo + nivo vs comparator (£/QALY)**	**ICER incremental (£/QALY)**
All-risk								
Suni	£82,905	2.78	1.67	£0	0.00	0.00	£276,480	£0
Pazo	£83,572	2.84	1.69	£667	0.06	0.03	£289,554	£24,382
Tivo	£102,777	2.76	1.66				£238,496	(dominated)
Cabo + nivo	£236,395	3.71	2.22	£152,823	0.88	0.53		£289,554
Favourable risk								
Suni	£88,737	3.68	2.20	£0	0.00	0.00	£385,505	£0
Pazo	£89,326	3.73	2.23	£589	0.06	0.03	£408,449	£21,236
Tivo	£119,609	3.66	2.19				£315,998	(dominated)
Cabo + nivo	£269,148	4.52	2.67	£179,822	0.78	0.44		£408,449
Intermediate/ poor risk								
Suni	£80,234	2.45	1.46	£0	0.00	0.00	£246,157	£0
Pazo	£80,927	2.50	1.49	£693	0.05	0.03	£257,682	£25,595
Tivo	£95,735	2.43	1.45				£215,749	(dominated)
Nivo + ipi	£123,678	2.09	1.28				£125,189	(dominated)
Cabo	£165,035	3.46	2.07				Cabo+nivo dominated	(ext dominated)
Lenv + pembro	£185,897	3.62	2.23	£104,970	1.12	0.74	Cabo+nivo dominated	£141,169
Cabo + nivo	£214,402	3.36	2.00					(dominated)

Abbreviations: cabo, cabozantinib; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life years gained; n/a, not applicable; nivo, nivolumab; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year(s); suni, sunitinib; tivo, tivozanib

Q.2.2. Qualification for the severity modifier

Table 2 presents the base case calculation of the absolute and proportional QALY shortfall. Cabozantinib + nivolumab does not qualify for a severity modifier using the EAG definition of standard of care as “best practice” i.e. the treatment with the largest absolute QALYs which is not ruled out via the rules of dominance / extended dominance within incremental analysis. In the intermediate/poor risk population a severity modifier would have been applied if tyrosine kinase inhibitor (TKI) monotherapy was used as the standard for comparison. The EAG also note that the proportional shortfall is extremely close to 0.85 in the all-risk population. This result may at first take appear counterintuitive when compared to the key comparator in the subgroups. In both the all-risk and favourable risk groups only TKI monotherapies are available via routine commissioning. In the intermediate/poor risk groups a number of novel combinations are available which increase the expected standard of care (SOC) QALYs. This highlights the importance of consideration of results by risk subgroup.

Table 2: Application of the severity modifier to the base case

Risk	SOC QALYs	Gen pop QALYs	Abs SF	Prop SF	Modifier	Treatment considered SOC
All	1.695	10.382	8.687	0.837	1.0	Pazo
Fav	2.226	10.382	8.156	0.786	1.0	Pazo
Int/poor	2.229	10.382	8.153	0.785	1.0	Pem+lenv
Int/poor	1.485	10.382	8.897	0.857	1.2	Pazo
Int/poor	2.070	10.382	8.312	0.801	1.0	Cabo

Abbreviations: Abs, absolute; cabo, cabozantinib; Fav, favourable; Gen, general; Int, intermediate; lenv, lenvatinib; pazo, pazopanib; pem, pembrolizumab; pop, population; Prop, proportional; QALYs, quality adjusted life years; SF, shortfall; SOC, standard of care

The QALY shortfall-related modifier has not been directly incorporated within the calculations provided given the uncertainty around which, if any, modifier to apply. A modifier of 1.2 equates to a willingness to pay threshold of £24,000 - £36,000 using the standard NICE thresholds.

Q.2.3. Breakdowns by health state and cost category

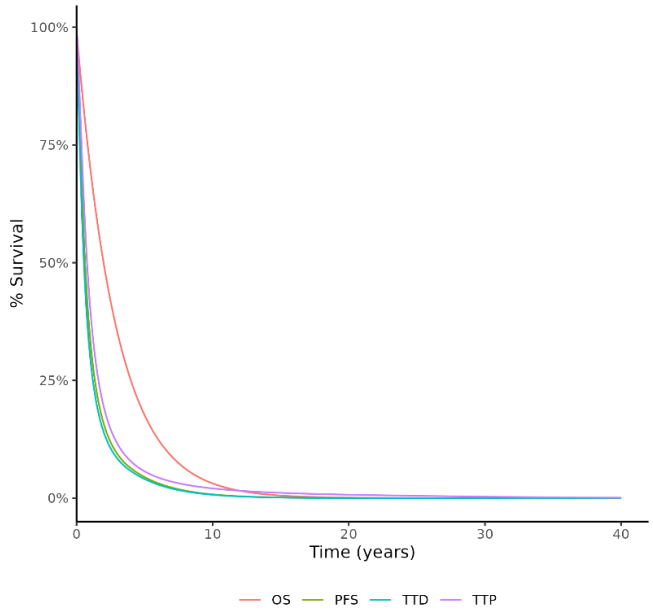
Summary of life years gained by health state is provided for the all-risk population (Table 3), favourable risk population (Table 4), and intermediate/poor risk population (Table 5 cabozantinib + nivolumab vs pembrolizumab + lenvatinib and **Error! Reference source not found.** cabozantinib + nivolumab vs cabozantinib).

Summary of QALYs gained by health state is provided for the all-risk population (Table 6), favourable risk population (Table 7), and intermediate/poor risk population (Table 8 cabozantinib + nivolumab vs pembrolizumab + lenvatinib and **Error! Reference source not found.** cabozantinib + nivolumab vs cabozantinib).

A summary of costs by health state is provided in Table 9 and summary of predicted resource use by category of cost is provided for all risk groups (Table 10), favourable risk group (Table 11), and intermediate/poor risk group (Table 12).

The majority of the time for all treatments is spent in 1st line with relatively few patients making it to the later lines of therapy in line with available RWE data. A relatively high proportion of the time in 1st line treatment is spent off therapy which is driven by the curve selection for TTP. As can be seen in the example below the TTP curve selected has a longer tail than either TTD or PFS and as this drives patients entry to next treatment within the state transition model a relatively long time has been predicted to be spent off treatment in 1st line. Alternative curve selections will be tested in scenario analysis.

Figure 1: Curve selection example for PFS relative to TTP (suni, 1st line, all risk)



Abbreviations: OS, overall survival; PFS, progression free survival; suni, sunitinib; TTD, time to discontinuation; TTP, time to progression

When looking at cost break-downs the majority of the cost incurred for TKI monotherapies was associated with subsequent treatments (nivolumab and cabozantinib in particular) and resource use associated with subsequent treatment. For combination therapies the majority of the costs were incurred upfront as drug costs during 1st line treatment which slightly lower costs for subsequent lines of therapy.

Table 3: Summary of LY gain by health state (all risk, cabo+nivo vs next best non-dominated comparator [pazo])

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.109	0.115	-0.006	0.006	0%
1L: on treatment	1.945	1.144	0.801	0.801	50%
2L: off treatment	0.288	0.158	0.130	0.130	8%
2L: on treatment	0.843	0.541	0.302	0.302	19%
3L: off treatment	0.026	0.109	-0.083	0.083	5%
3L: on treatment	0.142	0.365	-0.223	0.223	14%
4L: off treatment	0.001	0.009	-0.007	0.007	0%
4L: on treatment	0.007	0.054	-0.048	0.048	3%
BSC	0.353	0.341	0.011	0.011	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.715**	**2.837**	**0.878**	**1.611**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; cabo, cabozantinib; LY, life years; nivo, nivolumab; suni, sunitinib; pazo, pazopanib; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 4: Summary of LY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator [pazo])

Health state	LY cabo+nivo (X)	LY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.274	0.266	0.008	0.008	1%
1L: on treatment	2.582	1.828	0.753	0.753	49%
2L: off treatment	0.288	0.164	0.124	0.124	8%
2L: on treatment	0.844	0.562	0.282	0.282	18%
3L: off treatment	0.026	0.113	-0.087	0.087	6%
3L: on treatment	0.142	0.379	-0.237	0.237	15%
4L: off treatment	0.001	0.009	-0.008	0.008	1%
4L: on treatment	0.007	0.056	-0.050	0.050	3%
BSC	0.353	0.355	-0.001	0.001	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**4.517**	**3.733**	**0.784**	**1.549**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; cabo, cabozantinib; LY, life years; nivo, nivolumab; pazo, pazopanib; vs, versus

Table 5: Summary of LY gain by health state (intermediate/poor risk, cabo+nivo vs next best non-dominated comparator [lenv+pem])

Health state	LY cabo+nivo (X)	LY lenv+pem (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.076	0.093	-0.016	0.016	1%
1L: on treatment	1.636	2.289	-0.653	0.653	54%
2L: off treatment	0.285	0.170	0.115	0.115	10%
2L: on treatment	0.834	0.530	0.304	0.304	25%
3L: off treatment	0.026	0.034	-0.008	0.008	1%
3L: on treatment	0.141	0.153	-0.013	0.013	1%
4L: off treatment	0.001	0.008	-0.006	0.006	1%
4L: on treatment	0.007	0.046	-0.039	0.039	3%
BSC	0.349	0.296	0.053	0.053	4%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.356**	**3.618**	**-0.263**	**1.209**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; cabo, cabozantinib; lenv, lenvatinib; LY, life years; nivo, nivolumab; pem, pembrolizumab; suni, sunitinib; vs, versus

Table 6: Summary of QALY gain by health state (all risk, cabo+nivo vs next best non-dominated comparator [pazo])

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.074	0.079	-0.005	0.005	1%
1L: on treatment	1.315	0.790	0.525	0.525	59%
2L: off treatment	0.130	0.082	0.048	0.048	5%
2L: on treatment	0.455	0.322	0.134	0.134	15%
3L: off treatment	0.013	0.048	-0.035	0.035	4%
3L: on treatment	0.064	0.185	-0.121	0.121	14%
4L: off treatment	0.001	0.004	-0.003	0.003	0%
4L: on treatment	0.003	0.021	-0.018	0.018	2%
BSC	0.166	0.164	0.003	0.003	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.223**	**1.695**	**0.528**	**0.892**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; cabo, cabozantinib; nivo, nivolumab; QALYs, quality adjusted life years; pazo, pazopanib; vs, versus

Table 7: Summary of QALY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator [pazo])

Health state	QALY cabo+nivo (X)	QALY pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.177	0.175	0.002	0.002	0%
1L: on treatment	1.670	1.214	0.456	0.456	56%
2L: off treatment	0.128	0.083	0.045	0.045	6%
2L: on treatment	0.448	0.326	0.122	0.122	15%
3L: off treatment	0.013	0.049	-0.036	0.036	4%
3L: on treatment	0.063	0.187	-0.125	0.125	15%
4L: off treatment	0.001	0.004	-0.004	0.004	0%
4L: on treatment	0.003	0.021	-0.018	0.018	2%
BSC	0.164	0.166	-0.002	0.002	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.666**	**2.226**	**0.440**	**0.809**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; cabo, cabozantinib; nivo, nivolumab; pazo, pazopanib; QALYs, quality adjusted life years; vs, versus

Table 8: Summary of QALY gain by health state (intermediate/poor risk, cabo+nivo vs next best non-dominated comparator [pem+lenv])

Health state	QALY cabo+nivo (X)	QALY lenv+pem (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.052	0.062	-0.009	0.009	1%
1L: on treatment	1.117	1.525	-0.409	0.409	61%
2L: off treatment	0.130	0.083	0.047	0.047	7%
2L: on treatment	0.456	0.303	0.153	0.153	23%
3L: off treatment	0.013	0.017	-0.003	0.003	0%
3L: on treatment	0.064	0.073	-0.009	0.009	1%
4L: off treatment	0.001	0.003	-0.003	0.003	0%
4L: on treatment	0.003	0.021	-0.017	0.017	3%
BSC	0.167	0.142	0.025	0.025	4%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.003**	**2.229**	**-0.226**	**0.675**	**100%**

Abbreviations: Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; cabo, cabozantinib; lenv, lenvatinib; nivo, nivolumab; pem, pembrolizumab; QALYs, quality adjusted life years; vs, versus

Table 9: Summary of costs by health state

	1L costs			Subsequent treatment			MRU			
	Drug cost (£)	Admin cost (£)	AE cost (£)	Drug cost (£)	Admin cost (£)	AE cost	1L (£)	Subsequent treatment (£)	EOL cost (£)	Total cost (£)
All risk										
Suni	£6,836	£275	£604	£48,629	£916	£692	£2,628	£14,362	£7,962	£82,905
Pazo	£6,481	£324	£512	£49,665	£903	£688	£2,628	£14,422	£7,949	£83,572
Tivo	£27,787	£336	£408	£47,686	£979	£660	£2,628	£14,328	£7,966	£102,777
Cabo+nivo	£178,438	£3,282	£1,127	£27,651	£261	£920	£4,088	£12,897	£7,732	£236,395
Favourable Risk										
Suni	£10,336	£320	£604	£49,439	£932	£704	£4,058	£14,602	£7,743	£88,737
Pazo	£9,859	£395	£512	£50,491	£919	£699	£4,058	£14,662	£7,730	£89,326
Tivo	£42,269	£413	£408	£48,480	£996	£671	£4,058	£14,567	£7,747	£119,609
Cabo+nivo	£210,511	£3,496	£1,127	£27,240	£257	£907	£5,354	£12,707	£7,549	£269,148
Intermediate/ poor risk										
Suni	£5,443	£258	£604	£48,029	£905	£684	£2,080	£14,185	£8,048	£80,234
Pazo	£5,137	£296	£512	£49,052	£892	£679	£2,080	£14,244	£8,035	£80,927
Tivo	£22,024	£305	£408	£47,097	£967	£652	£2,080	£14,151	£8,052	£95,735
Nivo+ipi	£76,613	£3,045	£335	£20,719	£232	£606	£2,277	£11,714	£8,139	£123,678
Cabo	£98,157	£412	£732	£38,718	£1,026	£671	£3,753	£13,775	£7,791	£165,035
Pem+lenv	£124,634	£1,771	£1,062	£33,511	£241	£732	£4,622	£11,578	£7,745	£185,897
Cabo+nivo	£157,237	£3,024	£1,127	£27,637	£261	£920	£3,487	£12,889	£7,822	£214,402

Abbreviations: admin, administration; AE, adverse event; cabo, cabozantinib; EoL, end of life; ipi, ipilimumab; lenv, lenvatinib; MRU, medical resource use; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib

Table 10: Summary of predicted resource use by category of cost (all risk, cabo+nivo vs next best non-dominated comparator [pazo])

Item	Cost (£) cabo+nivo (X)	Cost (£) pazo (Y)	Increment (£)	Absolute increment (£)	% absolute increment
Drug acquisition cost (1L)	£178,438	£6,481	£171,957	£171,957	85%
Admin cost (1L)	£3,282	£324	£2,958	£2,958	1%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition (2L+)	£27,651	£49,665	£-22,014	£22,014	11%
Admin cost (2L+)	£261	£903	£-643	£643	0%
AE cost (2L+)	£920	£688	£233	£233	0%
MRU 1L	£4,088	£2,628	£1,460	£1,460	1%
MRU 2L+	£12,897	£14,422	£-1,525	£1,525	1%
EoL cost	£7,732	£7,949	£-217	£217	0%
Total	**£236,395**	**£83,572**	**£152,823**	**£201,622**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; cabo, cabozantinib; EoL, end of life; MRU, medical resource use; nivo, nivolumab; pazo, pazopanib; suni, sunitinib

Table 11: Summary of predicted resource use by category of cost (favourable risk, cabo+nivo vs next best non-dominated comparator [pazo])

Item	Cost (£) cabo+nivo (X)	Cost pazo (£) (Y)	Increment (£)	Absolute increment (£)	% absolute increment
Drug acquisition cost (1L)	£210,511	£9,859	£200,652	£200,652	87%
Admin cost (1L)	£3,496	£395	£3,101	£3,101	1%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition (2L+)	£27,240	£50,491	£-23,251	£23,251	10%
Admin cost (2L+)	£257	£919	£-662	£662	0%
AE cost (2L+)	£907	£699	£208	£208	0%
MRU 1L	£5,354	£4,058	£1,296	£1,296	1%
MRU 2L+	£12,707	£14,662	£-1,956	£1,956	1%
EoL cost	£7,549	£7,730	£-181	£181	0%
Total	**£269,148**	**£89,326**	**£179,822**	**£231,921**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; cabo, cabozantinib; EoL, end of life; MRU, medical resource use; nivo, nivolumab; pazo, pazopanib; suni, sunitinib

Table 12: Summary of predicted resource use by category of cost (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator [pem+lenv])

Item	Cost (£) cabo+nivo (X)	Cost pem+lenv (Y)	Increment (£)	Absolute increment (£)	% absolute increment
Drug acquisition cost (1L)	£157,237	£124,634	£32,603	£32,603	77%
Admin cost (1L)	£3,024	£1,771	£1,252	£1,252	3%
AE cost (1L)	£1,127	£1,062	£65	£65	0%
Drug acquisition (2L+)	£27,637	£33,511	£-5,874	£5,874	14%
Admin cost (2L+)	£261	£241	£20	£20	0%
AE cost (2L+)	£920	£732	£187	£187	0%
MRU 1L	£3,487	£4,622	£-1,135	£1,135	3%
MRU 2L+	£12,889	£11,578	£1,311	£1,311	3%
EoL cost	£7,822	£7,745	£76	£76	0%
Total	**£214,402**	**£185,897**	**£28,505**	**£42,525**	**100%**

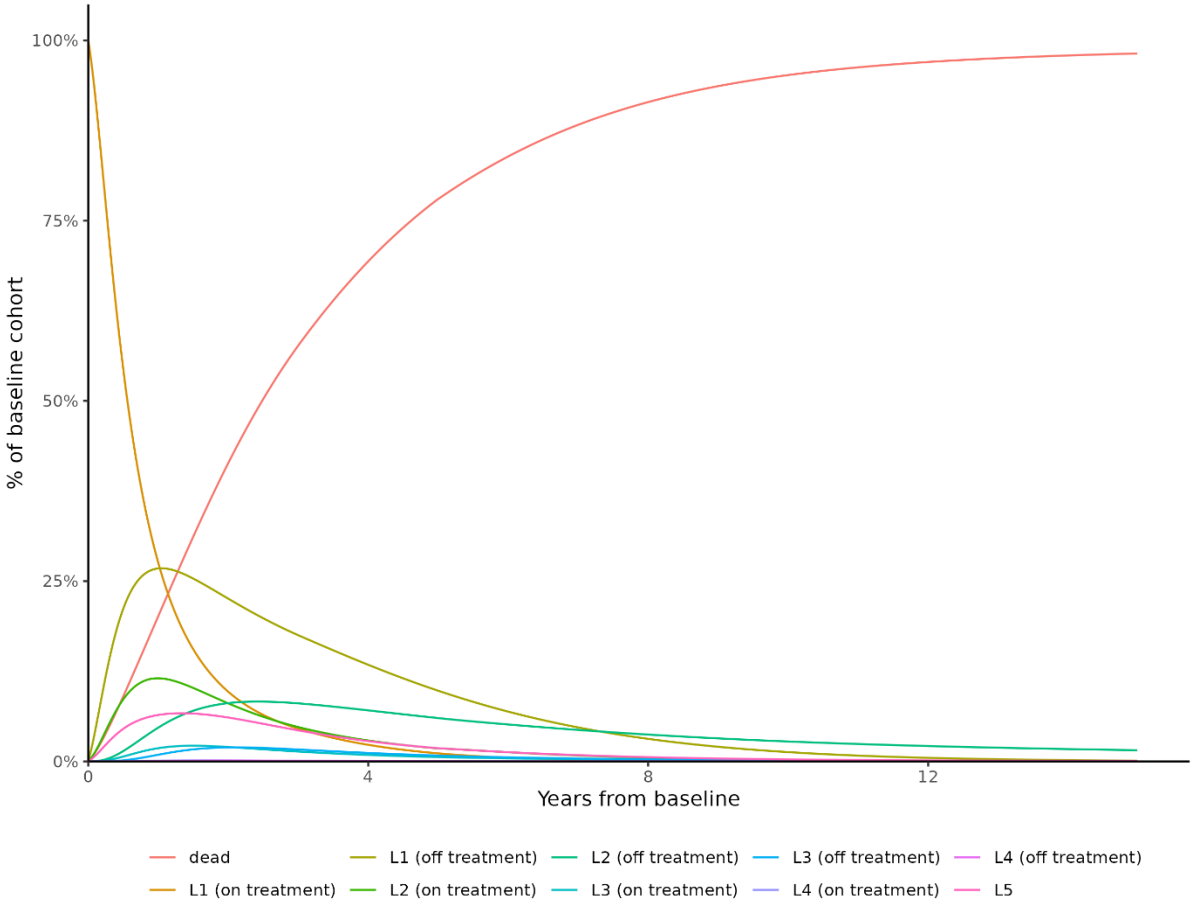
Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; cabo, cabozantinib; EoL, end of life; MRU, medical resource use; nivo, nivolumab; pazo, pazopanib; suni, sunitinib

The Markov trace for all risk groups is provided by treatment in Figure 2 (cabozantinib + nivolumab), Figure 3 (pazopanib), Figure 4 (tivozanib), and Figure 5 (sunitinib).

The Markov trace for the favourable risk group is provided by treatment in Figure 6 (cabozantinib + nivolumab), Figure 7 (pazopanib), Figure 8 (tivozanib), and Figure 9 (sunitinib).

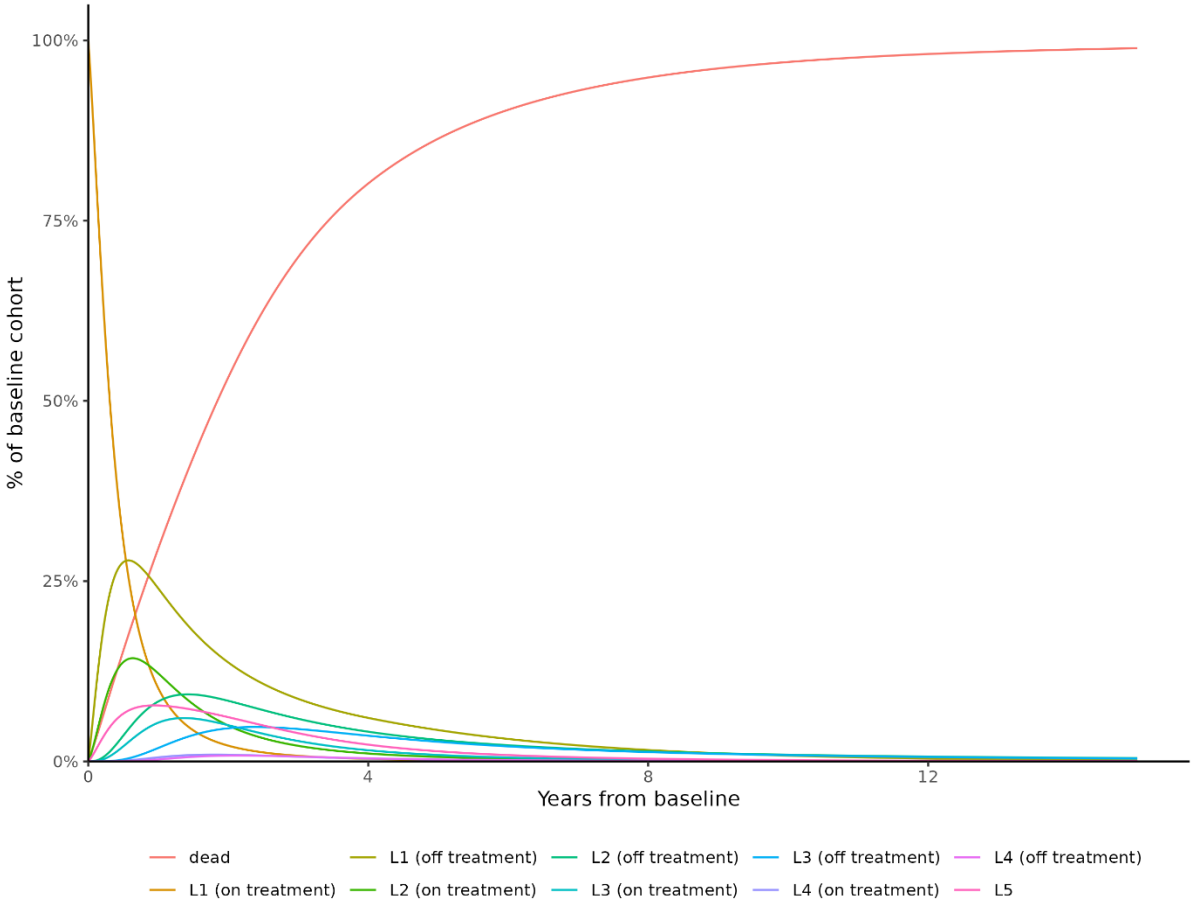
The Markov trace for the intermediate/poor risk group is provided by treatment in Figure 10 (cabozantinib + nivolumab), Figure 11 (nivolumab + ipilimumab), Figure 12 (pembrolizumab + lenvatinib), Figure 13 (pazopanib), Figure 14 (tivozanib), Figure 15 (sunitinib), and cabozantinib (Figure 16).

Figure 2: Markov trace (all risk groups): cabo+nivo



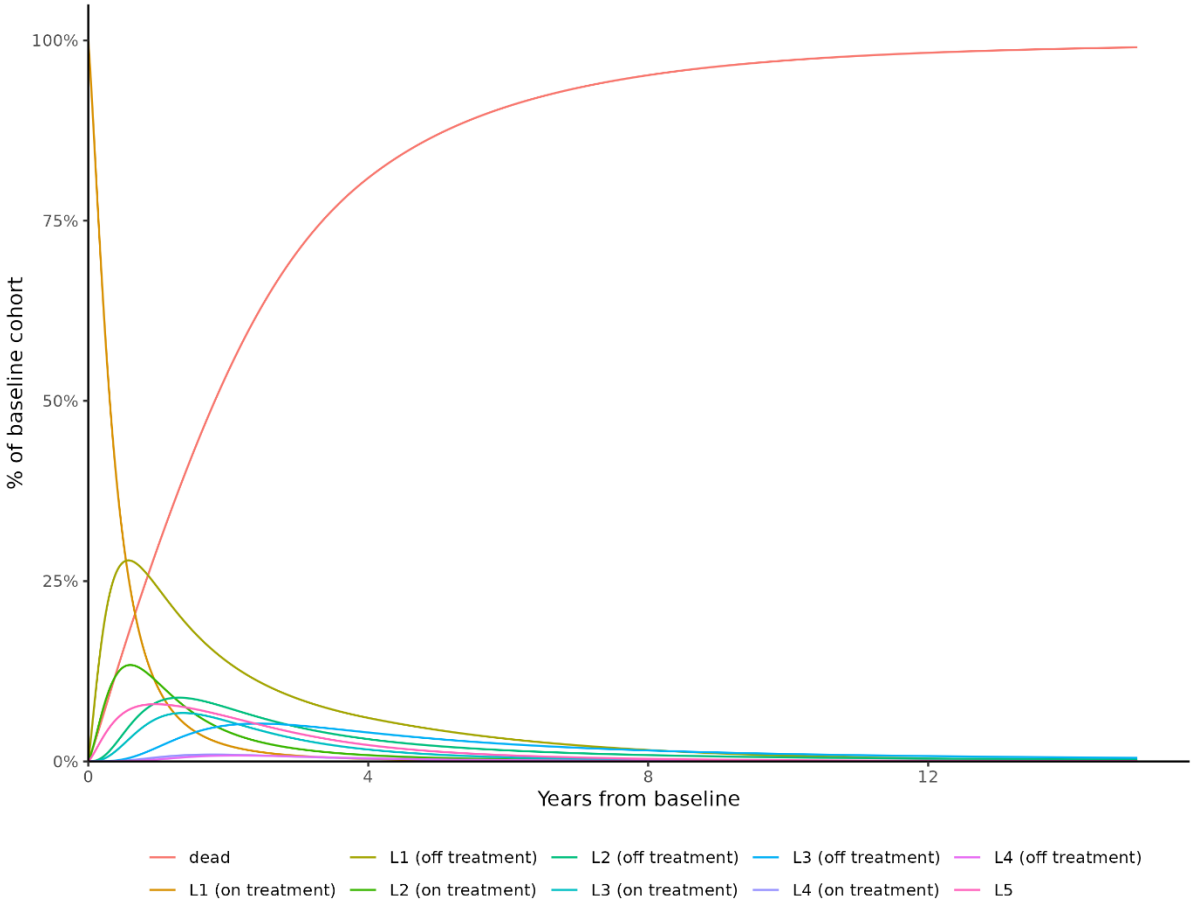
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; cabo, cabozantinib; nivo, nivolumab

Figure 3: Markov trace (all risk groups): pazo



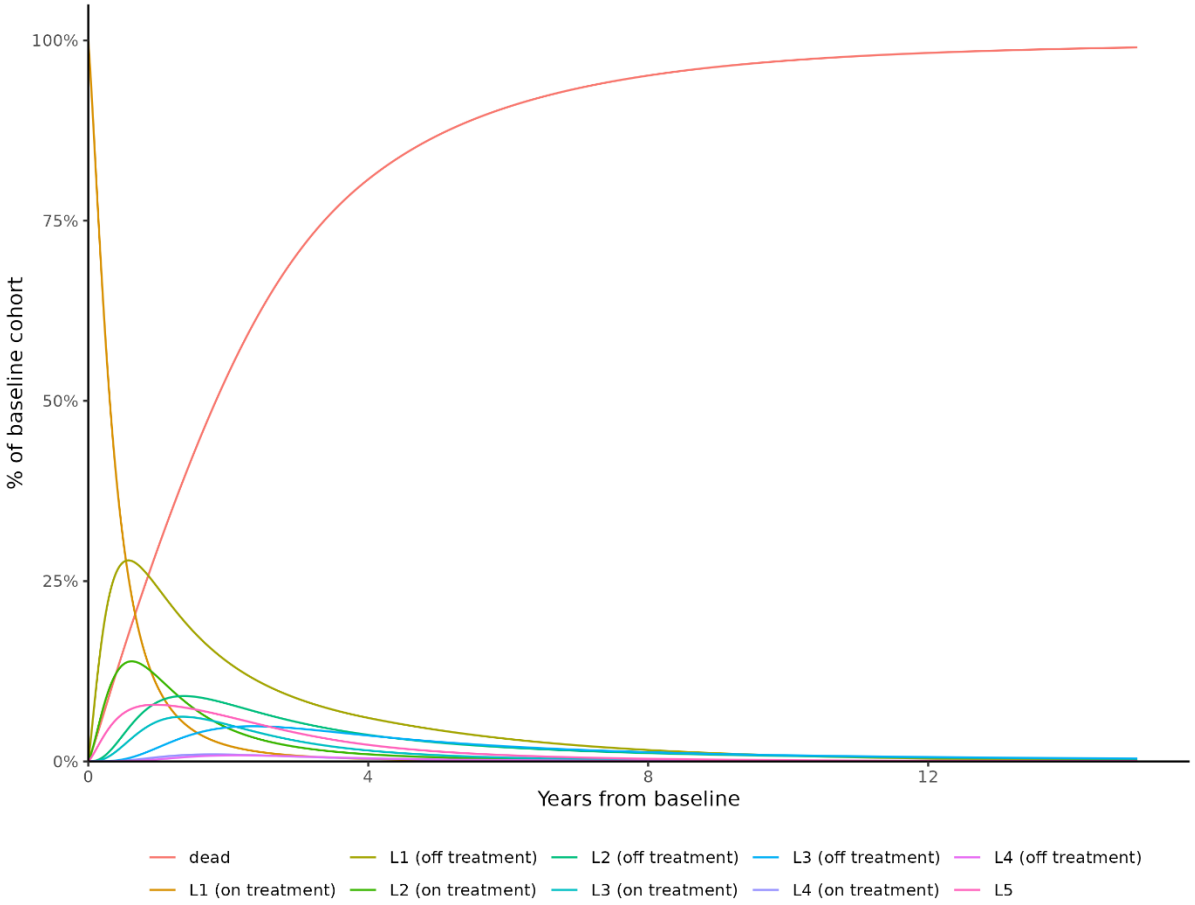
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; pazo, pazopanib

Figure 4: Markov trace (all risk groups): tivo



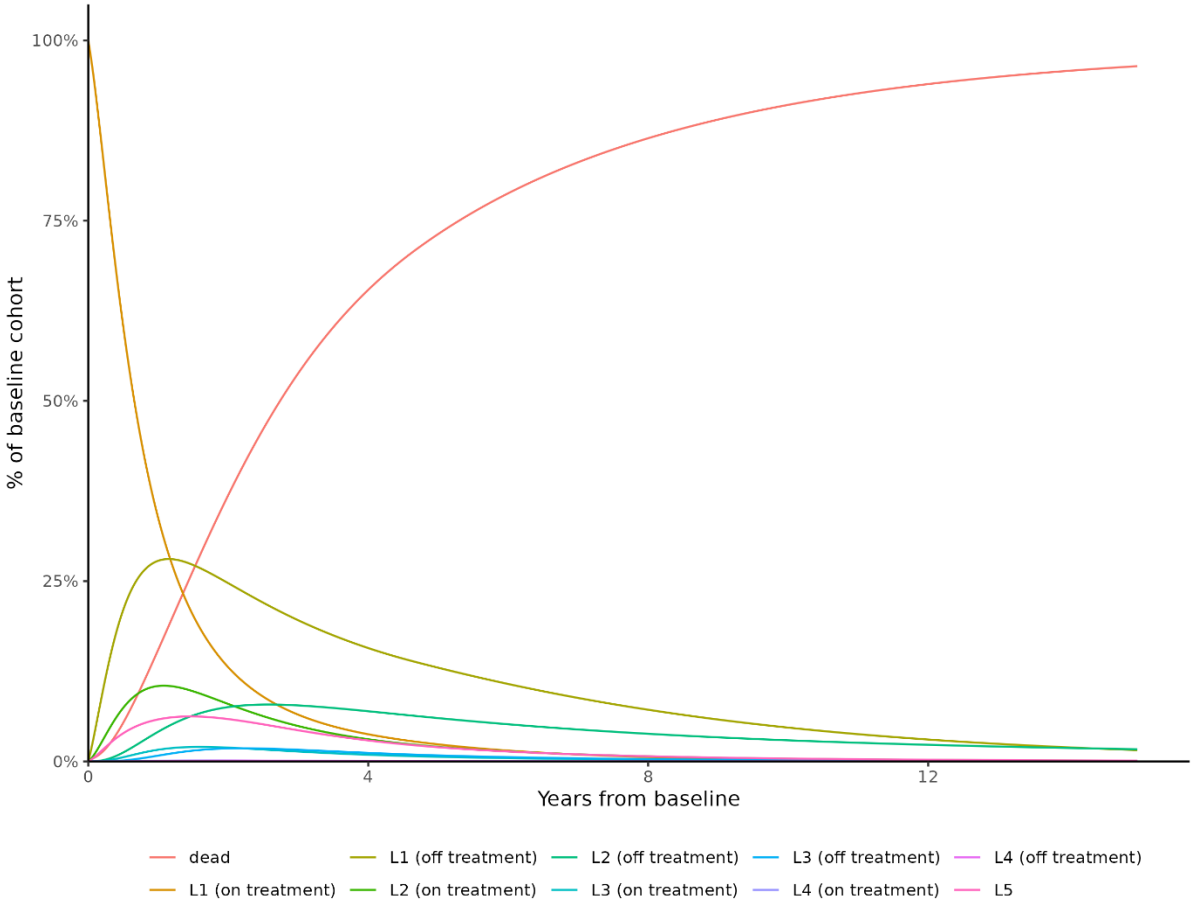
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; tivo, tivozanib

Figure 5: Markov trace (all risk groups): suni



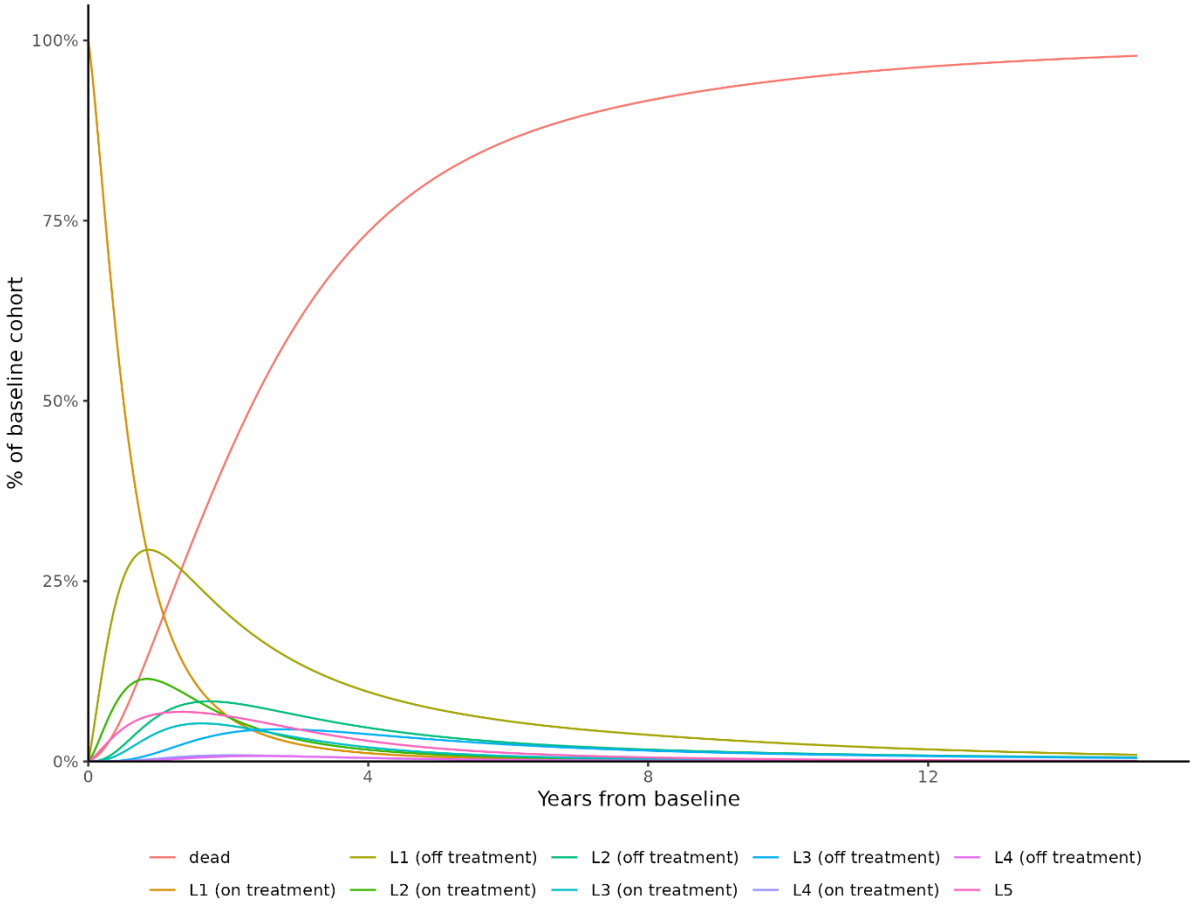
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; suni, sunitinib

Figure 6: Markov trace (favourable risk group): cabo+nivo



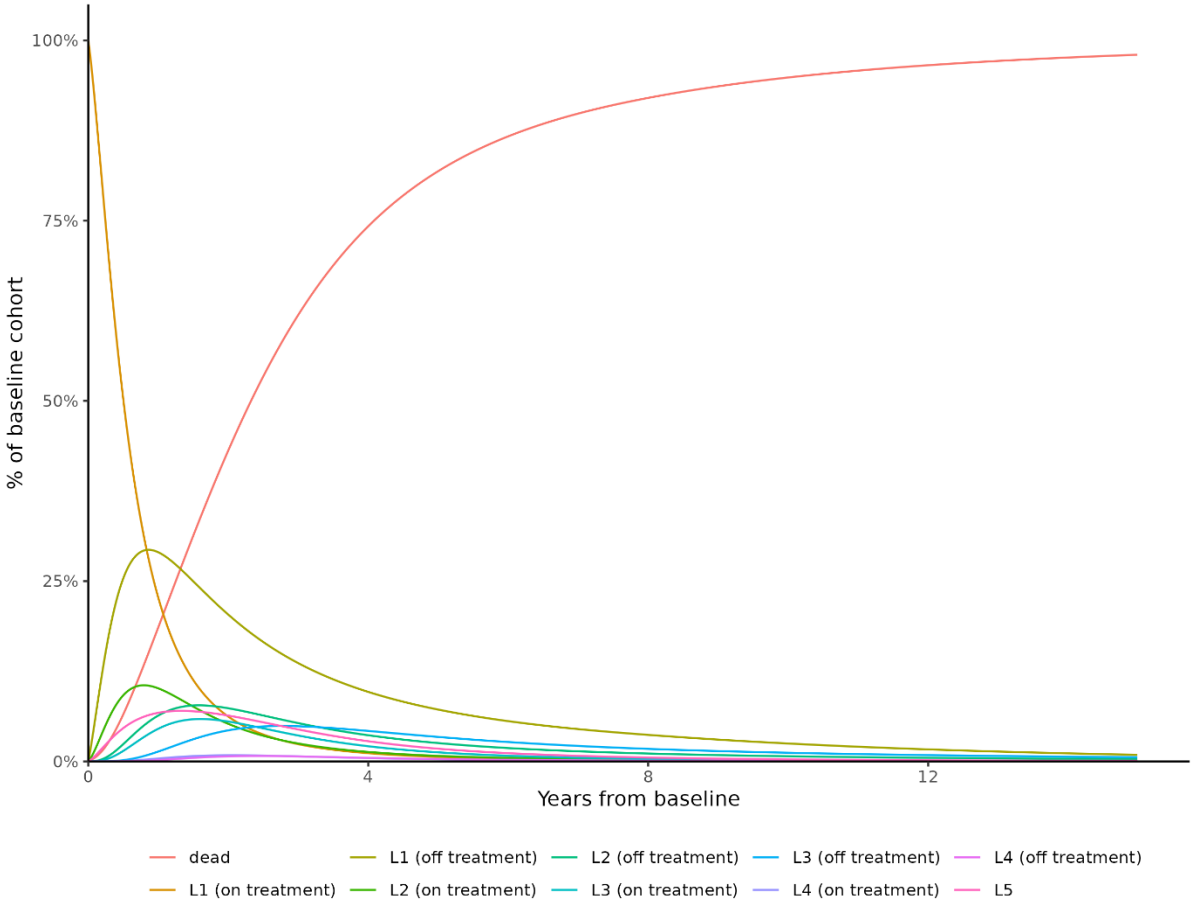
Abbreviations: cabo, cabozantinib; L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; nivo, nivolumab

Figure 7: Markov trace (favourable risk group): pazo



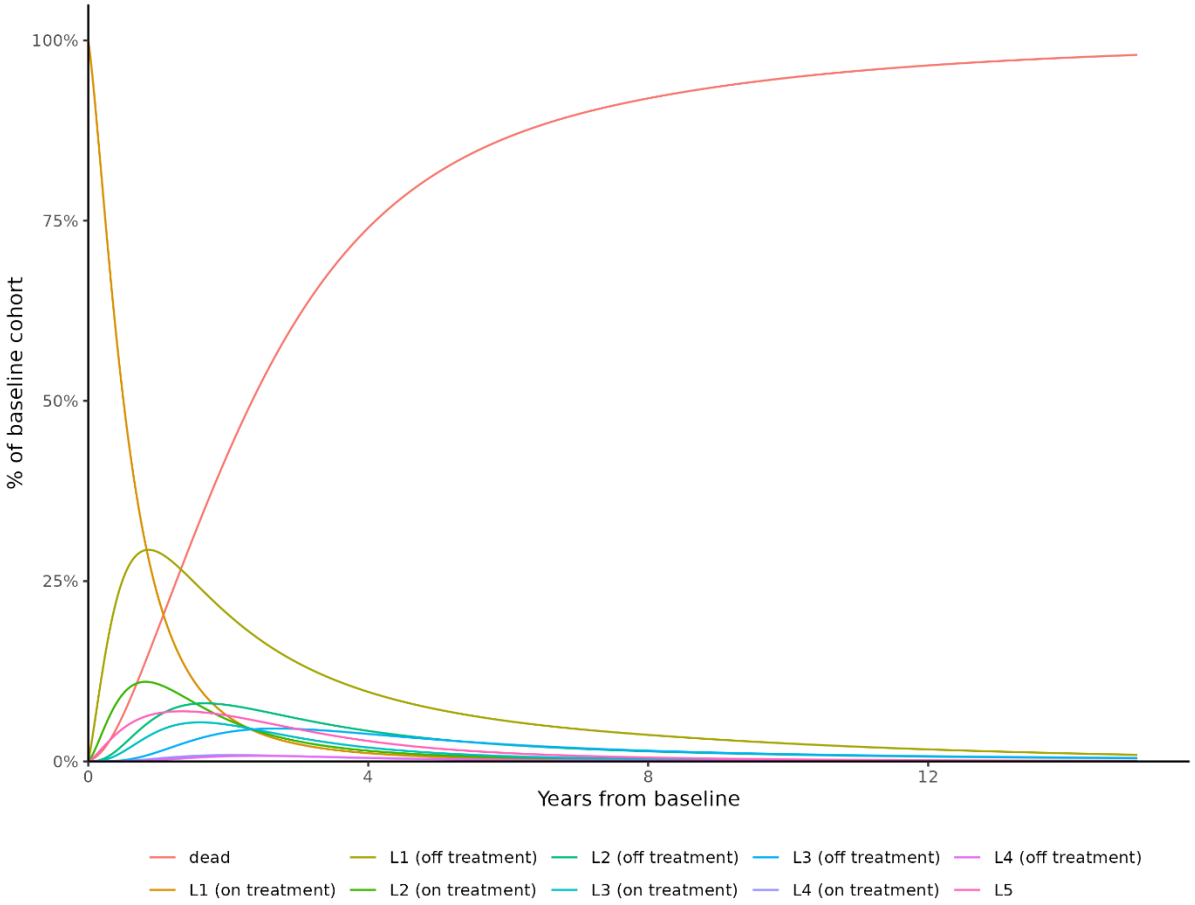
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; pazo, pazopanib

Figure 8: Markov trace (favourable risk group): tivo



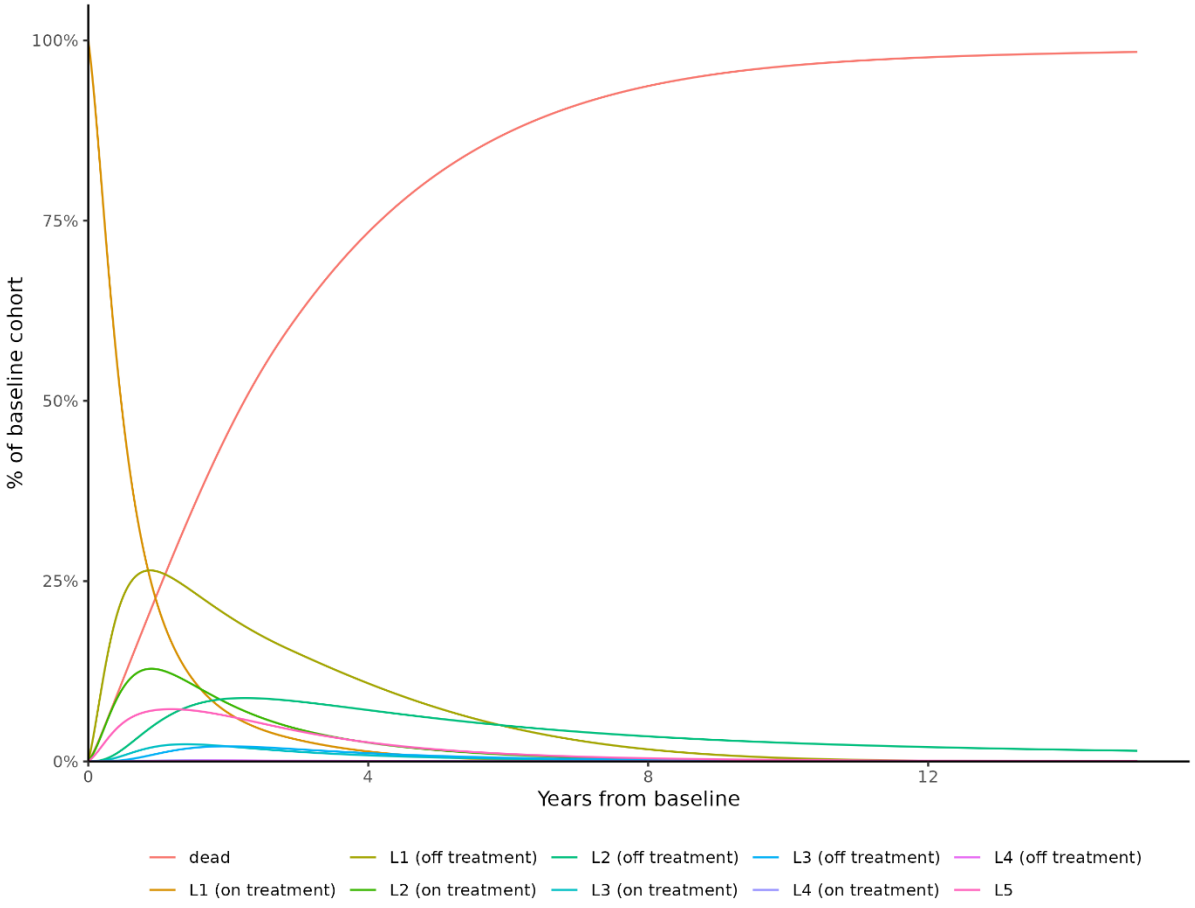
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; tivo, tivozanib

Figure 9: Markov trace (favourable risk group): suni



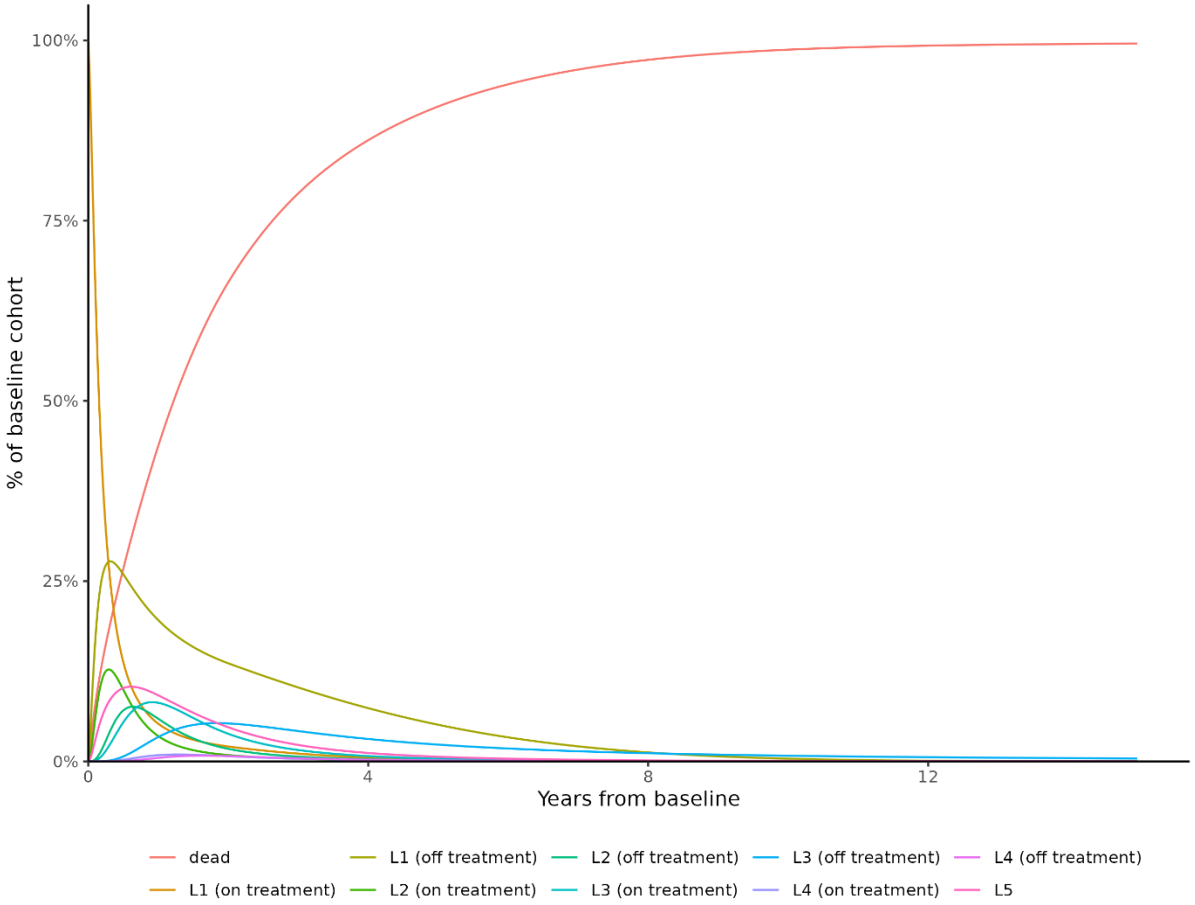
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; suni, sunitinib

Figure 10: Markov trace (intermediate/ poor risk group): cabo+nivo



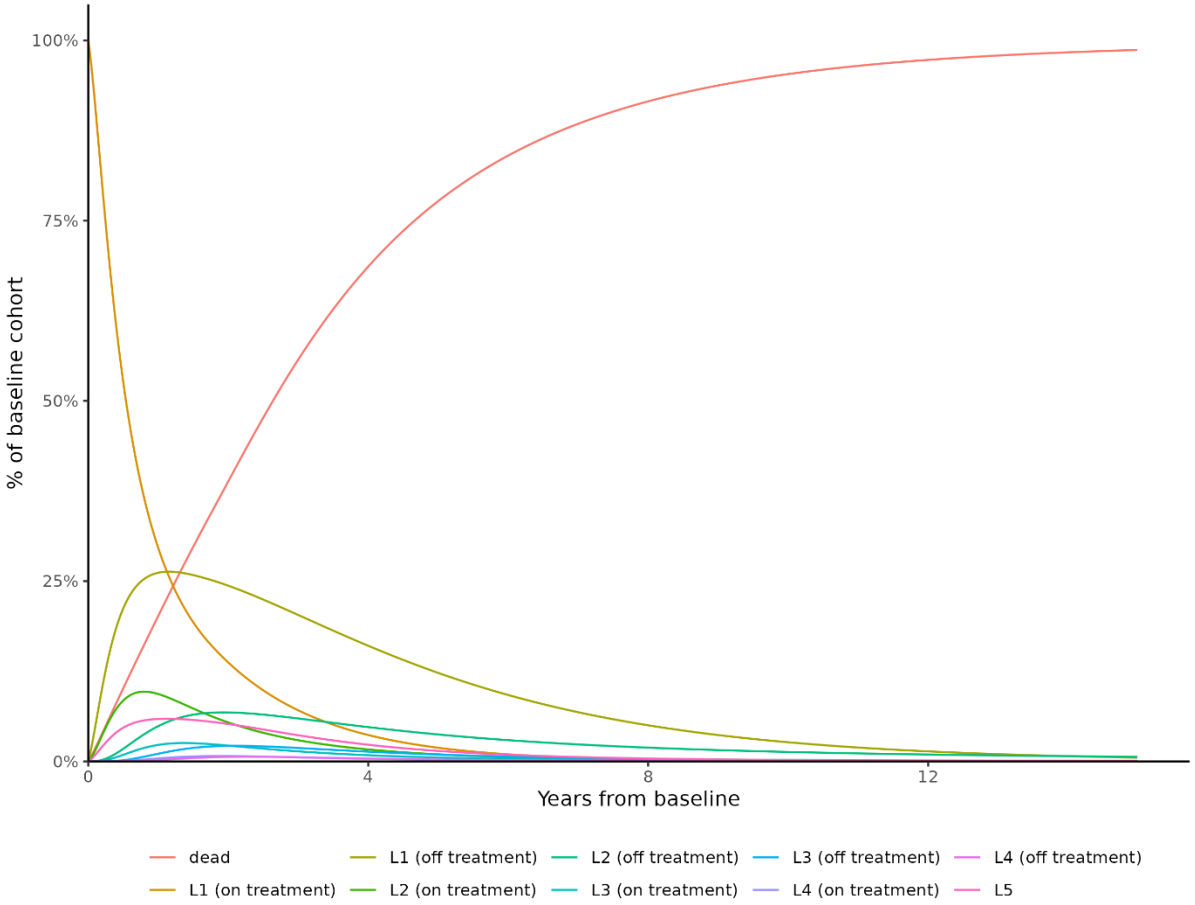
Abbreviations: cabo, cabozantinib; L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; nivo, nivolumab

Figure 11: Markov trace (intermediate/ poor risk group): nivo+ipi



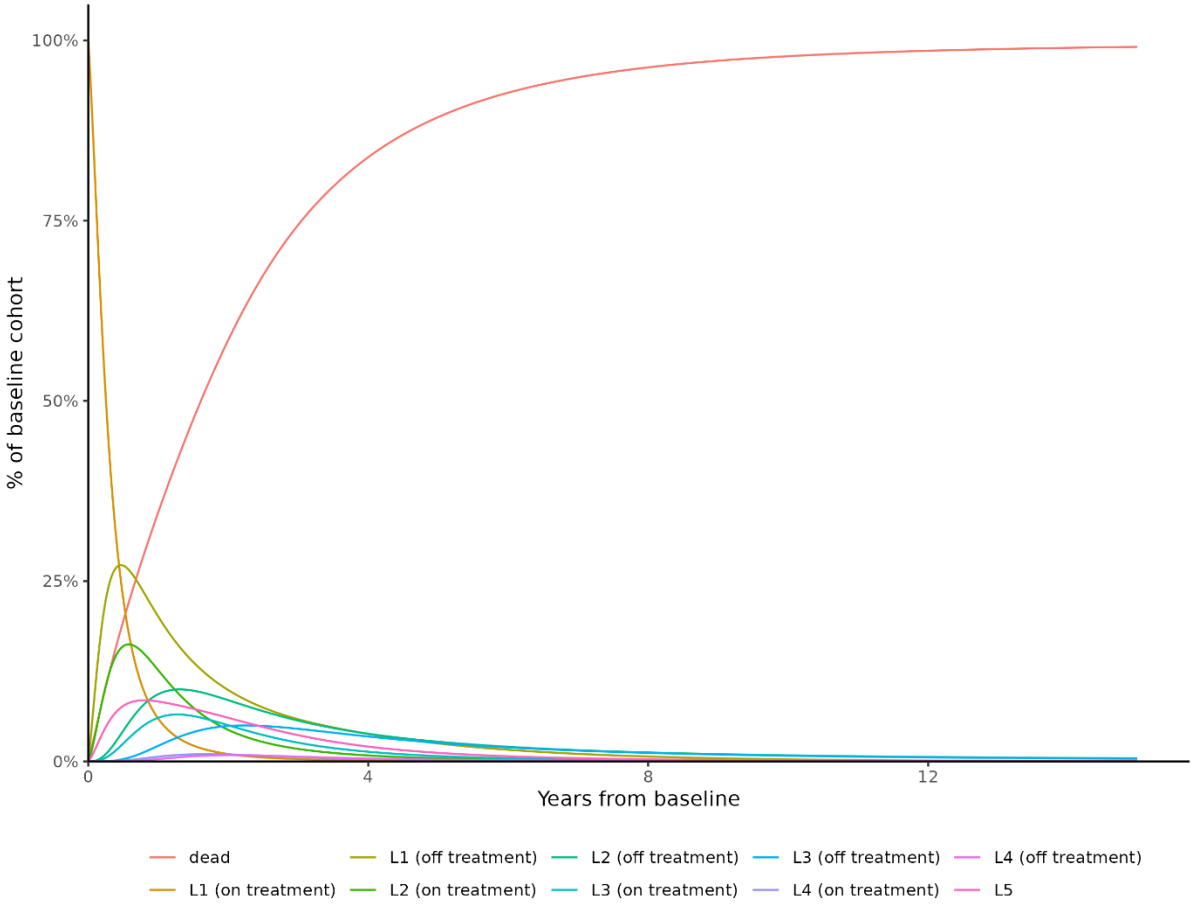
Abbreviations: ipi, ipilimumab; L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; nivo, nivolumab

Figure 12: Markov trace (intermediate/ poor risk group): pem+lenv



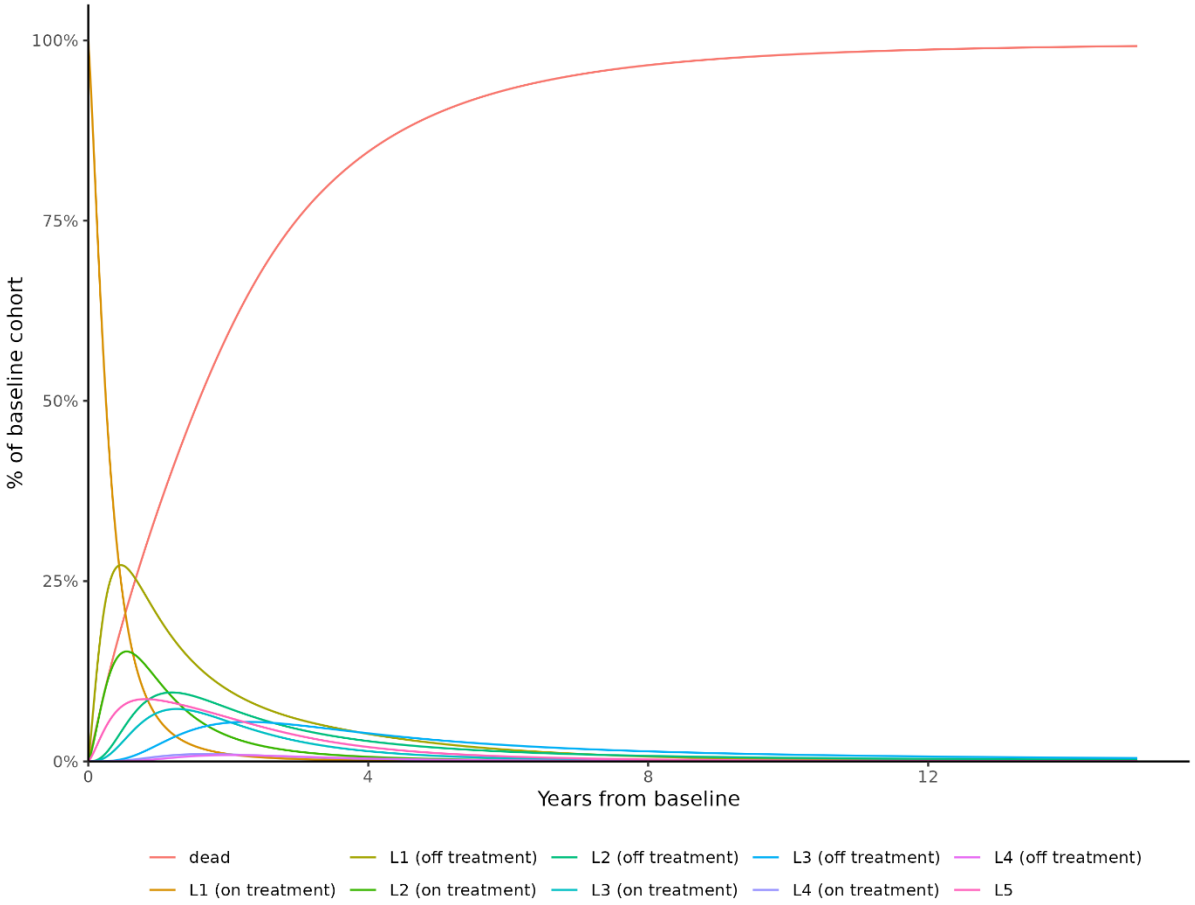
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; lenv, lenvatinib; pem, pembrolizumab

Figure 13: Markov trace (intermediate/ poor risk group): pazo



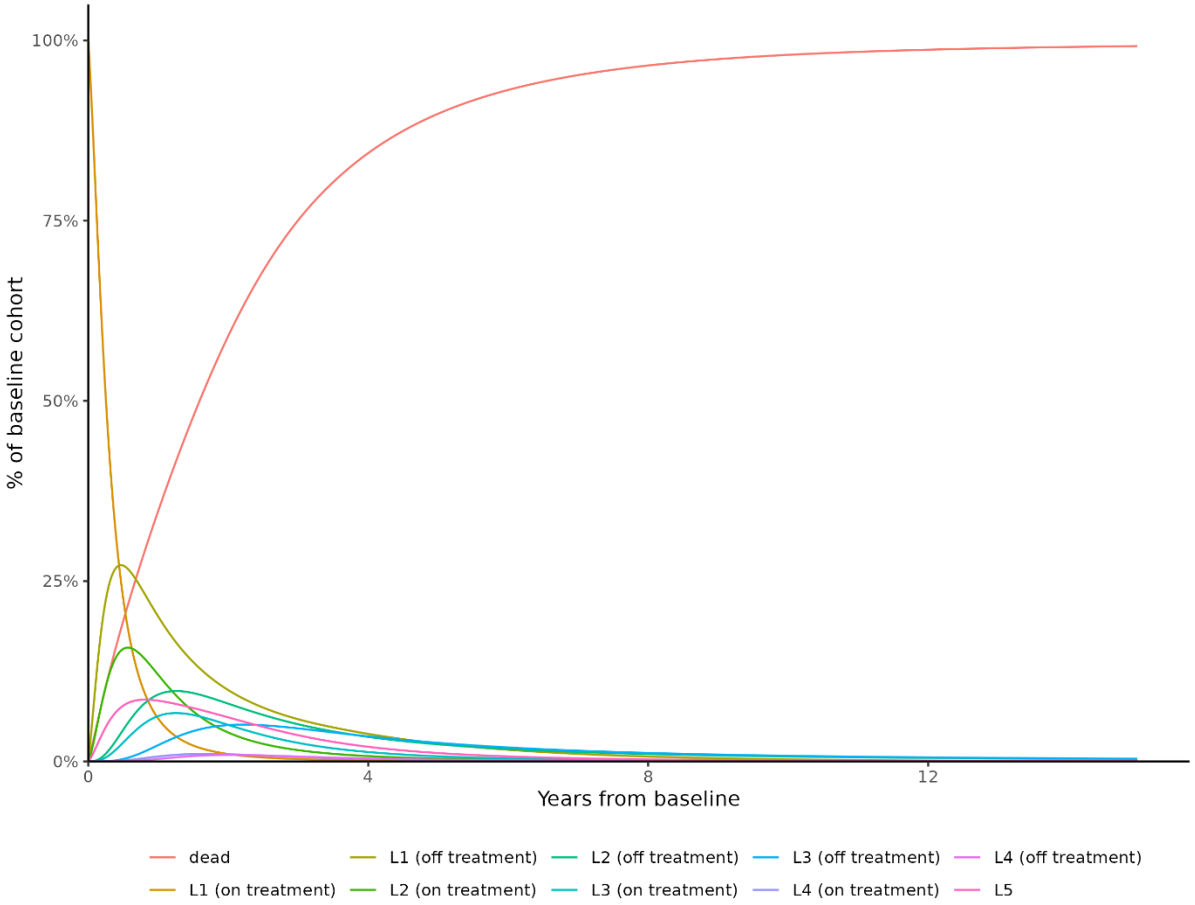
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; pazo, pazopanib

Figure 14: Markov trace (intermediate/ poor risk group): tivo



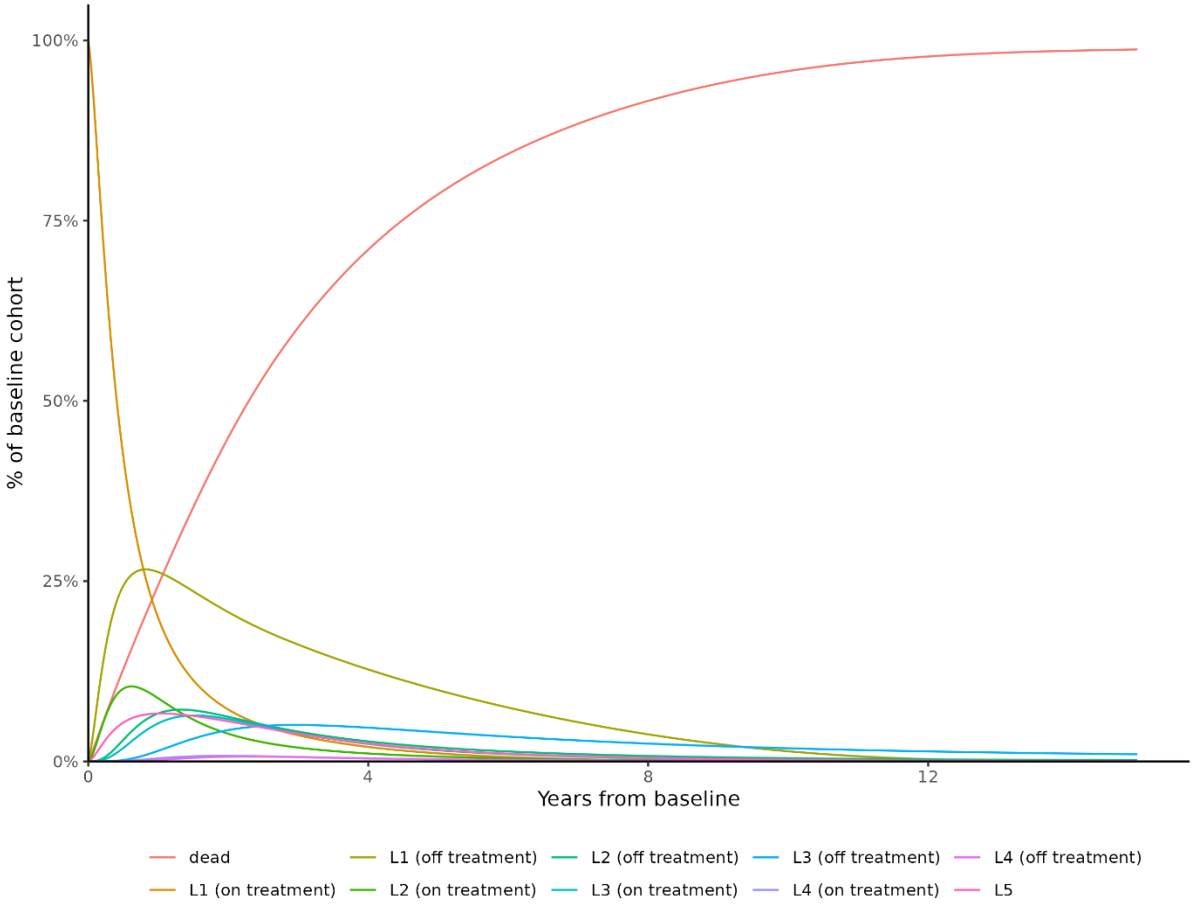
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; tivo, tivozanib

Figure 15: Markov trace (intermediate/ poor risk group): suni



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line; suni, sunitinib

Figure 16: Markov trace (intermediate/ poor risk group): cabo

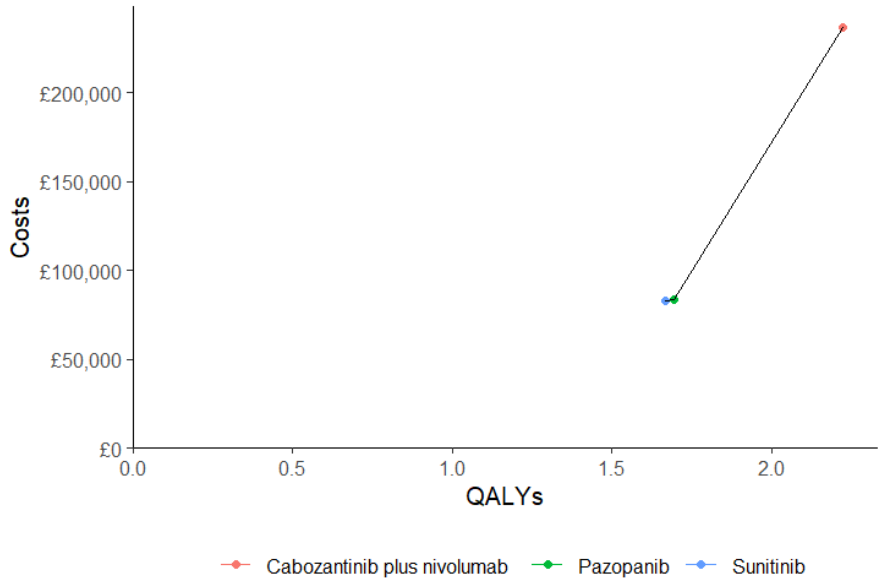


Abbreviations: cabo, cabozantinib; L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Q.2.4. Cost-effectiveness acceptability frontiers

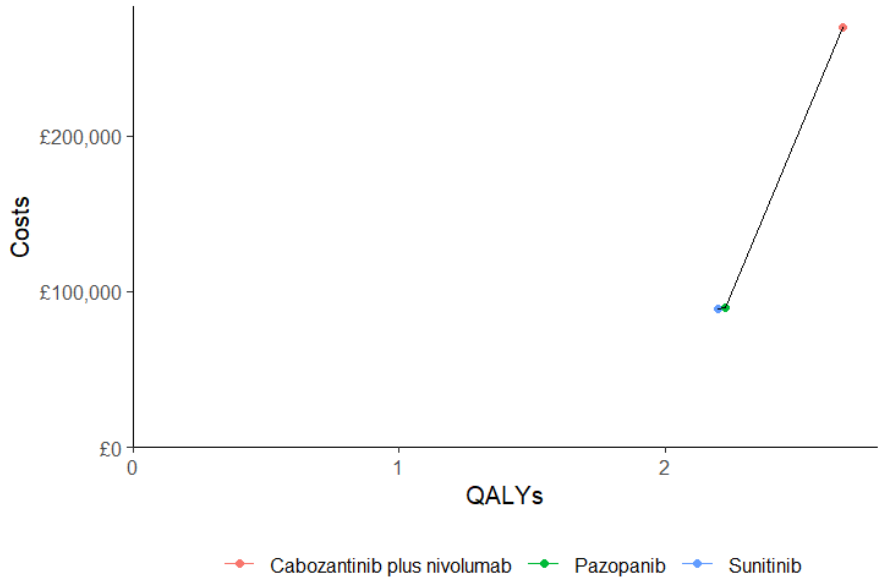
Figure 17 to Figure 19 present the cost-effectiveness acceptability frontiers for all non-dominated treatments for each of the risk groups.

Figure 17: Cost-effectiveness acceptability frontier – all risk



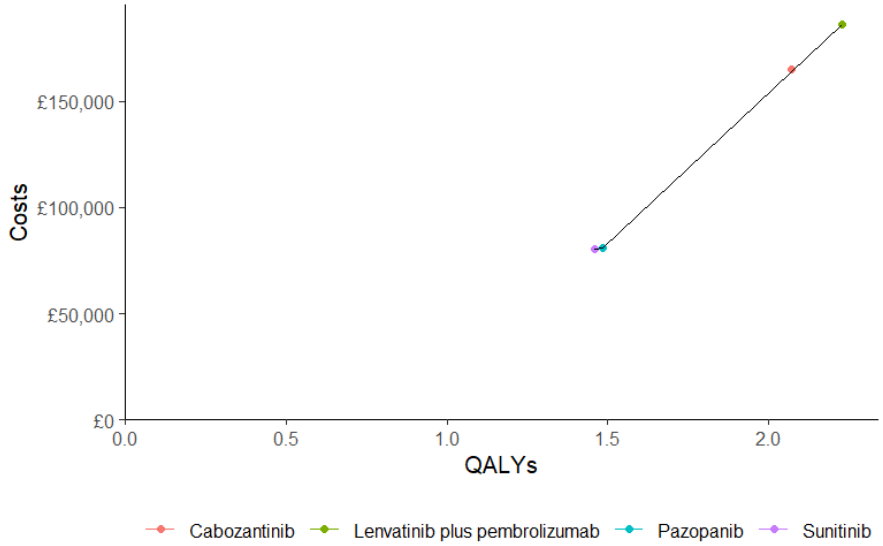
Abbreviations: QALYs, quality-adjusted life-years

Figure 18: Cost-effectiveness acceptability frontier – favourable risk



Abbreviations: QALYs, quality-adjusted life-years

Figure 19: Cost-effectiveness acceptability frontier– intermediate / poor risk



Abbreviations: QALYs, quality-adjusted life-years

Q.2.5. Uncertainty: scenario analysis

Scenario analyses are presented in Table 13 to Table 15. One way sensitivity analysis was not conducted as the parameters of key influence are correlated which would make such analyses biased. A detailed results breakdown is provided in Appendix 1 for the PartSA analysis given that prior renal cell cancer (RCC) models used this structure and the difference in results between this and the state transition model.

Q.2.5.1. All risk

In the all-risk population cabozantinib + nivolumab was not cost-effective at list prices in any scenario. The most optimistic scenario is where time to discontinuation is set equal to PFS (Scenario 18), yielding an ICER of £176,827. The most pessimistic was when FP NMA was substituted for PH NMA to model 2nd line + outcomes (Scenario 12).

The scenarios which had the most impact on cost-effectiveness were:

- The model structure chosen (PartSA [Scenario 1] led to a higher ICER).
- The approach to network meta-analysis for effectiveness of 2nd line + (Scenario 12 described above: use of FP NMA considerably increased the ICER to £1,266,501).

Table 13: Scenario analyses (All risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				Pazo	£152,823	0.528	£289,554
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Pazo	£155,968	0.295	£528,126
		2	State transition 3 lines	Pazo	£155,471	0.542	£286,863
		3	State transition 2 lines	Pazo	£168,186	0.695	£242,097
Discount rate							
Discount rate	3.5%	4	Discount rate-0%	Pazo	£162,357	0.639	£254,200

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		5	Discount rate-6%	Pazo	£147,142	0.471	£312,493
Primary data source							
Data source for baseline risk and patient characteristics	UK RWE, state transition model	6	Trial-based analyses, state transition model	Suni	£170,733	0.431	£395,868
	UK RWE, state transition model	7	Trial-based analyses, PartSA	Pazo	£170,505	0.273	£624,939
Population characteristics							
Data source	UK RWE	8	Data source-CheckMate 9ER	Pazo	£152,794	0.527	£289,866
Use means or IPD	IPD	9	Mean	Pazo	£152,781	0.526	£290,722
Effectiveness							
Baseline risk	UK RWE	10	Mean	Pazo	£181,541	0.755	£240,413
Preferred 1st line NMA	FP NMA	11	PH NMA	Pazo	£160,187	0.656	£244,271
Preferred 2nd line NMA	PH NMA	12	FP NMA	Pazo	£129,809	0.102	£1,266,501
Preferred NMA for pem+lenv	PH NMA	13	FP NMA	Pazo	£152,823	0.528	£289,554
Method used to adjust crossing curves	Hazards	14	Survivor function	Pazo	£160,171	0.587	£272,803
Assume pazo equal to suni	Yes	15	No	Suni	£153,491	0.555	£276,480
Assume tivo equal to suni	Yes	16	No	Pazo	£152,823	0.528	£289,554
Assume axi equal to evero	No	17	Yes	Pazo	£153,779	0.544	£282,737

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Time on treatment data taken from	TTD	18	TTD equal to PFS	Pazo	£91,126	0.515	£176,827
	TTD	19	TTD equal to PFS, PartSA	Pazo	£100,346	0.295	£339,783
	Relative effectiveness for nivo + ipi from PFS consistent with other treatments	20	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	Pazo	£152,823	0.528	£289,554
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Pazo	£163,750	0.511	£320,243
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints, based on hazards	22	10 years for IO/TKIs, all endpoints, based on hazards	Pazo	£152,359	0.519	£293,754
		23	10 years all IO combinations, all endpoints, based on hazards	Pazo			
		24	Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	Pazo	£152,390	0.519	£293,472
		25	Between 5 and 20 years all IO combinations, all endpoints, based on hazards	Pazo			
		26	No treatment effect waning	Pazo	£152,338	0.518	£293,937
		27	PartSA: 5 years for IO/TKIs, OS only, based on hazards	Pazo	£155,968	0.295	£528,126

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		28	PartSA: between 4 and 6 years for IO/TKIs, OS only, based on absolute survival	Pazo	£154,383	0.256	£602,933
Parametric curves							
Suni RWE 1L							
PFS	Log-logistic	29	Weibull	Pazo	£149,972	0.404	£371,493
TTD	Log-logistic	30	Weibull	Pazo	£140,720	0.529	£266,182
TTP	Log-logistic	31	Generalised gamma	Pazo	£156,333	0.594	£263,368
Cabo RWE 2L							
PFS	Log-logistic	32	Generalised gamma	Pazo	£153,727	0.545	£281,932
PFS	Log-normal	33	Weibull	Pazo	£155,691	0.579	£268,737
TTP	Log-normal	34	Weibull	Pazo	£152,806	0.527	£289,919
Cabo RWE 3L							
PFS	Log-logistic	35	Generalised gamma	Pazo	£151,487	0.479	£316,186
PFS	Log-logistic	36	Weibull	Pazo	£149,455	0.410	£364,559
TTP	Log-normal	37	Log-logistic	Pazo	£152,748	0.526	£290,246
TTP	Log-normal	38	Generalised gamma	Pazo	£152,784	0.527	£290,052
BSC							
4th line PPS pooled	Log-normal	39	Exponential	Pazo	£152,819	0.527	£289,863
Costs/RDI							
Number of administrations for fixed duration	TTD	40	Mean number of administrations	Pazo	£166,693	0.528	£315,833

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
treatments based on							
RDI	Applied	41	All RDI set to 100%	Pazo	£178,369	0.528	£337,956
RDI	Applied	42	RDI proportions based on RWE	Pazo	£178,598	0.528	£338,390
RDI and effectiveness of pem+lenv	Per base case	43	Assume effectiveness of pem+lenv same as cabo+nivo, using company alternative RDIs	Pazo	£117,686	0.528	£222,979
RDI and effectiveness of pem+lenv	Per base case	44	Assume effectiveness of pem+lenv same as cabo+nivo	Pazo	£152,823	0.528	£289,554
RDI	Original values	45	All company alternative RDIs	Pazo	£117,686	0.528	£222,979
RDI	Original values	46	All company RDIs (IOs only)	Pazo	£108,162	0.528	£204,935
RDI	Original values	47	All company alternative RDIs, PartSA	Pazo	£114,567	0.295	£387,939
RDI	Original values	48	All company RDIs (IOs only), PartSA	Pazo	£106,809	0.295	£361,668
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	49	CheckMate 9ER for 1L	Pazo	£152,823	0.574	£266,215
		50	CheckMate 9ER for all lines	Pazo	£152,823	0.549	£278,324
		51	CheckMate 9ER for all lines (PartSA)	Pazo	£155,968	0.307	£507,431

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		52	CheckMate 9ER for all lines (no age adjustment)	Pazo	£152,823	0.564	£271,033
		53	CheckMate 9ER for all lines (no age adjustment, PartSA)	Pazo	£155,968	0.311	£501,914
		54	Same PFS and PD utilities from 2L onwards	Pazo	£152,823	0.524	£291,879
		55	Higher proportional decrease for 3L and 4L	Pazo	£152,823	0.530	£288,091
Utilities for BSC	Assumed same as progressed: current line	56	Assumed same as progression free: current line	Pazo	£152,823	0.531	£287,792
		57	Assume same as final health state	Pazo	£152,823	0.527	£290,225
Adverse events							
Data source used for AEs	NMA	58	Individual trials	Pazo	£152,009	0.548	£277,557
AEs applied	One off	59	Per cycle	Pazo	£152,822	0.527	£290,130
AE disutilities not considered	Yes	60	No	Pazo	£152,823	0.550	£277,698
Scale of impact	Per analysis	61	Doubled	Pazo	£153,671	0.505	£304,145
Axi AE impact	Per NMA	62	Set the same as tivo	Pazo	£152,671	0.532	£287,171
Subsequent treatments							
Data source	RWE	63	Trial	Suni	£152,538	0.343	£445,314
Adjuvant treatments							
	0%	64	20%	Pazo	£150,556	0.484	£310,912

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
% of eligible patients receiving adjuvant pem	0%	65	65%	Pazo	£145,387	0.382	£380,446
Uncertainty around inputs for pem+lenv							
Pem+lenv inputs	Pem+lenv data used for RDI FP NMA used for cabo+nivo and PH NMA for pem+lenv	66	Pem+lenv assumed to have same RDI as nivo+cabo PH NMA used for all 1st line treatments	Pazo	£160,187	0.656	£244,271
Time horizon							
Time horizon	40	67	5	Pazo	£141,005	0.352	£401,026
Time horizon	40	68	10	Pazo	£151,181	0.478	£316,465
Time horizon	40	69	20	Pazo	£152,534	0.514	£297,023
Time horizon	40	70	5, PartSA	Pazo	£144,138	0.273	£527,412
Time horizon	40	71	10, PartSA	Pazo	£155,160	0.310	£500,592
Time horizon	40	72	20, PartSA	Pazo	£155,978	0.296	£526,831

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

*Next best comparator defined as next most efficient non-dominated comparator.

Q.2.5.2. Favourable risk

In the favourable risk population at list price cabozantinib + nivolumab was not cost-effective in any of the scenarios run. The scenarios which had the most impact on cost-effectiveness were:

- The model structure chosen as the trial data indicated an overall survival (OS) hazard ratio (HR) >1 in this population a PartSA model structure led to a dominated result.
- The primary data source chosen (use of trial data increased the ICER as the CheckMate 9ER the primary driver again being that more patients went on to receive BSC rather than an active treatment in 2nd line based upon the data supplied).
- Choice of NMA approach for 2nd line + therapy (the FPNMA led to substantial increases in the ICER).
- The assumptions made for time on treatment particularly whether direct data on the number of administrations from the trial were used. This scenario can be considered pessimistic as they do not account for any potential impact on effectiveness.

We note that application of treatment effect waning does not impact the results in the favourable risk population. This is because the hazard functions for the IO / TKI combination therapies were above those for TKI monotherapy at the end of the available trial data.

Table 14: Scenario analyses (favourable risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				Pazo	£179,822	0.44	£408,449
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Tivo	£0	0	Cabo+nivo dominated
		2	State transition 3 lines	Pazo	£182,518	0.455	£401,398
		3	State transition 2 lines	Pazo	£195,710	0.612	£320,033
Discount rate							
Discount rate	3.50%	4	Discount rate-0%	Pazopanib	£196,418	0.572	£343,387
		5	Discount rate-6%	Pazo	£170,603	0.375	£455,161

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Primary data source							
Data source for baseline risk and patient characteristics	UK RWE, state transition model	6	Trial-based analyses, state transition model	Suni	£200,646	0.315	£637,037
	UK RWE, state transition model	7	Trial-based analyses, PartSA	Tivo	£0	0	Cabo+nivo dominated
Population characteristics							
Data source	UK RWE	8	CheckMate 9ER	Pazo	£179,785	0.44	£408,945
Use means or IPD	IPD	9	Age-Mean	Pazo	£179,769	0.438	£410,118
Effectiveness							
Baseline risk	UK RWE	10	CheckMate 9ER	Pazo	£210,550	0.627	£335,854
Preferred 1st line NMA	PH NMA	11	PH NMA	Pazo	£179,822	0.44	£408,449
Preferred 2nd line NMA	PH NMA	12	FP NMA	Pazo	£156,873	0.02	£7,743,976
Preferred NMA for pem+lenv	PH NMA	13	FP NMA	Pazo	£179,822	0.44	£408,449
Method used to adjust crossing curves	Hazards	14	Survivor function	Pazo	£191,672	0.562	£341,261
Assume pazo equal to suni	Yes	15	No	Pazo	£179,770	0.462	£388,785
Assume tivo equal to suni	Yes	16	No	Pazo	£179,822	0.44	£408,449
Assume axi equal to evero	No	17	Yes	Pazo	£180,745	0.456	£396,528
Time on treatment data taken from	TTD	18	TTD equal to PFS	Pazo	£137,568	0.43	£320,107
	TTD	19	TTD equal to PFS, PartSA	Tivo	£0	0	Cabo+nivo dominated
	Relative effectiveness for	20	Relative effectiveness for nivo + ipi from	Pazo	£179,822	0.44	£408,449

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	nivo + ipi from PFS consistent with other treatments		simple HR between PFS and TTD from CheckMate 214				
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Tivo	£0	0	Cabo+nivo dominated
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints, based on hazards	22	10 years for IO/TKIs, all endpoints, based on hazards	Pazo	£179,822	0.44	£408,449
		23	10 years all IO combinations, all endpoints, based on hazards	Pazo	£179,822	0.44	£408,449
		24	Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	Pazo	£179,822	0.44	£408,449
		25	Between 5 and 20 years all IO combinations, all endpoints, based on hazards	Pazo	£179,822	0.44	£408,449
		26	No treatment effect waning	Pazo	£179,822	0.44	£408,449
		27	PartSA: 5 years for IO/TKIs, OS only, based on hazards	Tivo	£0	0	Cabo+nivo dominated
		28	Between 4 and 6 years for IO/TKIs, OS only, based on absolute survival	Tivo	£0	0	Cabo+nivo dominated
Parametric curves							
Suni RWE 1L							
PFS	Log-logistic	29	Weibull	Pazo	£179,829	0.441	£407,957

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
TTD	Log-logistic	30	Generalised gamma	Pazo	£161,577	0.443	£364,734
TTP	Log-logistic	31	Weibull	Pazo	£179,829	0.441	£407,957
CaboRWE 2L							
PFS	Log-logistic	32	Generalised gamma	Pazo	£180,752	0.459	£393,715
PFS	Log-normal	33	Weibull	Pazo	£182,755	0.494	£370,179
TTP	Log-normal	34	Weibull	Pazo	£179,815	0.441	£408,065
Cabo RWE 3L							
PFS	Log-logistic	35	Generalised gamma	Pazo	£178,556	0.394	£452,781
PFS	Log-logistic	36	Weibull	Pazo	£176,600	0.327	£539,346
TTP	Log-normal	37	Log-logistic	Pazo	£179,756	0.44	£408,677
TTP	Log-normal	38	Generalised gamma	Pazo	£179,792	0.44	£408,312
BSC							
4th line PPS pooled	Log-normal	39	Exponential	Pazo	£179,829	0.441	£407,957
Costs/RDI							
Number of administrations for fixed duration treatments based on	TTD	40	Mean number of administrations	Pazo	£189,632	0.44	£430,730
RDI	Applied	41	All RDI set to 100%	Pazo	£209,546	0.44	£475,963
RDI	Applied	42	RDI proportions based on RWE	Pazo	£206,030	0.44	£467,977
RDI and effectiveness of pem+lenv	Per base case	43	Assume effectiveness of pem+lenv same as cabo+nivo, using company alternative RDIs	Pazo	£138,225	0.44	£313,965

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RDI and effectiveness of pem+lenv	Per base case	44	Assume effectiveness of pem+lenv same as cabo+nivo	Pazo	£179,822	0.44	£408,449
RDI	Original values	45	All company alternative RDIs	Pazo	£138,225	0.440	£313,965
RDI	Original values	46	All company RDIs (IOs only)	Pazo	£128,544	0.440	£291,974
RDI	Original values	47	All company alternative RDIs, PartSA	Tivo	£0	0	Cabo+nivo dominated
RDI	Original values	48	All company RDIs (IOs only), PartSA	Tivo	£0	0	Cabo+nivo dominated
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	49	CheckMate 9ER for 1L	Pazo	£179,822	0.487	£368,892
		50	CheckMate 9ER for all lines	Pazo	£179,822	0.456	£394,449
		51	CheckMate 9ER for all lines (PartSA)	Tivo	£0	0	Cabo+nivo dominated
		52	CheckMate 9ER for all lines (no age adjustment)	Pazo	£179,822	0.473	£380,035
		53	CheckMate 9ER for all lines (no age adjustment, PartSA)	Tivo	£0	0	Cabo+nivo dominated
		54	Same PFS and PD from 2L onwards	Pazo	£179,822	0.435	£413,033
		55	Higher proportional decrease for 3L and 4L	Pazo	£179,822	0.444	£405,354
Utilities for BSC	Assumed same as progressed: current line	56	Assumed same as progression free: current line	Pazo	£179,822	0.443	£405,984

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		57	Assume same as final health state	Pazo	£179,822	0.44	£409,008
Adverse events							
Data source used for AEs	NMA	58	Individual trials	Pazo	£179,016	0.46	£389,234
AEs applied	One off	59	Per cycle	Pazo	£179,672	0.443	£405,460
AE disutilities not considered	Yes	60	No	Pazo	£179,822	0.462	£389,060
Scale of impact	Per analysis	61	Doubled	Pazo	£180,645	0.418	£431,840
Axi AE impact	Per NMA	62	Set the same as tivo	Pazo	£179,679	0.444	£404,789
Subsequent treatments							
Data source	RWE	63	Trial	Suni	£180,026	0.264	£681,904
Adjuvant treatments							
% of eligible patients receiving adjuvant pem	0%	64	20%	Pazo	£177,185	0.383	£462,701
	0%	65	65%	Pazo	£171,192	0.248	£688,903
Uncertainty around inputs for pem+lenv							
Pem+lenv inputs	Pem+lenv data used for RDI	66	Pem+lenv assumed to have same RDI as nivo+cabo	Pazo	######	0.44	£408,449
	FP NMA used for cabo+nivo and PH NMA for pem+lenv		PH NMA used for all 1st line treatments				
Time horizon							
Time horizon	40	67	5	Pazo	£153,364	0.193	£794,802
Time horizon	40	68	10	Pazo	£172,069	0.358	£481,219
Time horizon	40	69	20	Pazo	£179,047	0.424	£421,904
Time horizon	40	70	5, PartSA	Tivo	£0	0	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Time horizon	40	71	10, PartSA	Tivo	£0	0	Cabo+nivo dominated
Time horizon	40	72	20, PartSA	Tivo	£0	0	Cabo+nivo dominated

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

*Next best comparator defined as next most efficient non-dominated comparator.

Q.2.5.3. Intermediate / poor risk

In the intermediate / poor risk population at list price cabozantinib + nivolumab again not cost-effective in any scenario.

The most optimistic (i.e. non-dominated) scenarios were the use of the PH NMA for all effectiveness estimates in the PartSA structure, yielding an ICER of £1,549,670, and use of a short time horizon of 5 years in the PartSA mode, yielding an ICER of £2,630,390.

The EAG note that there are a number of uncertainties in the comparison between pembrolizumab + lenvatinib and cabozantinib + nivolumab which combined are likely to impact on cost-effectiveness conclusions:

- The most reasonable assumption to make for comparative RDI – currently individual trial data is used, the quality of which was poor for pembrolizumab + lenvatinib
- Difficulty making comparison to pembrolizumab + lenvatinib via FP NMA may bias results.

Table 15: Scenario analyses (Intermediate/poor risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				Pem+lenv			Cabo+nivo dominated
Model structure							
Overall structure	State transition 4 lines	**1**	PartSA 4 lines	Pem+lenv	£0	0.000	Cabo+nivo dominated
		2	State transition 3 lines	Pem+lenv	£0	0.000	Cabo+nivo dominated
		3	State transition 2 lines	Pem+lenv	£0	0.000	Cabo+nivo dominated
Discount rate							
Discount rate	3.5%	4	0%	Pem+lenv	£0	0.000	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		5	6%	Pem+lenv	£0	0.000	Cabo+nivo dominated
Primary data source							
Data source for baseline risk and patient characteristics	UK RWE, state transition model	6	Trial-based analyses, state transition model	Pem+lenv	£0	0.000	Cabo+nivo dominated
	UK RWE, state transition model	7	Trial-based analyses, PartSA	Pem+lenv	£0	0.000	Cabo+nivo dominated
Population characteristics							
Data source	UK RWE	8	Data source-CheckMate 9ER	Pem+lenv	£0	0.000	Cabo+nivo dominated
Use means or IPD	IPD	9	Mean	Pem+lenv	£0	0.000	Cabo+nivo dominated
Effectiveness							
Baseline risk	UK RWE	10	CheckMate 9ER	Pem+lenv	£0	0.000	Cabo+nivo dominated
Preferred 1st line NMA	FP NMA	11	PH NMA	Pem+lenv	£0	0.000	Cabo+nivo dominated
Preferred 2nd line NMA	PH NMA	12	FP NMA	Pem+lenv	£0	0.000	Cabo+nivo dominated
Preferred NMA for pem+lenv	PH NMA	13	FP NMA	Cabo	£0	0.000	Cabo+nivo dominated
Method used to adjust crossing curves	Hazards	14	Survivor function	Pem+lenv	£0	0.000	Cabo+nivo dominated
Assume pazo equal to suni	Yes	15	No	Pem+lenv	£0	0.000	Cabo+nivo dominated
Assume tivo equal to suni	Yes	16	No	Pem+lenv	£0	0.000	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Assume axi equal to evero	No	17	Yes	Pem+lenv	£0	0.000	Cabo+nivo dominated
Time on treatment data taken from	TTD	18	TTD equal to PFS	Pem+lenv	£0	0.000	Cabo+nivo dominated
	TTD	19	TTD equal to PFS, PartSA	Pem+lenv	£0	0.000	Cabo+nivo dominated
	Relative effectiveness for nivo + ipi from PFS consistent with other treatments	20	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	Pem+lenv	£0	0.000	Cabo+nivo dominated
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Nivo+ipi	£69,403	0.045	£1,549,670
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints	22	10 years for IO/TKIs, all endpoints, based on hazards	Pem+lenv	£0	0.000	Cabo+nivo dominated
		23	10 years all IO combinations, all endpoints, based on hazards	Pem+lenv	£0	0.000	Cabo+nivo dominated
		24	Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	Pem+lenv	£0	0.000	Cabo+nivo dominated
		25	Between 5 and 20 years all IO combinations, all endpoints, based on hazards	Pem+lenv	£0	0.000	Cabo+nivo dominated
		26	No treatment effect waning	Pem+lenv	£0	0.000	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
		27	PartSA: 5 years for IO/TKIs, OS only, based on hazards	Pem+lenv	£0	0.000	Cabo+nivo dominated
		28	Between 4 and 6 years for IO/TKIs, OS only, based on absolute survival	Pem+lenv	£0	0.000	Cabo+nivo dominated
Parametric curves							
Sunitinib RWE 1L							
PFS	Log-logistic	29	Weibull	Pem+lenv	£0	0.000	Cabo+nivo dominated
TTD	Log-logistic	30	Weibull	Pem+lenv	£0	0.000	Cabo+nivo dominated
TTP	Log-logistic	31	Weibull	Pem+lenv	£0	0.000	Cabo+nivo dominated
Cabozantinib RWE 2L							
PFS	Log-logistic	32	Generalised gamma	Pem+lenv	£0	0.000	Cabo+nivo dominated
PFS	Log-normal	33	Weibull	Pem+lenv	£0	0.000	Cabo+nivo dominated
TTP	Log-normal	34	Weibull	Pem+lenv	£0	0.000	Cabo+nivo dominated
Cabozantinib RWE 3L							
PFS	Log-logistic	35	Generalised gamma	Pem+lenv	£0	0.000	Cabo+nivo dominated
PFS	Log-logistic	36	Weibull	Pem+lenv	£0	0.000	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
TTP	Log-normal	37	Log-logistic	Pem+lenv	£0	0.000	Cabo+nivo dominated
TTP	Log-normal	38	Generalised gamma	Pem+lenv	£0	0.000	Cabo+nivo dominated
BSC				Pem+lenv			
4th line PPS pooled	Log-normal	39	Exponential	Pem+lenv	£0	0.000	Cabo+nivo dominated
Costs/RDI							
Number of administrations for fixed duration treatments based on	TTD	40	Mean number of administrations	Pem+lenv	£0	0.000	Cabo+nivo dominated
RDI	Applied	41	All RDI set to 100%	Pem+lenv	£0	0.000	Cabo+nivo dominated
RDI	Applied	42	RDI proportions based on RWE	Pem+lenv	£0	0.000	Cabo+nivo dominated
RDI and effectiveness of pem+lenv	Per base case	43	Assume effectiveness of pem+lenv same as cabo+nivo, using company alternative RDIs	Cabo	£0	0.000	Cabo+nivo dominated
RDI and effectiveness of pem+lenv	Per base case	44	Assume effectiveness of pem+lenv same as cabo+nivo	Cabo	£0	0.000	Cabo+nivo dominated
RDI	Original values	45	All company alternative RDIs	Pem+lenv	£0	0.000	Cabo+nivo dominated
RDI	Original values	46	All company RDIs (IOs only)	Pem+lenv	£0	0.000	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
RDI	Original values	47	All company alternative RDIs, PartSA	Pem+lenv	£0	0.000	Cabo+nivo dominated
RDI	Original values	48	All company RDIs (IOs only), PartSA	Cabo+nivo extendedly dominated Pairwise ICERs vs pem+lenv SW quadrant £108,235 and vs nivo+ipi £4,910,635			
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	49	CheckMate 9ER for 1L	Pem+lenv	£0	0.000	Cabo+nivo dominated
		50	CheckMate 9ER for all lines	Pem+lenv	£0	0.000	Cabo+nivo dominated
		51	CheckMate 9ER for all lines, PartSA	Pem+lenv	£0	0.000	Cabo+nivo dominated
		52	CheckMate 9ER for all lines (no age adjustment)	Pem+lenv	£0	0.000	Cabo+nivo dominated
		53	CheckMate 9ER for all lines (no age adjustment, PartSA)	Pem+lenv	£0	0.000	Cabo+nivo dominated
		54	Same PFS and PD from 2L onwards	Pem+lenv	£0	0.000	Cabo+nivo dominated
		55	Higher proportional decrease for 3L and 4L	Pem+lenv	£0	0.000	Cabo+nivo dominated
Utilities for BSC	Assumed same as progressed: current line	56	Assumed same as progression free: current line	Pem+lenv	£0	0.000	Cabo+nivo dominated
		57	Assume same as final health state	Pem+lenv	£0	0.000	Cabo+nivo dominated
Adverse events							

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Data source used for AEs	NMA	58	Individual trials	Pem+lenv	£0	0.000	Cabo+nivo dominated
AEs applied	One off	59	Per cycle	Pem+lenv	£0	0.000	Cabo+nivo dominated
AE disutilities not considered	Yes	60	No	Pem+lenv	£0	0.000	Cabo+nivo dominated
Scale of impact	Per analysis	61	Doubled	Pem+lenv	£0	0.000	Cabo+nivo dominated
Axi AE impact	Per NMA	62	Set the same as tivo	Pem+lenv	£0	0.000	Cabo+nivo dominated
Subsequent treatments							
Data source	RWE	63	Trial	Pem+lenv	£0	0.000	Cabo+nivo dominated
Adjuvant treatments							
% of eligible patients receiving adjuvant pem	0%	64	20%	Pem+lenv	£0	0.000	Cabo+nivo dominated
	0%	65	65%	Pem+lenv	£0	0.000	Cabo+nivo dominated
Uncertainty around inputs for pem+lenv							
Pem+lenv inputs	Pem+lenv data used for RDI FP NMA used for cabo+nivo and PH NMA for pem+lenv	66	Pem+lenv assumed to have same RDI as nivo+cabo PH NMA used for all 1st line treatments	Pem+lenv	£0	0.000	Cabo+nivo dominated
Time Horizon							
Time horizon	40	67	5	Pem+lenv	£0	0.000	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Time horizon	40	68	10	Pem+lenv	£0	0.000	Cabo+nivo dominated
Time horizon	40	69	20	Pem+lenv	£0	0.000	Cabo+nivo dominated
Time horizon	40	70	5, PartSA	Nivo+ipi	£81,976	0.031	£2,630,390
Time horizon	40	71	10, PartSA	Pem+lenv	£0	0.000	Cabo+nivo dominated
Time horizon	40	72	20, PartSA	Pem+lenv	£0	0.000	Cabo+nivo dominated

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; inc, incremental; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

*Next best comparator defined as next most efficient non-dominated comparator.

Q.2.6. Probabilistic base case results

The probabilistic analysis (Table 16) yields the same conclusions as the deterministic. In the all-risk population, cabozantinib + nivolumab is associated with an ICER of £315,109 compared with the next best non-dominated comparator (pazopanib), itself associated with an ICER of £25,472 versus sunitinib. In the favourable risk population, the ICER of cabozantinib + nivolumab is £443,970 (versus pazopanib). Pazopanib is associated with an ICER of £31,936 compared with sunitinib. In the intermediate / poor risk population, cabozantinib + nivolumab is dominated by cabozantinib monotherapy and lenvatinib + pembrolizumab. Lenvatinib + pembrolizumab is associated with an ICER of £143,469 vs pazopanib, and pazopanib an ICER of £17,740 compared with sunitinib. In all populations the probability that cabozantinib + nivolumab is cost effective is approximately zero (Figure 20 to Figure 22).

Table 16: Base-case results at list price (probabilistic, ordered in increasing cost)

Tech	Costs (£) (95% CI)	QALYs (95% CI)	LYG (95% CI)	Inc. Costs (95% CI)	Inc. LYG (95% CI)	Inc. QALYs (95% CI)	ICER Pairwise	ICER f.inc.	Severity modifier
Risk population: All risk									
Suni	85,907 (61,027, 119,767)	3.032 (2.441, 3.829)	1.845 (1.458, 2.29)						1
Pazo	86,557 (60,299, 119,305)	3.073 (2.446, 3.857)	1.871 (1.488, 2.332)	650 (-9,098, 10,351)	0.041 (-0.175, 0.242)	0.026 (-0.255, 0.332)		25,472	1
Tivo	106,075 (75,426, 140,435)	3.021 (2.403, 3.794)	1.843 (1.44, 2.31)						1
Cabo+nivo	234,537 (184,298, 275,935)	3.793 (3.041, 4.777)	2.34 (1.839, 2.933)	147,980 (106,917, 184,569)	0.72 (0.109, 1.424)	0.47 (-0.01, 0.983)		315,109	1
Risk population: Favourable risk									
Suni	90,575 (59,928, 125,997)	3.936 (3.117, 4.88)	2.377 (1.825, 2.97)						1
Pazo	91,140 (59,620, 128,301)	3.978 (3.113, 4.948)	2.395 (1.841, 3)	565 (-9,360, 10,588)	0.042 (-0.183, 0.255)	0.018 (-0.402, 0.458)		31,936	1
Tivo	121,973 (87,182, 161,284)	3.925 (3.056, 4.965)	2.37 (1.811, 2.978)						1
Cabo+nivo	270,118 (187,712, 359,262)	4.659 (3.149, 6.548)	2.798 (1.914, 3.844)	178,978 (104,613, 2665,41)	0.681 (-0.569, 2.106)	0.403 (-0.388, 1.384)		443,970	1
Risk population: Intermediate / poor risk									
Suni	83,165 (54,213, 115,521)	2.701 (2.111, 3.498)	1.641 (1.272, 2.114)						1.2
Pazo	83,516 (55,144, 116,868)	2.735 (2.12, 3.524)	1.661 (1.298, 2.1)	352 (-8,834, 10,307)	0.034 (-0.168, 0.245)	0.02 (-0.207, 0.241)		17,740	1.2
Tivo	98,665 (68,322, 134,045)	2.682 (2.084, 3.513)	1.634 (1.283, 2.092)						1.2
Nivo+ipi	118,314 (89,848, 146,498)	2.321 (1.639, 3.372)	1.442 (1.041, 1.987)						1
Cabo	166,044 (122,409, 200,914)	3.66 (2.945, 4.512)	2.233 (1.778, 2.747)						1
Pem+lenv	184,683 (143,856, 225,715)	3.817 (3.072, 4.813)	2.366 (1.845, 2.969)	101,167 (69,623, 134,260)	1.082 (0.426, 1.778)	0.705 (0.21, 1.261)		143,469	1
Cabo+nivo	212,254 (165,233, 250,672)	3.432 (2.698, 4.431)	2.127 (1.65, 2.697)						1

Abbreviations: cabo, cabozantinib; ext, extended; f.inc: fully incremental. ICER, incremental cost-effectiveness ratio; inc, incremental; ipi, ipilimumab; lenv, lenvatinib; LYG, life years gained; nivo, nivolumab; pazo, pazopanib; QALYs, quality adjusted life years; suni, sunitinib; tivo, tivozanib; vs, versus

Figure 20: Cost Effectiveness Acceptability Curve, All risk population

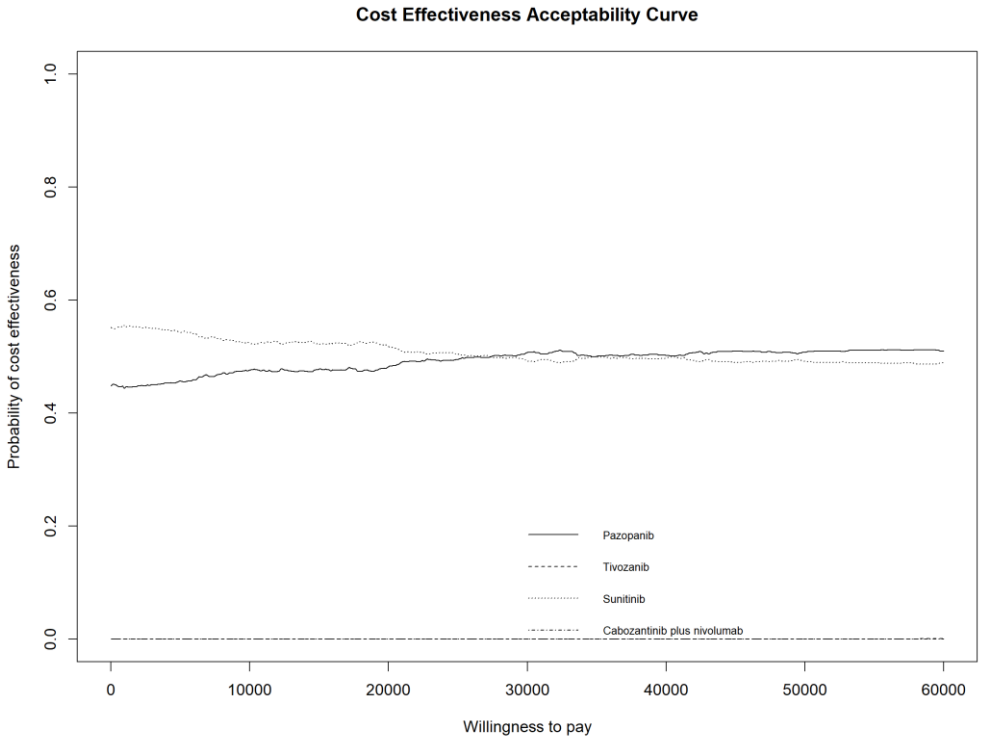


Figure 21: Cost Effectiveness Acceptability Curve, Favourable risk population

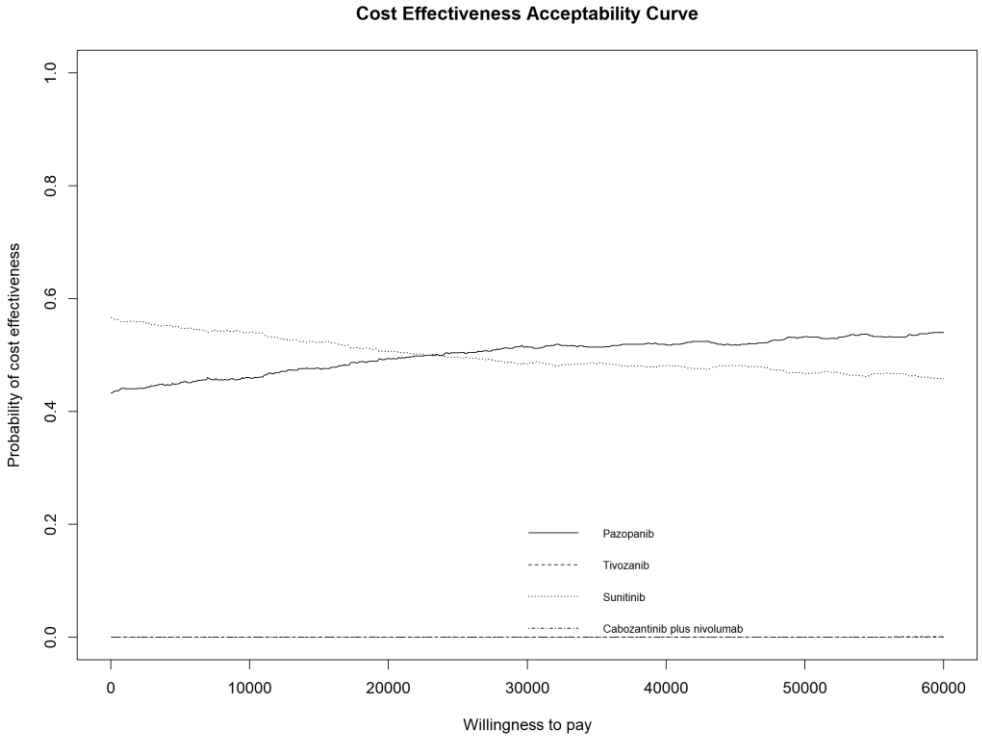
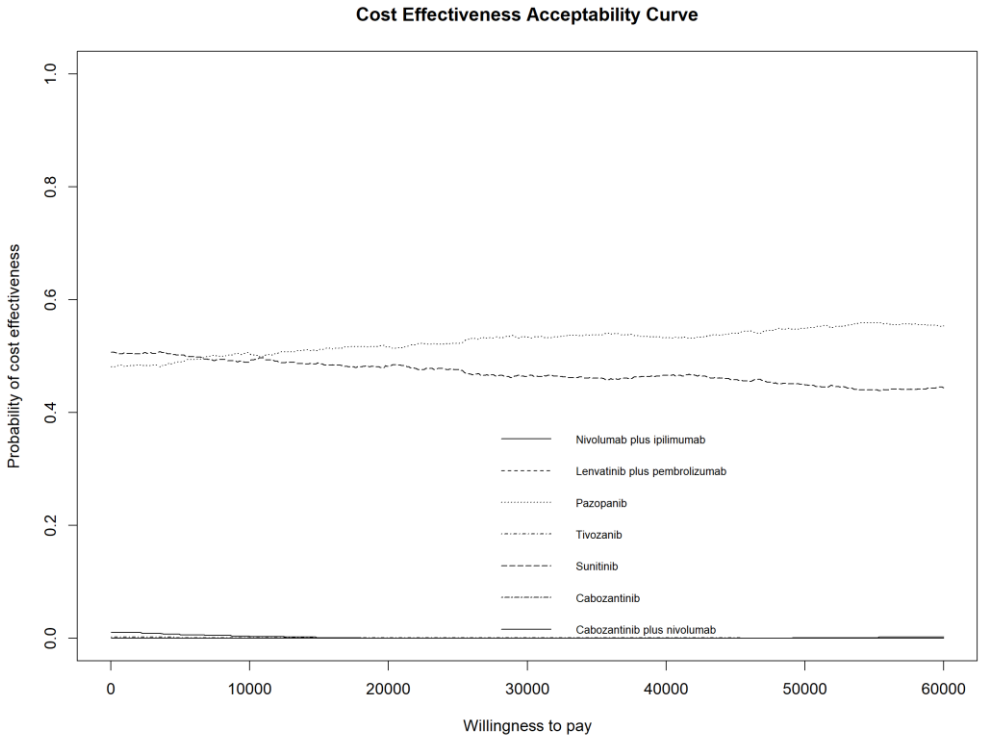


Figure 22: Cost Effectiveness Acceptability Curve, Intermediate/poor risk population



Q.2.7. Validation of cost-effectiveness analysis

We have previously presented fits to Kaplan-Meier curves in Appendix K as well as state occupancy plots. Comparison has been provided to findings from prior technology appraisals within the cPAS appendix provided to the Committee due to the heavy level of redacting in many of the prior submissions.

Q.3. Interpretation and conclusions of economic evidence

The LYs and QALYs predicted in the base case of this appraisal are generally lower than those in previous appraisals; consistent with the UK RWE Kaplan Meier data showing reduced PFS and OS compared to trial data. This is true regardless of whether a state transition or PartSA model structure is used and for all therapies.

The cost-effectiveness results presented are considered to be more generalisable to clinical practice in England than previous renal oncology submissions to NICE given that baseline risk, patient characteristics and treatment pathways are based upon a rich source of UK specific evidence from the UK RWE data set. As expected, use of UK RWE for baseline risk resulted in lower absolute LYs and QALYs for all treatments.

Cost-effectiveness conclusions differ by risk subgroup as the comparators available differ and the evidence for the effectiveness of cabozantinib + nivolumab and other IO / TKIs is considerably stronger in the intermediate / poor risk population.

All the results presented in this addendum are at list prices and therefore should be interpreted with caution as patient access schemes are available for the majority of treatments involved.

Conclusions from the probabilistic and deterministic analyses were identical. In the favourable risk population cabozantinib + nivolumab was not cost-effective in any of the scenarios run. The scenarios which had the most impact on cost-effectiveness were:

- The model structure chosen as the trial data indicated an overall survival (OS) hazard ratio (HR) >1 in this population a PartSA model structure led to a dominated result.
- The primary data source chosen (use of trial data increased the ICER as the CheckMate 9ER the primary driver again being that more patients went on to receive BSC rather than an active treatment in 2nd line based upon the data supplied).
- Choice of NMA approach for 2nd line + therapy (the FP NMA led to substantial increases in the ICER).
- The assumptions made for costs:
  - The source of data used for RDI – using the companies alternative values reduces the ICERs
  - Assumptions around TTD, assuming TTD = PFS reduces the ICER as the TTD curve lay slightly above the PFS curve in the RWE

There are major uncertainties in the economic and clinical case for cabozantinib + nivolumab in the favourable risk subgroup. It is likely that cost-effectiveness estimates for novel treatments drawing on comparatively less mature trials may be unduly optimistic.

In the intermediate / poor risk population cabozantinib + nivolumab was again not cost-effective in any scenario, being dominated in most cases by lenvatinib + pembrolizumab.

The only non-dominated scenarios were the use of the PH NMA for all effectiveness estimates in the PartSA structure, yielding an ICER of £1,549,670, and use of a short time horizon of 5 years in the PartSA, yielding an ICER of £2,630,390.

In both subgroups a number of additional uncertainties and areas for exploration remain:

- Difficultly making comparison to pembrolizumab + lenvatinib via FP NMA may bias results in favour of pembrolizumab + lenvatinib which is likely to impact on cost-effectiveness conclusions.
- How and if the severity modifier should be applied (the EAG note that in probabilistic analysis it is highly likely that a number of scenarios would result in application of the modifier, it is not clear how the modifier should be handled in such analyses).
- The accuracy with which the toxicity of TKI treatments has been captured.
- The EAG note that use of the current state transition structure likely disadvantages nivolumab + ipilimumab as only gains in PFS are considered. Some clinical experts considered that PFS may not be as useful a measurement for this treatment and trial data does show a higher-than-expected level of post-progression survival.

Appendix 1: Detailed breakdown of PartSA results

Table 17: PartSA analysis life years

	PFS on treatment	PFS off treatment	PPS on treatment	PPS off treatment	Total
All risk					
cabo+nivo	1.945	0.100	0	1.305	3.351
pazo	1.144	0.107	0	1.648	2.900
tivo	1.144	0.107	0	1.648	2.900
suni	1.144	0.107	0	1.648	2.900
Favourable risk					
cabo+nivo	2.571	0.127	0	1.702	4.411
pazo	1.789	0.145	0	2.931	4.905
tivo	1.789	0.145	0	2.931	4.905
suni	1.789	0.145	0	2.931	4.905
Intermediate/poor risk					
cabo+nivo	1.636	0.076	0	1.236	2.948
nivo+ipi	0.977	0.108	0	1.831	2.917
pem+lenv	2.289	0.093	0	0.660	3.042
pazo	0.887	0.069	0	1.322	2.278
tivo	0.887	0.069	0	1.322	2.278
suni	0.887	0.069	0	1.322	2.278
cabo	1.788	0.095	0	0.926	2.808

Abbreviations: cabo, cabozantinib; lenv, lenvatinib; LYG, life years gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; PPS, post progression survival; suni, sunitinib; tivo, tivozanib

Table 18: PartSA QALYs

	PFS	PPS	AE	AE PPS	Total
All risk					
cabo+nivo	1.413	0.783	-0.029	-0.044	2.123
pazo	0.878	0.984	-0.013	-0.021	1.828
tivo	0.878	0.984	-0.007	-0.016	1.839
suni	0.878	0.984	-0.013	-0.021	1.828
Favourable risk					
cabo+nivo	1.784	0.952	-0.029	-0.044	2.664
pazo	1.311	1.622	-0.013	-0.021	2.900
tivo	1.311	1.622	-0.007	-0.016	2.911

	PFS	PPS	AE	AE PPS	Total
suni	1.311	1.622	-0.013	-0.021	2.900
Intermediate/poor risk					
cabo+nivo	1.198	0.754	-0.029	-0.045	1.878
nivo+ipi	0.759	1.125	-0.006	-0.010	1.867
pem+lenv	1.614	0.395	-0.027	-0.037	1.944
pazo	0.682	0.811	-0.013	-0.021	1.459
tivo	0.682	0.811	-0.007	-0.016	1.470
suni	0.682	0.811	-0.013	-0.021	1.459
cabo	1.295	0.558	-0.017	-0.023	1.813

Abbreviations:AE, adverse event; cabo, cabozantinib; env, lenvatinib; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; PPS, post progression survival; QALYs, quality adjusted life years; suni, sunitinib; tivo, tivozanib

Table 19: PartSA costs

				Subsequent treatment			MRU				
	Drug cost (£)	Admin cost (£)	AE cost (£)	Drug cost (£)	Admin cost (£)	AE cost	Pre-progression cost (£)	Post progression cost (£)	EOL cost (£)	On progression cost (£)	Total cost (£)
All risk											
cabo+nivo	£178,438	£3,282	£1,127	£22,626	£499	£1,765	£4,074	£2,346	£7,797	£4,528	£226,481
pazo	£6,481	£324	£512	£40,793	£3,393	£871	£2,615	£2,955	£7,923	£4,648	£70,514
tivo	£27,787	£336	£408	£42,683	£4,032	£774	£2,615	£2,955	£7,923	£4,648	£94,161
suni	£6,836	£275	£604	£40,407	£3,471	£958	£2,615	£2,955	£7,923	£4,648	£70,691
Favourable risk											
cabo+nivo	£210,511	£3,496	£1,127	£22,202	£490	£1,731	£5,101	£2,873	£7,565	£4,443	£259,539
pazo	£9,859	£395	£512	£39,934	£3,321	£853	£3,807	£4,907	£7,455	£4,550	£75,592
tivo	£42,269	£413	£408	£41,785	£3,947	£758	£3,807	£4,907	£7,455	£4,550	£110,299
suni	£10,336	£320	£604	£39,556	£3,398	£938	£3,807	£4,907	£7,455	£4,550	£75,870
Intermediate/ poor risk											
cabo+nivo	£157,237	£3,024	£1,127	£22,868	£505	£1,783	£3,486	£2,257	£7,898	£4,576	£204,761
nivo+ipi	£76,613	£3,045	£335	£21,072	£594	£505	£2,277	£3,381	£7,910	£4,674	£120,405
pem+lenv	£124,634	£1,771	£1,062	£25,646	£504	£1,551	£4,622	£1,183	£7,888	£4,482	£173,343
pazo	£5,137	£296	£512	£41,179	£3,425	£879	£2,079	£2,432	£8,081	£4,692	£68,710
tivo	£22,024	£305	£408	£43,087	£4,070	£782	£2,079	£2,432	£8,081	£4,692	£87,959
suni	£5,443	£258	£604	£40,789	£3,504	£967	£2,079	£2,432	£8,081	£4,692	£68,847
cabo	£98,157	£412	£732	£36,466	£4,502	£982	£3,753	£1,674	£7,945	£4,554	£159,176

Abbreviations: admin, administration; AE, adverse event; cabo, cabozantinib; EOL, end of life; ipi, ipilimumab; lenv, lenvatinib; mru, medical resource use; nivo, nivolumab; PartSA, partitioned survival analysis; PAS, patient access scheme; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib

Table 20: PartSA results (ordered in increasing cost)

	Total			Incremental				
Technologies	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER cabo + nivo vs comparator(£/QALY)	ICER incremental (£/QALY)
All-risk								
cabo+nivo	£70,514	2.90	1.83	£0	0.00	0.00	£528126	£0
pazo	£70,691	2.90	1.83				£527866	(ext dominated)
tivo	£94,161	2.90	1.84				£466095	(ext dominated)
suni	£226,481	3.35	2.12	£155,968	0.45	0.30		£528126
Favourable risk								
cabo+nivo	£75,592	4.90	2.90	£0	0.00	0.00	Cabo+nivo dominated	£0
pazo	£75,870	4.90	2.90	£278	0.00	0.00	Cabo+nivo dominated	£1439582
tivo	£110,299	4.90	2.91	£34,429	0.00	0.01	Cabo+nivo dominated	£3093868
suni	£259,539	4.41	2.66					(dominated)
Intermediate/ poor risk								
cabo+nivo	£68,710	2.28	1.46	£0	0.00	0.00	£324003	£0
nivo+ipi	£68,847	2.28	1.46				£323823	(ext dominated)
pem+lenv	£87,959	2.28	1.47				£285981	(ext dominated)
pazo	£120,405	2.92	1.87	£51,695	0.64	0.41	£7537719	£126481
tivo	£159,176	2.81	1.81				£700321	(dominated)
suni	£173,343	3.04	1.94	£52,938	0.13	0.08	Cabo+nivo dominated	£687154

	Total			Incremental				
cabo	£204,761	2.95	1.88					(dominated)

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Appendix 2: Scenario Analysis Pairwise Tables

Table 21**: Base case pairwise comparison table**

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.22	3.71				
pazo	£83,572	1.69	2.84	£152,823	0.53	0.88	£289,554
tivo	£102,777	1.66	2.76	£133,618	0.56	0.95	£238,496
suni	£82,905	1.67	2.78	£153,491	0.56	0.93	£276,480
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 22: Scenario analysis 1 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£226,481	2.12	3.35				
pazo	£70,514	1.83	2.90	£155,968	0.30	0.45	£528,126
tivo	£94,161	1.84	2.90	£132,320	0.28	0.45	£466,095
suni	£70,691	1.83	2.90	£155,790	0.30	0.45	£527,866
Risk population: Favourable risk							
cabo+nivo	£259,539	2.66	4.41				
pazo	£75,592	2.90	4.90	£183,947	-0.24	-0.49	Cabo+nivo dominated
tivo	£110,299	2.91	4.90	£149,240	-0.25	-0.49	Cabo+nivo dominated
suni	£75,870	2.90	4.90	£183,669	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£204,761	1.88	2.95				
nivo+ipi	£120,405	1.87	2.92	£84,356	0.01	0.03	£7,537,719
pem+lenv	£173,343	1.94	3.04	£31,418	-0.07	-0.09	Cabo+nivo dominated
pazo	£68,710	1.46	2.28	£136,051	0.42	0.67	£324,003
tivo	£87,959	1.47	2.28	£116,802	0.41	0.67	£285,981
suni	£68,847	1.46	2.28	£135,913	0.42	0.67	£323,823
cabo	£159,176	1.81	2.81	£45,585	0.07	0.14	£700,321

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 23: Scenario analysis 2 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,261	2.22	3.71				
pazo	£80,791	1.68	2.79	£155,471	0.54	0.92	£286,863
tivo	£100,118	1.64	2.72	£136,143	0.57	0.99	£236,795
suni	£80,227	1.65	2.74	£156,034	0.57	0.97	£273,693
Risk population: Favourable risk							
cabo+nivo	£269,016	2.66	4.51				
pazo	£86,498	2.21	3.69	£182,518	0.45	0.82	£401,398
tivo	£116,906	2.18	3.61	£152,110	0.49	0.90	£311,579
suni	£86,014	2.18	3.63	£183,002	0.48	0.88	£378,718
Risk population: Intermediate / poor risk							
cabo+nivo	£214,268	2.00	3.35				
nivo+ipi	£121,618	1.27	2.06	£92,650	0.74	1.29	£126,021
pem+lenv	£184,862	2.21	3.58	£29,406	-0.21	-0.23	Cabo+nivo dominated
pazo	£78,180	1.47	2.46	£136,088	0.53	0.89	£255,817
tivo	£93,109	1.44	2.39	£121,159	0.56	0.96	£214,626
suni	£77,589	1.44	2.40	£136,678	0.56	0.95	£244,157
cabo	£161,919	2.06	3.42	£52,349	-0.06	-0.07	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 24: Scenario analysis 3 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£227,757	2.15	3.54				
pazo	£59,571	1.46	2.32	£168,186	0.69	1.22	£242,097
tivo	£77,252	1.40	2.19	£150,505	0.75	1.35	£199,361
suni	£58,830	1.43	2.26	£168,926	0.72	1.28	£233,051
Risk population: Favourable risk							
cabo+nivo	£260,637	2.60	4.35				
pazo	£64,926	1.99	3.20	£195,710	0.61	1.15	£320,033
tivo	£93,660	1.93	3.06	£166,976	0.67	1.28	£248,241
suni	£64,263	1.96	3.14	£196,374	0.64	1.21	£305,842
Risk population: Intermediate / poor risk							
cabo+nivo	£205,768	1.93	3.19				
nivo+ipi	£102,299	1.05	1.60	£103,469	0.89	1.58	£116,775
pem+lenv	£176,284	2.13	3.39	£29,484	-0.20	-0.21	Cabo+nivo dominated
pazo	£57,222	1.25	2.00	£148,546	0.68	1.19	£217,750
tivo	£70,525	1.19	1.87	£135,243	0.74	1.32	£182,346
suni	£56,457	1.22	1.94	£149,311	0.71	1.25	£209,709
cabo	£144,377	1.75	2.72	£61,391	0.19	0.47	£326,676

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 25: Scenario analysis 4 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£255,007	2.52	3.71				
pazo	£92,651	1.88	2.84	£162,357	0.64	0.88	£254,200
tivo	£112,599	1.83	2.76	£142,409	0.68	0.95	£208,664
suni	£91,599	1.84	2.78	£163,408	0.68	0.93	£242,073
Risk population: Favourable risk							
cabo+nivo	£297,718	3.09	4.52				
pazo	£101,300	2.52	3.73	£196,418	0.57	0.78	£343,387
tivo	£134,352	2.48	3.66	£163,366	0.62	0.86	£264,573
suni	£100,308	2.49	3.68	£197,410	0.61	0.84	£323,857
Risk population: Intermediate / poor risk							
cabo+nivo	£229,756	2.25	3.36				
nivo+ipi	£131,697	1.39	2.09	£98,060	0.86	1.26	£113,416
pem+lenv	£200,801	2.49	3.62	£28,956	-0.24	-0.26	Cabo+nivo dominated
pazo	£88,996	1.63	2.50	£140,760	0.62	0.85	£226,990
tivo	£104,017	1.59	2.43	£125,739	0.66	0.92	£189,662
suni	£87,930	1.60	2.45	£141,826	0.66	0.91	£216,272
cabo	£181,236	2.32	3.46	£48,520	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 26: Scenario analysis 5 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£225,595	2.06	3.71				
pazo	£78,453	1.59	2.84	£147,142	0.47	0.88	£312,493
tivo	£97,143	1.57	2.76	£128,452	0.50	0.95	£257,975
suni	£77,966	1.57	2.78	£147,629	0.49	0.93	£298,810
Risk population: Favourable risk							
cabo+nivo	£253,345	2.44	4.52				
pazo	£82,742	2.06	3.73	£170,603	0.37	0.78	£455,161
tivo	£111,440	2.04	3.66	£141,905	0.40	0.86	£353,087
suni	£82,338	2.04	3.68	£171,007	0.40	0.84	£429,639
Risk population: Intermediate / poor risk							
cabo+nivo	£205,457	1.87	3.36				
nivo+ipi	£118,926	1.21	2.09	£86,532	0.65	1.26	£132,343
pem+lenv	£177,207	2.08	3.62	£28,250	-0.21	-0.26	Cabo+nivo dominated
pazo	£76,358	1.40	2.50	£129,099	0.47	0.85	£277,261
tivo	£90,962	1.38	2.43	£114,495	0.49	0.92	£232,488
suni	£75,842	1.38	2.45	£129,615	0.49	0.91	£265,240
cabo	£155,637	1.93	3.46	£49,820	-0.06	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 27: Scenario analysis 6 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£239,975	2.08	3.35				
pazo	£60,905	1.55	2.49	£179,070	0.52	0.86	£341,637
tivo	£91,310	1.63	2.64	£148,665	0.45	0.70	£333,512
suni	£69,243	1.65	2.68	£170,733	0.43	0.66	£395,868
Risk population: Favourable risk							
cabo+nivo	£277,145	2.48	3.99				
pazo	£67,685	2.06	3.27	£209,460	0.41	0.72	£508,525
tivo	£110,236	2.15	3.44	£166,909	0.33	0.55	£505,272
suni	£76,499	2.16	3.48	£200,646	0.31	0.51	£637,037
Risk population: Intermediate / poor risk							
cabo+nivo	£226,243	1.99	3.21				
nivo+ipi	£149,124	1.73	2.85	£77,118	0.27	0.37	£290,345
pem+lenv	£199,915	3.05	5.42	£26,327	-1.06	-2.20	Cabo+nivo dominated
pazo	£58,531	1.40	2.24	£167,712	0.59	0.97	£284,656
tivo	£85,347	1.48	2.39	£140,895	0.51	0.82	£274,950
suni	£66,653	1.49	2.44	£159,590	0.50	0.78	£320,179
cabo	£149,991	2.02	3.20	£76,252	-0.03	0.02	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 28: Scenario analysis 7 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£243,381	3.63	6.76				
pazo	£72,876	3.36	6.55	£170,505	0.27	0.21	£624,939
tivo	£97,740	3.37	6.55	£145,641	0.26	0.21	£552,746
suni	£73,979	3.36	6.55	£169,402	0.27	0.21	£618,755
Risk population: Favourable risk							
cabo+nivo	£278,794	3.36	5.71				
pazo	£76,453	3.60	6.24	£202,342	-0.24	-0.53	Cabo+nivo dominated
tivo	£113,197	3.61	6.24	£165,597	-0.25	-0.53	Cabo+nivo dominated
suni	£77,647	3.60	6.24	£201,147	-0.24	-0.53	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£229,325	3.24	5.65				
nivo+ipi	£155,027	3.36	5.92	£74,298	-0.11	-0.27	Cabo+nivo dominated
pem+lenv	£194,993	4.01	7.82	£34,332	-0.76	-2.17	Cabo+nivo dominated
pazo	£70,834	2.90	5.53	£158,491	0.34	0.12	£464,958
tivo	£92,241	2.91	5.53	£137,084	0.33	0.12	£413,514
suni	£71,911	2.90	5.53	£157,414	0.34	0.12	£460,517
cabo	£159,256	3.13	5.37	£70,069	0.12	0.28	£596,082

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 29: Scenario analysis 8 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,312	2.22	3.70				
pazo	£83,518	1.70	2.83	£152,794	0.53	0.87	£289,866
tivo	£102,731	1.66	2.76	£133,582	0.56	0.94	£238,771
suni	£82,855	1.67	2.77	£153,457	0.55	0.92	£276,807
Risk population: Favourable risk							
cabo+nivo	£269,072	2.67	4.50				
pazo	£89,287	2.23	3.73	£179,785	0.44	0.77	£408,945
tivo	£119,576	2.19	3.65	£149,497	0.47	0.85	£316,413
suni	£88,703	2.20	3.67	£180,370	0.47	0.83	£386,024
Risk population: Intermediate / poor risk							
cabo+nivo	£214,317	2.00	3.34				
nivo+ipi	£123,643	1.28	2.09	£90,673	0.72	1.25	£125,332
pem+lenv	£185,842	2.23	3.61	£28,474	-0.23	-0.27	Cabo+nivo dominated
pazo	£80,872	1.49	2.49	£133,444	0.52	0.84	£258,091
tivo	£95,688	1.45	2.42	£118,628	0.55	0.91	£216,107
suni	£80,184	1.46	2.44	£134,132	0.54	0.90	£246,573
cabo	£164,977	2.07	3.45	£49,339	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 30: Scenario analysis 9 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,291	2.22	3.69				
pazo	£83,509	1.69	2.83	£152,781	0.53	0.86	£290,722
tivo	£102,724	1.66	2.76	£133,566	0.56	0.93	£239,502
suni	£82,848	1.67	2.77	£153,443	0.55	0.92	£277,647
Risk population: Favourable risk							
cabo+nivo	£269,078	2.66	4.50				
pazo	£89,309	2.22	3.72	£179,769	0.44	0.77	£410,118
tivo	£119,595	2.19	3.65	£149,484	0.47	0.85	£317,362
suni	£88,725	2.20	3.67	£180,353	0.47	0.83	£387,158
Risk population: Intermediate / poor risk							
cabo+nivo	£214,294	2.00	3.33				
nivo+ipi	£123,639	1.28	2.09	£90,655	0.72	1.25	£125,628
pem+lenv	£185,839	2.23	3.61	£28,455	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,863	1.48	2.49	£133,432	0.52	0.84	£258,760
tivo	£95,681	1.45	2.42	£118,614	0.55	0.91	£216,688
suni	£80,176	1.46	2.44	£134,119	0.54	0.89	£247,230
cabo	£164,968	2.07	3.45	£49,326	-0.07	-0.12	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 31: Scenario analysis 10 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£269,214	2.60	4.57				
pazo	£87,673	1.84	3.15	£181,541	0.76	1.41	£240,413
tivo	£107,670	1.79	3.02	£161,544	0.81	1.54	£199,576
suni	£86,076	1.80	3.06	£183,138	0.79	1.50	£230,933
Risk population: Favourable risk							
cabo+nivo	£306,279	2.99	5.22				
pazo	£95,729	2.36	3.98	£210,550	0.63	1.24	£335,854
tivo	£127,381	2.31	3.84	£178,899	0.68	1.38	£261,591
suni	£94,138	2.32	3.89	£212,141	0.67	1.33	£318,292
Risk population: Intermediate / poor risk							
cabo+nivo	£254,787	2.50	4.40				
nivo+ipi	£163,351	1.88	3.21	£91,435	0.62	1.19	£147,003
pem+lenv	£232,309	3.35	6.18	£22,478	-0.86	-1.78	Cabo+nivo dominated
pazo	£84,663	1.68	2.89	£170,124	0.81	1.51	£208,928
tivo	£101,317	1.63	2.76	£153,470	0.87	1.63	£176,967
suni	£83,085	1.65	2.80	£171,702	0.85	1.59	£201,688
cabo	£187,601	2.47	4.25	£67,186	0.03	0.15	£2,178,957

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 32: Scenario analysis 11 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£243,759	2.35	3.95				
pazo	£83,572	1.69	2.84	£160,187	0.66	1.12	£244,271
tivo	£102,777	1.66	2.76	£140,982	0.69	1.19	£204,844
suni	£82,905	1.67	2.78	£160,855	0.68	1.17	£235,461
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£225,867	2.16	3.65				
nivo+ipi	£155,777	1.62	2.66	£70,089	0.54	0.99	£129,331
pem+lenv	£185,897	2.23	3.62	£39,970	-0.07	0.03	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£144,940	0.68	1.15	£214,442
tivo	£95,735	1.45	2.43	£130,131	0.71	1.22	£183,820
suni	£80,234	1.46	2.45	£145,633	0.70	1.20	£207,171
cabo	£171,776	2.14	3.54	£54,090	0.02	0.10	£2,546,989

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 33: Scenario analysis 12 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£223,039	1.87	2.96				
pazo	£93,230	1.77	3.03	£129,809	0.10	-0.07	£1,266,501
tivo	£113,646	1.75	2.99	£109,393	0.12	-0.03	£922,848
suni	£93,666	1.77	3.03	£129,373	0.11	-0.07	£1,216,091
Risk population: Favourable risk							
cabo+nivo	£255,995	2.32	3.76				
pazo	£99,122	2.30	3.93	£156,873	0.02	-0.17	£7,743,976
tivo	£130,634	2.29	3.89	£125,361	0.04	-0.13	£3,423,837
suni	£99,654	2.30	3.93	£156,342	0.02	-0.17	£6,458,274
Risk population: Intermediate / poor risk							
cabo+nivo	£201,050	1.65	2.61				
nivo+ipi	£123,240	1.28	2.09	£77,811	0.37	0.52	£208,414
pem+lenv	£186,304	2.27	3.71	£14,746	-0.62	-1.10	Cabo+nivo dominated
pazo	£90,472	1.56	2.69	£110,578	0.09	-0.09	£1,188,094
tivo	£106,477	1.54	2.65	£94,573	0.11	-0.05	£868,728
suni	£90,869	1.56	2.69	£110,181	0.10	-0.08	£1,136,892
cabo	£171,330	1.99	3.28	£29,721	-0.34	-0.67	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 34: Scenario analysis 13 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.22	3.71				
pazo	£83,572	1.69	2.84	£152,823	0.53	0.88	£289,554
tivo	£102,777	1.66	2.76	£133,618	0.56	0.95	£238,496
suni	£82,905	1.67	2.78	£153,491	0.56	0.93	£276,480
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£165,306	1.76	2.78	£49,095	0.25	0.57	£198,854
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 35: Scenario analysis 14 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£247,105	2.37	4.00				
pazo	£86,933	1.79	3.02	£160,171	0.59	0.98	£272,803
tivo	£107,536	1.75	2.95	£139,569	0.62	1.05	£225,589
suni	£86,302	1.76	2.97	£160,803	0.61	1.04	£261,705
Risk population: Favourable risk							
cabo+nivo	£284,156	2.90	5.03				
pazo	£92,483	2.34	4.02	£191,672	0.56	1.01	£341,261
tivo	£124,585	2.31	3.95	£159,571	0.59	1.08	£268,891
suni	£91,942	2.31	3.96	£192,214	0.59	1.07	£326,265
Risk population: Intermediate / poor risk							
cabo+nivo	£223,644	2.13	3.59				
nivo+ipi	£140,233	1.48	2.45	£83,411	0.65	1.14	£128,875
pem+lenv	£195,381	2.45	4.00	£28,263	-0.31	-0.41	Cabo+nivo dominated
pazo	£84,375	1.56	2.65	£139,269	0.57	0.94	£245,705
tivo	£100,242	1.53	2.58	£123,401	0.60	1.01	£206,322
suni	£83,710	1.54	2.60	£139,933	0.59	0.99	£235,605
cabo	£174,857	2.20	3.71	£48,786	-0.07	-0.12	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 36: Scenario analysis 15 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.22	3.71				
pazo	£83,143	1.62	2.71	£153,252	0.61	1.00	£253102
tivo	£102,777	1.66	2.76	£133,618	0.56	0.95	£238496
suni	£82,905	1.67	2.78	£153,491	0.56	0.93	£276480
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,378	2.20	3.71	£179,770	0.46	0.81	£388785
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£81,290	1.51	2.54	£133,111	0.50	0.82	£267886
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 37: Scenario analysis 16 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.22	3.71				
pazo	£83,572	1.69	2.84	£152,823	0.53	0.88	£289,554
tivo	£109,937	1.70	2.86	£126,458	0.52	0.86	£241,591
suni	£82,905	1.67	2.78	£153,491	0.56	0.93	£276,480
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£121,202	2.24	3.74	£147,946	0.42	0.78	£348,808
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£98,342	1.53	2.55	£116,060	0.47	0.81	£245,149
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 38: Scenario analysis 17 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£237,944	2.25	3.77				
pazo	£84,165	1.70	2.85	£153,779	0.54	0.91	£282,737
tivo	£103,431	1.67	2.78	£134,513	0.58	0.98	£233,897
suni	£83,617	1.68	2.80	£154,328	0.57	0.96	£271,211
Risk population: Favourable risk							
cabo+nivo	£270,674	2.69	4.57				
pazo	£89,929	2.23	3.75	£180,745	0.46	0.82	£396,528
tivo	£120,274	2.20	3.68	£150,400	0.49	0.89	£308,507
suni	£89,461	2.21	3.70	£181,213	0.48	0.87	£376,519
Risk population: Intermediate / poor risk							
cabo+nivo	£215,950	2.03	3.41				
nivo+ipi	£123,983	1.28	2.10	£91,966	0.75	1.30	£123,397
pem+lenv	£187,035	2.25	3.66	£28,914	-0.22	-0.25	Cabo+nivo dominated
pazo	£81,513	1.49	2.52	£134,437	0.53	0.89	£251,657
tivo	£96,381	1.46	2.45	£119,569	0.56	0.96	£211,627
suni	£80,937	1.47	2.47	£135,013	0.56	0.94	£241,496
cabo	£165,635	2.08	3.48	£50,315	-0.05	-0.08	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 39: Scenario analysis 18 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£188,561	2.22	3.71				
pazo	£97,435	1.70	2.86	£91,126	0.52	0.85	£176,827
tivo	£117,791	1.67	2.79	£70,770	0.55	0.92	£129,213
suni	£96,353	1.68	2.80	£92,208	0.54	0.91	£169,994
Risk population: Favourable risk							
cabo+nivo	£241,656	2.59	4.38				
pazo	£104,088	2.16	3.62	£137,568	0.43	0.77	£320,107
tivo	£135,703	2.13	3.54	£105,953	0.46	0.84	£228,821
suni	£103,064	2.13	3.56	£138,592	0.46	0.83	£302,942
Risk population: Intermediate / poor risk							
cabo+nivo	£164,986	2.00	3.36				
nivo+ipi	£128,494	1.42	2.30	£36,491	0.58	1.06	£62,656
pem+lenv	£138,815	2.24	3.65	£26,171	-0.24	-0.29	Cabo+nivo dominated
pazo	£94,373	1.50	2.53	£70,612	0.51	0.83	£139,556
tivo	£109,672	1.47	2.46	£55,314	0.54	0.90	£102,837
suni	£93,267	1.47	2.48	£71,719	0.53	0.88	£134,624
cabo	£132,910	2.08	3.49	£32,076	-0.08	-0.13	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 40: Scenario analysis 19 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£171,456	2.12	3.35				
pazo	£71,110	1.83	2.90	£100,346	0.30	0.45	£339,783
tivo	£96,677	1.84	2.90	£74,778	0.28	0.45	£263,404
suni	£71,303	1.83	2.90	£100,152	0.30	0.45	£339,348
Risk population: Favourable risk							
cabo+nivo	£224,508	2.66	4.41				
pazo	£76,257	2.90	4.90	£148,252	-0.24	-0.49	Cabo+nivo dominated
tivo	£113,106	2.91	4.90	£111,402	-0.25	-0.49	Cabo+nivo dominated
suni	£76,552	2.90	4.90	£147,956	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£148,198	1.88	2.95				
nivo+ipi	£121,552	1.87	2.92	£26,646	0.01	0.03	£2,380,986
pem+lenv	£117,526	1.94	3.04	£30,672	-0.07	-0.09	Cabo+nivo dominated
pazo	£69,098	1.46	2.28	£79,101	0.42	0.67	£188,377
tivo	£89,595	1.47	2.28	£58,603	0.41	0.67	£143,486
suni	£69,245	1.46	2.28	£78,953	0.42	0.67	£188,111
cabo	£116,700	1.81	2.81	£31,498	0.07	0.14	£483,907

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 41: Scenario analysis 20 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.22	3.71				
pazo	£83,572	1.69	2.84	£152,823	0.53	0.88	£289,554
tivo	£102,777	1.66	2.76	£133,618	0.56	0.95	£238,496
suni	£82,905	1.67	2.78	£153,491	0.56	0.93	£276,480
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£171,554	1.69	2.67	£42,848	0.31	0.68	£136,421
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 42: Scenario analysis 21 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£234,264	2.34	3.76				
pazo	£70,514	1.83	2.90	£163,750	0.51	0.86	£320,243
tivo	£94,161	1.84	2.90	£140,103	0.50	0.86	£280,262
suni	£70,691	1.83	2.90	£163,573	0.51	0.86	£320,015
Risk population: Favourable risk							
cabo+nivo	£259,539	2.66	4.41				
pazo	£75,592	2.90	4.90	£183,947	-0.24	-0.49	Cabo+nivo dominated
tivo	£110,299	2.91	4.90	£149,240	-0.25	-0.49	Cabo+nivo dominated
suni	£75,870	2.90	4.90	£183,669	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£217,306	2.14	3.47				
nivo+ipi	£147,903	2.10	3.33	£69,403	0.04	0.13	£1,549,670
pem+lenv	£173,343	1.94	3.04	£43,963	0.20	0.42	£223,754
pazo	£68,710	1.46	2.28	£148,596	0.68	1.19	£217,808
tivo	£87,959	1.47	2.28	£129,347	0.67	1.19	£192,838
suni	£68,847	1.46	2.28	£148,459	0.68	1.19	£217,668
cabo	£169,365	1.81	2.78	£47,941	0.34	0.69	£142,811

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 43: Scenario analysis 22 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,931	2.21	3.69				
pazo	£83,572	1.69	2.84	£152,359	0.52	0.86	£293,754
tivo	£102,777	1.66	2.76	£133,154	0.55	0.93	£241,603
suni	£82,905	1.67	2.78	£153,026	0.55	0.91	£280,251
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 44: Scenario analysis 23 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,931	2.21	3.69				
pazo	£83,572	1.69	2.84	£152,359	0.52	0.86	£293,754
tivo	£102,777	1.66	2.76	£133,154	0.55	0.93	£241,603
suni	£82,905	1.67	2.78	£153,026	0.55	0.91	£280,251
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 45: Scenario analysis 24 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,962	2.21	3.69				
pazo	£83,572	1.69	2.84	£152,390	0.52	0.86	£293,472
tivo	£102,777	1.66	2.76	£133,184	0.55	0.93	£241,395
suni	£82,905	1.67	2.78	£153,057	0.55	0.91	£279,998
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 46: Scenario analysis 25 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,962	2.21	3.69				
pazo	£83,572	1.69	2.84	£152,390	0.52	0.86	£293,472
tivo	£102,777	1.66	2.76	£133,184	0.55	0.93	£241,395
suni	£82,905	1.67	2.78	£153,057	0.55	0.91	£279,998
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 47: Scenario analysis 26 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,910	2.21	3.69				
pazo	£83,572	1.69	2.84	£152,338	0.52	0.85	£293,937
tivo	£102,777	1.66	2.76	£133,133	0.55	0.93	£241,739
suni	£82,905	1.67	2.78	£153,006	0.55	0.91	£280,416
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£185,897	2.23	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 48: Scenario analysis 27 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£226,481	2.12	3.35				
pazo	£70,514	1.83	2.90	£155,968	0.30	0.45	£528,126
tivo	£94,161	1.84	2.90	£132,320	0.28	0.45	£466,095
suni	£70,691	1.83	2.90	£155,790	0.30	0.45	£527,866
Risk population: Favourable risk							
cabo+nivo	£259,539	2.66	4.41				
pazo	£75,592	2.90	4.90	£183,947	-0.24	-0.49	Cabo+nivo dominated
tivo	£110,299	2.91	4.90	£149,240	-0.25	-0.49	Cabo+nivo dominated
suni	£75,870	2.90	4.90	£183,669	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£204,761	1.88	2.95				
nivo+ipi	£120,405	1.87	2.92	£84,356	0.01	0.03	£7,537,719
pem+lenv	£173,343	1.94	3.04	£31,418	-0.07	-0.09	Cabo+nivo dominated
pazo	£68,710	1.46	2.28	£136,051	0.42	0.67	£324,003
tivo	£87,959	1.47	2.28	£116,802	0.41	0.67	£285,981
suni	£68,847	1.46	2.28	£135,913	0.42	0.67	£323,823
cabo	£159,176	1.81	2.81	£45,585	0.07	0.14	£700,321

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 49: Scenario analysis 28 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£225,364	2.08	3.28				
pazo	£70,982	1.83	2.90	£154,383	0.26	0.38	£602,933
tivo	£94,629	1.84	2.90	£130,736	0.24	0.38	£534,440
suni	£71,159	1.83	2.90	£154,205	0.26	0.38	£602,690
Risk population: Favourable risk							
cabo+nivo	£259,998	2.66	4.41				
pazo	£76,055	2.90	4.90	£183,942	-0.24	-0.49	Cabo+nivo dominated
tivo	£110,763	2.91	4.90	£149,235	-0.25	-0.49	Cabo+nivo dominated
suni	£76,333	2.90	4.90	£183,665	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£205,226	1.88	2.95				
nivo+ipi	£120,874	1.87	2.92	£84,352	0.01	0.03	£7,537,331
pem+lenv	£173,804	1.94	3.04	£31,422	-0.07	-0.09	Cabo+nivo dominated
pazo	£69,180	1.46	2.28	£136,046	0.42	0.67	£323,991
tivo	£88,429	1.47	2.28	£116,796	0.41	0.67	£285,968
suni	£69,317	1.46	2.28	£135,908	0.42	0.67	£323,811
cabo	£159,640	1.81	2.81	£45,586	0.07	0.14	£700,336

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 50: Scenario analysis 29 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£223,114	2.04	3.22				
pazo	£73,142	1.64	2.62	£149,972	0.40	0.60	£371,493
tivo	£92,666	1.61	2.56	£130,448	0.43	0.66	£303,268
suni	£72,643	1.61	2.58	£150,471	0.43	0.65	£352,543
Risk population: Favourable risk							
cabo+nivo	£268,832	2.63	4.43				
pazo	£89,003	2.19	3.65	£179,829	0.44	0.78	£407,957
tivo	£119,287	2.16	3.57	£149,545	0.47	0.86	£315,682
suni	£88,414	2.16	3.59	£180,418	0.47	0.84	£385,054
Risk population: Intermediate / poor risk							
cabo+nivo	£214,081	1.97	3.27				
nivo+ipi	£123,399	1.25	2.02	£90,682	0.72	1.25	£125,948
pem+lenv	£185,624	2.20	3.55	£28,457	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,614	1.45	2.42	£133,467	0.52	0.85	£258,175
tivo	£95,423	1.42	2.35	£118,658	0.55	0.92	£216,156
suni	£79,921	1.42	2.37	£134,160	0.54	0.91	£246,596
cabo	£164,734	2.04	3.38	£49,347	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 51: Scenario analysis 30 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£222,945	2.23	3.69				
pazo	£82,225	1.70	2.81	£140,720	0.53	0.88	£266,182
tivo	£99,374	1.67	2.74	£123,571	0.56	0.95	£220,362
suni	£81,549	1.67	2.76	£141,396	0.56	0.93	£254,387
Risk population: Favourable risk							
cabo+nivo	£249,459	2.55	4.30				
pazo	£87,883	2.11	3.50	£161,577	0.44	0.80	£364,734
tivo	£112,929	2.08	3.43	£136,530	0.48	0.87	£286,616
suni	£87,237	2.08	3.44	£162,222	0.47	0.85	£344,376
Risk population: Intermediate / poor risk							
cabo+nivo	£203,773	2.02	3.36				
nivo+ipi	£123,239	1.32	2.12	£80,534	0.71	1.24	£113,565
pem+lenv	£180,111	2.26	3.65	£23,662	-0.24	-0.29	Cabo+nivo dominated
pazo	£79,668	1.50	2.50	£124,105	0.52	0.86	£237,276
tivo	£93,485	1.47	2.43	£110,289	0.55	0.93	£198,881
suni	£78,982	1.47	2.44	£124,792	0.55	0.91	£226,983
cabo	£147,245	2.11	3.49	£56,528	-0.08	-0.13	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 52: Scenario analysis 31 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£239,489	2.25	3.79				
pazo	£83,156	1.66	2.76	£156,333	0.59	1.02	£263,368
tivo	£102,365	1.62	2.69	£137,124	0.63	1.10	£219,086
suni	£82,490	1.63	2.71	£156,999	0.62	1.08	£252,857
Risk population: Favourable risk							
cabo+nivo	£268,832	2.63	4.43				
pazo	£89,003	2.19	3.65	£179,829	0.44	0.78	£407,957
tivo	£119,287	2.16	3.57	£149,545	0.47	0.86	£315,682
suni	£88,414	2.16	3.59	£180,418	0.47	0.84	£385,054
Risk population: Intermediate / poor risk							
cabo+nivo	£214,081	1.97	3.27				
nivo+ipi	£123,399	1.25	2.02	£90,682	0.72	1.25	£125,948
pem+lenv	£185,624	2.20	3.55	£28,457	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,614	1.45	2.42	£133,467	0.52	0.85	£258,175
tivo	£95,423	1.42	2.35	£118,658	0.55	0.92	£216,156
suni	£79,921	1.42	2.37	£134,160	0.54	0.91	£246,596
cabo	£164,734	2.04	3.38	£49,347	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 53: Scenario analysis 32 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,947	2.18	3.63				
pazo	£82,220	1.64	2.70	£153,727	0.55	0.93	£281,932
tivo	£101,762	1.61	2.65	£134,184	0.57	0.98	£235,409
suni	£81,609	1.61	2.65	£154,338	0.57	0.98	£270,048
Risk population: Favourable risk							
cabo+nivo	£268,706	2.63	4.43				
pazo	£87,953	2.17	3.59	£180,752	0.46	0.84	£393,715
tivo	£118,579	2.14	3.54	£150,127	0.48	0.89	£310,010
suni	£87,421	2.14	3.54	£181,285	0.49	0.89	£373,243
Risk population: Intermediate / poor risk							
cabo+nivo	£213,953	1.96	3.27				
nivo+ipi	£123,420	1.25	2.02	£90,533	0.72	1.25	£126,070
pem+lenv	£184,223	2.17	3.46	£29,730	-0.20	-0.19	Cabo+nivo dominated
pazo	£79,591	1.43	2.37	£134,363	0.53	0.90	£251,235
tivo	£94,733	1.41	2.32	£119,220	0.56	0.95	£213,197
suni	£78,953	1.40	2.31	£135,000	0.56	0.95	£240,739
cabo	£164,431	2.03	3.37	£49,522	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 54: Scenario analysis 33 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,795	2.18	3.62				
pazo	£80,104	1.60	2.62	£155,691	0.58	1.00	£268,737
tivo	£100,243	1.59	2.60	£135,553	0.59	1.02	£229,054
suni	£79,532	1.58	2.57	£156,263	0.60	1.05	£258,511
Risk population: Favourable risk							
cabo+nivo	£268,557	2.63	4.42				
pazo	£85,802	2.13	3.51	£182,755	0.49	0.91	£370,179
tivo	£117,034	2.12	3.49	£151,523	0.51	0.94	£299,213
suni	£85,311	2.11	3.46	£183,246	0.52	0.97	£352,971
Risk population: Intermediate / poor risk							
cabo+nivo	£213,802	1.96	3.26				
nivo+ipi	£123,034	1.24	2.01	£90,769	0.72	1.25	£125,874
pem+lenv	£181,544	2.12	3.35	£32,258	-0.15	-0.09	Cabo+nivo dominated
pazo	£77,501	1.39	2.29	£136,301	0.57	0.97	£239,761
tivo	£93,232	1.38	2.27	£120,570	0.58	0.99	£207,620
suni	£76,903	1.37	2.24	£136,899	0.59	1.02	£230,728
cabo	£163,737	2.02	3.35	£50,066	-0.06	-0.08	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 55: Scenario analysis 34 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,074	2.19	3.63				
pazo	£83,268	1.66	2.75	£152,806	0.53	0.87	£289,919
tivo	£102,467	1.63	2.68	£133,607	0.56	0.95	£238,776
suni	£82,600	1.63	2.70	£153,475	0.55	0.93	£276,799
Risk population: Favourable risk							
cabo+nivo	£268,832	2.63	4.43				
pazo	£89,017	2.19	3.65	£179,815	0.44	0.78	£408,065
tivo	£119,294	2.16	3.57	£149,538	0.47	0.86	£315,717
suni	£88,427	2.16	3.59	£180,405	0.47	0.84	£385,143
Risk population: Intermediate / poor risk							
cabo+nivo	£214,081	1.97	3.27				
nivo+ipi	£123,399	1.25	2.02	£90,682	0.72	1.25	£125,948
pem+lenv	£185,640	2.20	3.55	£28,441	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,627	1.45	2.42	£133,454	0.52	0.85	£258,223
tivo	£95,429	1.42	2.35	£118,652	0.55	0.92	£216,172
suni	£79,933	1.42	2.37	£134,148	0.54	0.91	£246,636
cabo	£164,734	2.04	3.38	£49,347	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 56: Scenario analysis 35 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£233,566	2.11	3.41				
pazo	£82,079	1.63	2.68	£151,487	0.48	0.73	£316,186
tivo	£101,086	1.60	2.60	£132,480	0.51	0.81	£257,416
suni	£81,532	1.61	2.63	£152,034	0.50	0.78	£302,229
Risk population: Favourable risk							
cabo+nivo	£266,367	2.56	4.21				
pazo	£87,811	2.17	3.57	£178,556	0.39	0.64	£452,781
tivo	£117,893	2.13	3.49	£148,474	0.43	0.73	£344,933
suni	£87,344	2.14	3.52	£179,023	0.42	0.69	£427,656
Risk population: Intermediate / poor risk							
cabo+nivo	£211,571	1.89	3.05				
nivo+ipi	£122,091	1.22	1.95	£89,480	0.67	1.10	£133,223
pem+lenv	£185,421	2.19	3.54	£26,150	-0.30	-0.48	Cabo+nivo dominated
pazo	£79,451	1.43	2.35	£132,120	0.47	0.71	£282,029
tivo	£94,064	1.39	2.27	£117,507	0.50	0.79	£233,358
suni	£78,877	1.40	2.30	£132,694	0.49	0.75	£269,634
cabo	£163,030	1.99	3.23	£48,541	-0.09	-0.18	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 57: Scenario analysis 36 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£230,087	2.01	3.18				
pazo	£80,632	1.60	2.60	£149,455	0.41	0.58	£364,559
tivo	£99,339	1.56	2.50	£130,748	0.45	0.67	£290,141
suni	£80,362	1.58	2.57	£149,725	0.43	0.61	£350,067
Risk population: Favourable risk							
cabo+nivo	£262,940	2.46	3.98				
pazo	£86,340	2.13	3.49	£176,600	0.33	0.50	£539,346
tivo	£116,117	2.09	3.39	£146,822	0.37	0.59	£398,197
suni	£86,155	2.11	3.45	£176,785	0.35	0.53	£511,797
Risk population: Intermediate / poor risk							
cabo+nivo	£208,093	1.79	2.82				
nivo+ipi	£121,196	1.21	1.90	£86,897	0.58	0.92	£148,654
pem+lenv	£185,629	2.20	3.54	£22,465	-0.41	-0.72	Cabo+nivo dominated
pazo	£78,022	1.39	2.27	£130,072	0.40	0.56	£326,133
tivo	£92,338	1.35	2.18	£115,755	0.44	0.65	£263,686
suni	£77,722	1.38	2.24	£130,371	0.42	0.59	£313,114
cabo	£161,194	1.92	3.07	£46,899	-0.13	-0.25	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 58: Scenario analysis 37 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,074	2.19	3.63				
pazo	£83,327	1.66	2.76	£152,748	0.53	0.87	£290,246
tivo	£102,552	1.63	2.69	£133,523	0.56	0.94	£239,113
suni	£82,658	1.63	2.70	£153,416	0.55	0.93	£277,106
Risk population: Favourable risk							
cabo+nivo	£268,832	2.63	4.43				
pazo	£89,076	2.19	3.65	£179,756	0.44	0.78	£408,677
tivo	£119,380	2.16	3.58	£149,452	0.47	0.86	£316,308
suni	£88,486	2.16	3.59	£180,346	0.47	0.84	£385,704
Risk population: Intermediate / poor risk							
cabo+nivo	£214,081	1.97	3.27				
nivo+ipi	£123,491	1.25	2.02	£90,590	0.72	1.25	£126,034
pem+lenv	£185,636	2.20	3.55	£28,445	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,684	1.45	2.42	£133,397	0.52	0.85	£258,504
tivo	£95,513	1.42	2.35	£118,568	0.55	0.92	£216,465
suni	£79,990	1.42	2.37	£134,091	0.54	0.90	£246,900
cabo	£164,734	2.04	3.38	£49,347	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 59: Scenario analysis 38 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,074	2.19	3.63				
pazo	£83,291	1.66	2.76	£152,784	0.53	0.87	£290,052
tivo	£102,506	1.63	2.68	£133,569	0.56	0.95	£238,932
suni	£82,622	1.63	2.70	£153,452	0.55	0.93	£276,926
Risk population: Favourable risk							
cabo+nivo	£268,832	2.63	4.43				
pazo	£89,039	2.19	3.65	£179,792	0.44	0.78	£408,312
tivo	£119,333	2.16	3.57	£149,499	0.47	0.86	£315,991
suni	£88,450	2.16	3.59	£180,382	0.47	0.84	£385,375
Risk population: Intermediate / poor risk							
cabo+nivo	£214,081	1.97	3.27				
nivo+ipi	£123,444	1.25	2.02	£90,637	0.72	1.25	£125,990
pem+lenv	£185,630	2.20	3.55	£28,451	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,649	1.45	2.42	£133,432	0.52	0.85	£258,337
tivo	£95,467	1.42	2.35	£118,614	0.55	0.92	£216,308
suni	£79,955	1.42	2.37	£134,126	0.54	0.90	£246,746
cabo	£164,734	2.04	3.38	£49,347	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 60: Scenario analysis 39 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,074	2.19	3.63				
pazo	£83,255	1.66	2.75	£152,819	0.53	0.88	£289,863
tivo	£102,461	1.63	2.68	£133,614	0.56	0.95	£238,757
suni	£82,587	1.63	2.70	£153,487	0.55	0.93	£276,752
Risk population: Favourable risk							
cabo+nivo	£268,832	2.63	4.43				
pazo	£89,003	2.19	3.65	£179,829	0.44	0.78	£407,957
tivo	£119,287	2.16	3.57	£149,545	0.47	0.86	£315,682
suni	£88,414	2.16	3.59	£180,418	0.47	0.84	£385,054
Risk population: Intermediate / poor risk							
cabo+nivo	£214,081	1.97	3.27				
nivo+ipi	£123,399	1.25	2.02	£90,682	0.72	1.25	£125,948
pem+lenv	£185,624	2.20	3.55	£28,457	-0.23	-0.28	Cabo+nivo dominated
pazo	£80,614	1.45	2.42	£133,467	0.52	0.85	£258,175
tivo	£95,423	1.42	2.35	£118,658	0.55	0.92	£216,156
suni	£79,921	1.42	2.37	£134,160	0.54	0.91	£246,596
cabo	£164,734	2.04	3.38	£49,347	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 61**: Scenario analysis 40 pairwise comparison table**

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£250,265	2.22	3.71				
pazo	£83,572	1.69	2.84	£166,693	0.53	0.88	£315,833
tivo	£102,777	1.66	2.76	£147,488	0.56	0.95	£263,252
suni	£82,905	1.67	2.78	£167,360	0.56	0.93	£301,463
Risk population: Favourable risk							
cabo+nivo	£278,957	2.67	4.52				
pazo	£89,326	2.23	3.73	£189,632	0.44	0.78	£430,730
tivo	£119,609	2.19	3.66	£159,348	0.47	0.86	£336,727
suni	£88,737	2.20	3.68	£190,221	0.47	0.84	£406,466
Risk population: Intermediate / poor risk							
cabo+nivo	£234,201	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£110,523	0.72	1.26	£152,510
pem+lenv	£247,236	2.23	3.62	£-13,035	-0.23	-0.26	SW quadrant £57,781
pazo	£80,927	1.49	2.50	£153,274	0.52	0.85	£295,907
tivo	£95,735	1.45	2.43	£138,466	0.55	0.92	£251,747
suni	£80,234	1.46	2.45	£153,967	0.55	0.91	£282,483
cabo	£165,035	2.07	3.46	£69,167	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 62: Scenario analysis 41 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£268,351	2.22	3.71				
pazo	£89,981	1.69	2.84	£178,369	0.53	0.88	£337,956
tivo	£109,194	1.66	2.76	£159,157	0.56	0.95	£284,080
suni	£89,336	1.67	2.78	£179,014	0.56	0.93	£322,455
Risk population: Favourable risk							
cabo+nivo	£305,930	2.67	4.52				
pazo	£96,384	2.23	3.73	£209,546	0.44	0.78	£475,963
tivo	£127,032	2.19	3.66	£178,898	0.47	0.86	£378,039
suni	£96,080	2.20	3.68	£209,851	0.47	0.84	£448,411
Risk population: Intermediate / poor risk							
cabo+nivo	£243,309	2.00	3.36				
nivo+ipi	£139,085	1.28	2.09	£104,224	0.72	1.26	£143,818
pem+lenv	£256,230	2.23	3.62	£-12,921	-0.23	-0.26	SW quadrant £57,275
pazo	£87,047	1.49	2.50	£156,262	0.52	0.85	£301,675
tivo	£101,725	1.45	2.43	£141,584	0.55	0.92	£257,417
suni	£86,275	1.46	2.45	£157,034	0.55	0.91	£288,109
cabo	£185,625	2.07	3.46	£57,684	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 63: Scenario analysis 42 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£233,770	2.22	3.71				
pazo	£55,172	1.69	2.84	£178,598	0.53	0.88	£338,390
tivo	£78,693	1.66	2.76	£155,077	0.56	0.95	£276,798
suni	£55,871	1.67	2.78	£177,899	0.56	0.93	£320,446
Risk population: Favourable risk							
cabo+nivo	£266,562	2.67	4.52				
pazo	£60,532	2.23	3.73	£206,030	0.44	0.78	£467,977
tivo	£95,275	2.19	3.66	£171,286	0.47	0.86	£361,954
suni	£61,593	2.20	3.68	£204,968	0.47	0.84	£437,979
Risk population: Intermediate / poor risk							
cabo+nivo	£211,778	2.00	3.36				
nivo+ipi	£107,778	1.28	2.09	£103,999	0.72	1.26	£143,507
pem+lenv	£157,064	2.23	3.62	£54,714	-0.23	-0.26	Cabo+nivo dominated
pazo	£52,847	1.49	2.50	£158,931	0.52	0.85	£306,827
tivo	£71,890	1.45	2.43	£139,888	0.55	0.92	£254,332
suni	£53,403	1.46	2.45	£158,375	0.55	0.91	£290,570
cabo	£64,238	2.07	3.46	£147,540	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 64: Scenario analysis 43 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£191,812	2.22	3.71				
pazo	£74,126	1.69	2.84	£117,686	0.53	0.88	£222,979
tivo	£94,809	1.66	2.76	£97,003	0.56	0.95	£173,142
suni	£73,719	1.67	2.78	£118,092	0.56	0.93	£212,717
Risk population: Favourable risk							
cabo+nivo	£217,948	2.67	4.52				
pazo	£79,723	2.23	3.73	£138,225	0.44	0.78	£313,965
tivo	£111,508	2.19	3.66	£106,439	0.47	0.86	£224,922
suni	£79,399	2.20	3.68	£138,549	0.47	0.84	£296,052
Risk population: Intermediate / poor risk							
cabo+nivo	£174,713	2.00	3.36				
nivo+ipi	£105,532	1.28	2.09	£69,180	0.72	1.26	£95,461
pem+lenv	£154,828	1.91	3.12	£19,884	0.09	0.23	£210,378
pazo	£71,597	1.49	2.50	£103,116	0.52	0.85	£199,071
tivo	£87,865	1.45	2.43	£86,848	0.55	0.92	£157,899
suni	£71,162	1.46	2.45	£103,551	0.55	0.91	£189,984
cabo	£137,268	2.07	3.46	£37,444	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 65: Scenario analysis 44 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.22	3.71				
pazo	£83,572	1.69	2.84	£152,823	0.53	0.88	£289,554
tivo	£102,777	1.66	2.76	£133,618	0.56	0.95	£238,496
suni	£82,905	1.67	2.78	£153,491	0.56	0.93	£276,480
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.00	3.36				
nivo+ipi	£123,678	1.28	2.09	£90,724	0.72	1.26	£125,189
pem+lenv	£169,541	1.91	3.12	£44,861	0.09	0.23	£474,636
pazo	£80,927	1.49	2.50	£133,475	0.52	0.85	£257,682
tivo	£95,735	1.45	2.43	£118,666	0.55	0.92	£215,749
suni	£80,234	1.46	2.45	£134,168	0.55	0.91	£246,157
cabo	£165,035	2.07	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 66: Scenario analysis 45 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£191,812	2.22	3.71				
pazo	£74,126	1.69	2.84	£117,686	0.53	0.88	£222979
tivo	£94,809	1.66	2.76	£97,003	0.56	0.95	£173142
suni	£73,719	1.67	2.78	£118,092	0.56	0.93	£212717
Risk population: Favourable risk							
cabo+nivo	£217,948	2.67	4.52				
pazo	£79,723	2.23	3.73	£138,225	0.44	0.78	£313965
tivo	£111,508	2.19	3.66	£106,439	0.47	0.86	£224922
suni	£79,399	2.20	3.68	£138,549	0.47	0.84	£296052
Risk population: Intermediate / poor risk							
cabo+nivo	£174,713	2.00	3.36				
nivo+ipi	£105,532	1.28	2.09	£69,180	0.72	1.26	£95461
pem+lenv	£172,376	2.23	3.62	£2,337	-0.23	-0.26	Cabo+nivo dominated
pazo	£71,597	1.49	2.50	£103,116	0.52	0.85	£199071
tivo	£87,865	1.45	2.43	£86,848	0.55	0.92	£157899
suni	£71,162	1.46	2.45	£103,551	0.55	0.91	£189984
cabo	£137,268	2.07	3.46	£37,444	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 67: Scenario analysis 46 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£191,809	2.22	3.71				
pazo	£83,647	1.69	2.84	£108,162	0.53	0.88	£204,935
tivo	£102,839	1.66	2.76	£88,970	0.56	0.95	£158,804
suni	£82,938	1.67	2.78	£108,871	0.56	0.93	£196,107
Risk population: Favourable risk							
cabo+nivo	£217,945	2.67	4.52				
pazo	£89,402	2.23	3.73	£128,544	0.44	0.78	£291,974
tivo	£119,672	2.19	3.66	£98,273	0.47	0.86	£207,667
suni	£88,771	2.20	3.68	£129,174	0.47	0.84	£276,022
Risk population: Intermediate / poor risk							
cabo+nivo	£174,710	2.00	3.36				
nivo+ipi	£110,174	1.28	2.09	£64,537	0.72	1.26	£89053
pem+lenv	£182,334	2.23	3.62	£-7,624	-0.23	-0.26	SW quadrant £33795
pazo	£81,001	1.49	2.50	£93,709	0.52	0.85	£180912
tivo	£95,797	1.45	2.43	£78,914	0.55	0.92	£143475
suni	£80,267	1.46	2.45	£94,443	0.55	0.91	£173274
cabo	£165,568	2.07	3.46	£9,142	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 68: Scenario analysis 47 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£184,503	2.12	3.35				
pazo	£69,936	1.83	2.90	£114,567	0.30	0.45	£387,939
tivo	£94,599	1.84	2.90	£89,904	0.28	0.45	£316,685
suni	£70,279	1.83	2.90	£114,224	0.30	0.45	£387,029
Risk population: Favourable risk							
cabo+nivo	£210,897	2.66	4.41				
pazo	£75,032	2.90	4.90	£135,865	-0.24	-0.49	Cabo+nivo dominated
tivo	£110,733	2.91	4.90	£100,164	-0.25	-0.49	Cabo+nivo dominated
suni	£75,471	2.90	4.90	£135,426	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£167,712	1.88	2.95				
nivo+ipi	£107,559	1.87	2.92	£60,153	0.01	0.03	£5,375,004
pem+lenv	£166,696	1.94	3.04	£1,015	-0.07	-0.09	Cabo+nivo dominated
pazo	£68,125	1.46	2.28	£99,587	0.42	0.67	£237,165
tivo	£88,399	1.47	2.28	£79,312	0.41	0.67	£194,191
suni	£68,429	1.46	2.28	£99,283	0.42	0.67	£236,548
cabo	£133,847	1.81	2.81	£33,865	0.07	0.14	£520,265

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 69: Scenario analysis 48 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£184,498	2.12	3.35				
pazo	£77,689	1.83	2.90	£106,809	0.30	0.45	£361,668
tivo	£101,626	1.84	2.90	£82,872	0.28	0.45	£291,916
suni	£77,823	1.83	2.90	£106,675	0.30	0.45	£361,451
Risk population: Favourable risk							
cabo+nivo	£210,892	2.66	4.41				
pazo	£82,622	2.90	4.90	£128,270	-0.24	-0.49	Cabo+nivo dominated
tivo	£117,612	2.91	4.90	£93,280	-0.25	-0.49	Cabo+nivo dominated
suni	£82,857	2.90	4.90	£128,036	-0.24	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£167,707	1.88	2.95				
nivo+ipi	£112,751	1.87	2.92	£54,956	0.01	0.03	£4,910,635
pem+lenv	£174,834	1.94	3.04	-£7,127	-0.07	-0.09	SW quadrant £108235
pazo	£75,951	1.46	2.28	£91,755	0.42	0.67	£218,514
tivo	£95,493	1.47	2.28	£72,214	0.41	0.67	£176,811
suni	£76,044	1.46	2.28	£91,663	0.42	0.67	£218,393
cabo	£162,145	1.81	2.81	£5,561	0.07	0.14	£85,435

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 70: Scenario analysis 49 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.34	3.71				
pazo	£83,572	1.77	2.84	£152,823	0.57	0.88	£266,215
tivo	£102,777	1.74	2.76	£133,618	0.61	0.95	£220,301
suni	£82,905	1.74	2.78	£153,491	0.60	0.93	£255,209
Risk population: Favourable risk							
cabo+nivo	£269,148	2.85	4.52				
pazo	£89,326	2.37	3.73	£179,822	0.49	0.78	£368,892
tivo	£119,609	2.33	3.66	£149,539	0.52	0.86	£287,334
suni	£88,737	2.34	3.68	£180,411	0.52	0.84	£350,180
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.10	3.36				
nivo+ipi	£123,678	1.34	2.09	£90,724	0.76	1.26	£119,332
pem+lenv	£185,897	2.36	3.62	£28,505	-0.26	-0.26	Cabo+nivo dominated
pazo	£80,927	1.54	2.50	£133,475	0.56	0.85	£238,434
tivo	£95,735	1.51	2.43	£118,666	0.59	0.92	£200,506
suni	£80,234	1.51	2.45	£134,168	0.59	0.91	£228,618
cabo	£165,035	2.18	3.46	£49,367	-0.08	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 71: Scenario analysis 50 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.55	3.71				
pazo	£83,572	2.00	2.84	£152,823	0.55	0.88	£278,324
tivo	£102,777	1.96	2.76	£133,618	0.58	0.95	£228,583
suni	£82,905	1.97	2.78	£153,491	0.58	0.93	£264,358
Risk population: Favourable risk							
cabo+nivo	£269,148	3.05	4.52				
pazo	£89,326	2.60	3.73	£179,822	0.46	0.78	£394,449
tivo	£119,609	2.56	3.66	£149,539	0.49	0.86	£304,008
suni	£88,737	2.57	3.68	£180,411	0.49	0.84	£369,826
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.30	3.36				
nivo+ipi	£123,678	1.51	2.09	£90,724	0.80	1.26	£113,988
pem+lenv	£185,897	2.53	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.77	2.50	£133,475	0.54	0.85	£248,287
tivo	£95,735	1.73	2.43	£118,666	0.57	0.92	£207,246
suni	£80,234	1.74	2.45	£134,168	0.57	0.91	£235,893
cabo	£165,035	2.41	3.46	£49,367	-0.10	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 72: Scenario analysis 51 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£226,481	2.38	3.35				
pazo	£70,514	2.07	2.90	£155,968	0.31	0.45	£507,431
tivo	£94,161	2.08	2.90	£132,320	0.30	0.45	£447,126
suni	£70,691	2.07	2.90	£155,790	0.31	0.45	£507,169
Risk population: Favourable risk							
cabo+nivo	£259,539	3.00	4.41				
pazo	£75,592	3.31	4.90	£183,947	-0.30	-0.49	Cabo+nivo dominated
tivo	£110,299	3.32	4.90	£149,240	-0.31	-0.49	Cabo+nivo dominated
suni	£75,870	3.31	4.90	£183,669	-0.30	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£204,761	2.10	2.95				
nivo+ipi	£120,405	2.12	2.92	£84,356	-0.02	0.03	Cabo+nivo dominated
pem+lenv	£173,343	2.14	3.04	£31,418	-0.04	-0.09	Cabo+nivo dominated
pazo	£68,710	1.65	2.28	£136,051	0.45	0.67	£300,984
tivo	£87,959	1.66	2.28	£116,802	0.44	0.67	£265,133
suni	£68,847	1.65	2.28	£135,913	0.45	0.67	£300,807
cabo	£159,176	2.01	2.81	£45,585	0.09	0.14	£503,476

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 73: Scenario analysis 52 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.59	3.71				
pazo	£83,572	2.03	2.84	£152,823	0.56	0.88	£271,033
tivo	£102,777	1.99	2.76	£133,618	0.60	0.95	£222,392
suni	£82,905	2.00	2.78	£153,491	0.60	0.93	£257,251
Risk population: Favourable risk							
cabo+nivo	£269,148	3.12	4.52				
pazo	£89,326	2.64	3.73	£179,822	0.47	0.78	£380,035
tivo	£119,609	2.60	3.66	£149,539	0.51	0.86	£292,734
suni	£88,737	2.61	3.68	£180,411	0.51	0.84	£356,189
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.34	3.36				
nivo+ipi	£123,678	1.53	2.09	£90,724	0.82	1.26	£111,268
pem+lenv	£185,897	2.57	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.79	2.50	£133,475	0.55	0.85	£242,168
tivo	£95,735	1.75	2.43	£118,666	0.59	0.92	£201,949
suni	£80,234	1.76	2.45	£134,168	0.58	0.91	£229,910
cabo	£165,035	2.45	3.46	£49,367	-0.10	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 74: Scenario analysis 53 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£226,481	2.41	3.35				
pazo	£70,514	2.10	2.90	£155,968	0.31	0.45	£501,914
tivo	£94,161	2.11	2.90	£132,320	0.30	0.45	£442,079
suni	£70,691	2.10	2.90	£155,790	0.31	0.45	£501,652
Risk population: Favourable risk							
cabo+nivo	£259,539	3.06	4.41				
pazo	£75,592	3.37	4.90	£183,947	-0.31	-0.49	Cabo+nivo dominated
tivo	£110,299	3.38	4.90	£149,240	-0.32	-0.49	Cabo+nivo dominated
suni	£75,870	3.37	4.90	£183,669	-0.31	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£204,761	2.13	2.95				
nivo+ipi	£120,405	2.14	2.92	£84,356	-0.02	0.03	Cabo+nivo dominated
pem+lenv	£173,343	2.17	3.04	£31,418	-0.04	-0.09	Cabo+nivo dominated
pazo	£68,710	1.67	2.28	£136,051	0.46	0.67	£296,888
tivo	£87,959	1.68	2.28	£116,802	0.45	0.67	£261,433
suni	£68,847	1.67	2.28	£135,913	0.46	0.67	£296,712
cabo	£159,176	2.04	2.81	£45,585	0.09	0.14	£511,741

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 75: Scenario analysis 54 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.24	3.71				
pazo	£83,572	1.72	2.84	£152,823	0.52	0.88	£291,879
tivo	£102,777	1.69	2.76	£133,618	0.56	0.95	£240,332
suni	£82,905	1.69	2.78	£153,491	0.55	0.93	£278,666
Risk population: Favourable risk							
cabo+nivo	£269,148	2.69	4.52				
pazo	£89,326	2.25	3.73	£179,822	0.44	0.78	£413,033
tivo	£119,609	2.22	3.66	£149,539	0.47	0.86	£319,347
suni	£88,737	2.22	3.68	£180,411	0.46	0.84	£389,700
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.02	3.36				
nivo+ipi	£123,678	1.30	2.09	£90,724	0.72	1.26	£125,204
pem+lenv	£185,897	2.25	3.62	£28,505	-0.22	-0.26	Cabo+nivo dominated
pazo	£80,927	1.51	2.50	£133,475	0.51	0.85	£259,643
tivo	£95,735	1.48	2.43	£118,666	0.55	0.92	£217,324
suni	£80,234	1.48	2.45	£134,168	0.54	0.91	£248,004
cabo	£165,035	2.09	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 76: Scenario analysis 55 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.20	3.71				
pazo	£83,572	1.67	2.84	£152,823	0.53	0.88	£288,091
tivo	£102,777	1.64	2.76	£133,618	0.56	0.95	£237,322
suni	£82,905	1.64	2.78	£153,491	0.56	0.93	£275,091
Risk population: Favourable risk							
cabo+nivo	£269,148	2.65	4.52				
pazo	£89,326	2.20	3.73	£179,822	0.44	0.78	£405,354
tivo	£119,609	2.17	3.66	£149,539	0.48	0.86	£313,709
suni	£88,737	2.17	3.68	£180,411	0.47	0.84	£382,655
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	1.98	3.36				
nivo+ipi	£123,678	1.26	2.09	£90,724	0.72	1.26	£125,513
pem+lenv	£185,897	2.21	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.46	2.50	£133,475	0.52	0.85	£256,496
tivo	£95,735	1.43	2.43	£118,666	0.55	0.92	£214,779
suni	£80,234	1.43	2.45	£134,168	0.55	0.91	£245,026
cabo	£165,035	2.05	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 77: Scenario analysis 56 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.24	3.71				
pazo	£83,572	1.71	2.84	£152,823	0.53	0.88	£287,792
tivo	£102,777	1.68	2.76	£133,618	0.56	0.95	£237,126
suni	£82,905	1.68	2.78	£153,491	0.56	0.93	£274,879
Risk population: Favourable risk							
cabo+nivo	£269,148	2.69	4.52				
pazo	£89,326	2.24	3.73	£179,822	0.44	0.78	£405,984
tivo	£119,609	2.21	3.66	£149,539	0.48	0.86	£314,219
suni	£88,737	2.21	3.68	£180,411	0.47	0.84	£383,313
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.02	3.36				
nivo+ipi	£123,678	1.29	2.09	£90,724	0.73	1.26	£124,391
pem+lenv	£185,897	2.24	3.62	£28,505	-0.22	-0.26	Cabo+nivo dominated
pazo	£80,927	1.50	2.50	£133,475	0.52	0.85	£255,986
tivo	£95,735	1.47	2.43	£118,666	0.55	0.92	£214,409
suni	£80,234	1.47	2.45	£134,168	0.55	0.91	£244,615
cabo	£165,035	2.09	3.46	£49,367	-0.06	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 78: Scenario analysis 57 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.20	3.71				
pazo	£83,572	1.68	2.84	£152,823	0.53	0.88	£290,225
tivo	£102,777	1.64	2.76	£133,618	0.56	0.95	£239,059
suni	£82,905	1.65	2.78	£153,491	0.55	0.93	£277,113
Risk population: Favourable risk							
cabo+nivo	£269,148	2.65	4.52				
pazo	£89,326	2.21	3.73	£179,822	0.44	0.78	£409,008
tivo	£119,609	2.17	3.66	£149,539	0.47	0.86	£316,467
suni	£88,737	2.18	3.68	£180,411	0.47	0.84	£386,041
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	1.98	3.36				
nivo+ipi	£123,678	1.26	2.09	£90,724	0.72	1.26	£125,666
pem+lenv	£185,897	2.21	3.62	£28,505	-0.23	-0.26	Cabo+nivo dominated
pazo	£80,927	1.47	2.50	£133,475	0.52	0.85	£258,410
tivo	£95,735	1.43	2.43	£118,666	0.55	0.92	£216,361
suni	£80,234	1.44	2.45	£134,168	0.54	0.91	£246,839
cabo	£165,035	2.05	3.46	£49,367	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 79: Scenario analysis 58 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,583	2.25	3.71				
pazo	£83,574	1.70	2.84	£152,009	0.55	0.88	£277,557
tivo	£102,615	1.67	2.76	£132,967	0.58	0.95	£228,851
suni	£82,772	1.67	2.78	£152,811	0.57	0.93	£265,989
Risk population: Favourable risk							
cabo+nivo	£268,341	2.69	4.52				
pazo	£89,325	2.23	3.73	£179,016	0.46	0.78	£389,234
tivo	£119,445	2.20	3.66	£148,896	0.49	0.86	£301,546
suni	£88,602	2.20	3.68	£179,739	0.49	0.84	£368,995
Risk population: Intermediate / poor risk							
cabo+nivo	£213,589	2.03	3.36				
nivo+ipi	£123,579	1.28	2.09	£90,010	0.75	1.26	£120,811
pem+lenv	£185,427	2.24	3.62	£28,162	-0.22	-0.26	Cabo+nivo dominated
pazo	£80,930	1.49	2.50	£132,659	0.54	0.85	£246,622
tivo	£95,575	1.46	2.43	£118,014	0.57	0.92	£206,739
suni	£80,103	1.46	2.45	£133,487	0.56	0.91	£236,494
cabo	£164,963	2.08	3.46	£48,627	-0.05	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 80: Scenario analysis 59 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,878	2.21	3.71				
pazo	£84,056	1.68	2.84	£152,822	0.53	0.88	£290,130
tivo	£103,317	1.65	2.76	£133,561	0.56	0.95	£239,695
suni	£83,308	1.66	2.78	£153,570	0.55	0.93	£278,804
Risk population: Favourable risk							
cabo+nivo	£269,926	2.65	4.52				
pazo	£90,254	2.20	3.73	£179,672	0.44	0.78	£405,460
tivo	£120,587	2.18	3.66	£149,340	0.47	0.86	£317,610
suni	£89,611	2.18	3.68	£180,316	0.47	0.84	£386,779
Risk population: Intermediate / poor risk							
cabo+nivo	£214,718	1.99	3.36				
nivo+ipi	£123,772	1.28	2.09	£90,945	0.72	1.26	£126,733
pem+lenv	£186,526	2.21	3.62	£28,192	-0.22	-0.26	Cabo+nivo dominated
pazo	£81,233	1.48	2.50	£133,484	0.52	0.85	£258,383
tivo	£96,100	1.45	2.43	£118,617	0.55	0.92	£216,366
suni	£80,449	1.45	2.45	£134,269	0.54	0.91	£248,212
cabo	£166,340	2.04	3.46	£48,378	-0.05	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 81: Scenario analysis 60 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,395	2.27	3.71				
pazo	£83,572	1.72	2.84	£152,823	0.55	0.88	£277,698
tivo	£102,777	1.68	2.76	£133,618	0.59	0.95	£226,590
suni	£82,905	1.70	2.78	£153,491	0.58	0.93	£265,577
Risk population: Favourable risk							
cabo+nivo	£269,148	2.72	4.52				
pazo	£89,326	2.26	3.73	£179,822	0.46	0.78	£389,060
tivo	£119,609	2.22	3.66	£149,539	0.50	0.86	£297,836
suni	£88,737	2.23	3.68	£180,411	0.49	0.84	£368,045
Risk population: Intermediate / poor risk							
cabo+nivo	£214,402	2.05	3.36				
nivo+ipi	£123,678	1.30	2.09	£90,724	0.76	1.26	£119,925
pem+lenv	£185,897	2.27	3.62	£28,505	-0.22	-0.26	Cabo+nivo dominated
pazo	£80,927	1.51	2.50	£133,475	0.54	0.85	£246,858
tivo	£95,735	1.47	2.43	£118,666	0.58	0.92	£204,728
suni	£80,234	1.49	2.45	£134,168	0.57	0.91	£236,202
cabo	£165,035	2.10	3.46	£49,367	-0.05	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 82: Scenario analysis 61 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£238,443	2.17	3.71				
pazo	£84,771	1.67	2.84	£153,671	0.51	0.88	£304,145
tivo	£103,845	1.64	2.76	£134,598	0.53	0.95	£253,568
suni	£84,201	1.64	2.78	£154,242	0.53	0.93	£289,728
Risk population: Favourable risk							
cabo+nivo	£271,182	2.62	4.52				
pazo	£90,536	2.20	3.73	£180,645	0.42	0.78	£431,840
tivo	£120,688	2.17	3.66	£150,494	0.44	0.86	£338,669
suni	£90,044	2.17	3.68	£181,138	0.45	0.84	£406,333
Risk population: Intermediate / poor risk							
cabo+nivo	£216,448	1.95	3.36				
nivo+ipi	£124,618	1.26	2.09	£91,830	0.69	1.26	£132,532
pem+lenv	£187,691	2.19	3.62	£28,757	-0.23	-0.26	Cabo+nivo dominated
pazo	£82,118	1.46	2.50	£134,331	0.50	0.85	£271,228
tivo	£96,795	1.43	2.43	£119,653	0.52	0.92	£229,921
suni	£81,521	1.43	2.45	£134,927	0.52	0.91	£258,443
cabo	£166,438	2.04	3.46	£50,011	-0.09	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 83: Scenario analysis 62 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£236,035	2.23	3.71				
pazo	£83,364	1.70	2.84	£152,671	0.53	0.88	£287,171
tivo	£102,560	1.67	2.76	£133,474	0.56	0.95	£236,706
suni	£82,674	1.67	2.78	£153,361	0.56	0.93	£274,620
Risk population: Favourable risk							
cabo+nivo	£268,792	2.68	4.52				
pazo	£89,114	2.23	3.73	£179,679	0.44	0.78	£404,789
tivo	£119,388	2.20	3.66	£149,404	0.48	0.86	£313,458
suni	£88,502	2.20	3.68	£180,290	0.47	0.84	£382,748
Risk population: Intermediate / poor risk							
cabo+nivo	£214,041	2.01	3.36				
nivo+ipi	£123,556	1.28	2.09	£90,486	0.73	1.26	£123,831
pem+lenv	£185,626	2.24	3.62	£28,415	-0.22	-0.26	Cabo+nivo dominated
pazo	£80,721	1.49	2.50	£133,320	0.52	0.85	£255,456
tivo	£95,521	1.46	2.43	£118,520	0.55	0.92	£214,046
suni	£80,006	1.46	2.45	£134,035	0.55	0.91	£244,410
cabo	£164,808	2.08	3.46	£49,233	-0.06	-0.11	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 84: Scenario analysis 63 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£217,898	1.85	2.94				
pazo	£60,015	1.43	2.30	£157,883	0.42	0.64	£378,208
tivo	£84,703	1.50	2.41	£133,195	0.35	0.52	£379,342
suni	£65,360	1.51	2.44	£152,538	0.34	0.50	£445,314
Risk population: Favourable risk							
cabo+nivo	£250,928	2.30	3.74				
pazo	£65,379	1.96	3.17	£185,549	0.34	0.57	£545,881
tivo	£101,235	2.03	3.29	£149,693	0.27	0.45	£548,764
suni	£70,901	2.04	3.32	£180,026	0.26	0.42	£681,904
Risk population: Intermediate / poor risk							
cabo+nivo	£195,913	1.63	2.59				
nivo+ipi	£106,881	1.11	1.73	£89,031	0.52	0.85	£169,980
pem+lenv	£163,800	1.99	3.14	£32,112	-0.36	-0.56	Cabo+nivo dominated
pazo	£57,660	1.22	1.97	£138,253	0.40	0.61	£341,950
tivo	£77,883	1.29	2.09	£118,029	0.34	0.50	£348,530
suni	£62,906	1.30	2.11	£133,007	0.33	0.47	£402,773
cabo	£131,235	1.64	2.55	£64,677	-0.01	0.03	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 85: Scenario analysis 64 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,022	2.21	3.69				
pazo	£84,466	1.73	2.89	£150,556	0.48	0.80	£310,912
tivo	£104,096	1.69	2.82	£130,926	0.52	0.88	£252,565
suni	£83,781	1.70	2.84	£151,241	0.51	0.86	£295,438
Risk population: Favourable risk							
cabo+nivo	£267,426	2.65	4.49				
pazo	£90,241	2.27	3.81	£177,185	0.38	0.68	£462,701
tivo	£121,232	2.23	3.73	£146,194	0.42	0.76	£350,130
suni	£89,639	2.24	3.75	£177,787	0.41	0.74	£432,643
Risk population: Intermediate / poor risk							
cabo+nivo	£213,226	1.99	3.34				
nivo+ipi	£123,297	1.28	2.09	£89,929	0.72	1.25	£125,530
pem+lenv	£185,895	2.23	3.62	£27,331	-0.23	-0.28	Cabo+nivo dominated
pazo	£81,816	1.51	2.55	£131,411	0.48	0.79	£272,776
tivo	£96,927	1.48	2.48	£116,300	0.52	0.86	£225,613
suni	£81,104	1.48	2.49	£132,122	0.51	0.85	£259,497
cabo	£167,113	2.10	3.50	£46,113	-0.10	-0.16	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 86: **Scenario analysis 65 pairwise comparison table**

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£232,013	2.18	3.65				
pazo	£86,627	1.80	3.03	£145,387	0.38	0.62	£380,446
tivo	£107,289	1.76	2.95	£124,725	0.42	0.70	£296,709
suni	£85,901	1.77	2.97	£146,112	0.41	0.68	£355,881
Risk population: Favourable risk							
cabo+nivo	£263,652	2.61	4.42				
pazo	£92,460	2.36	4.00	£171,192	0.25	0.42	£688,903
tivo	£125,163	2.33	3.91	£138,489	0.29	0.51	£482,450
suni	£91,826	2.34	3.94	£171,826	0.28	0.48	£620,008
Risk population: Intermediate / poor risk							
cabo+nivo	£210,643	1.97	3.31				
nivo+ipi	£122,594	1.28	2.10	£88,050	0.70	1.20	£126,459
pem+lenv	£186,091	2.22	3.63	£24,552	-0.25	-0.32	Cabo+nivo dominated
pazo	£83,966	1.58	2.67	£126,677	0.40	0.64	£319,550
tivo	£99,810	1.54	2.58	£110,833	0.43	0.72	£255,217
suni	£83,209	1.55	2.61	£127,434	0.42	0.70	£300,123
cabo	£172,062	2.16	3.60	£38,581	-0.19	-0.29	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 87: Scenario analysis 66 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£243,759	2.35	3.95				
pazo	£83,572	1.69	2.84	£160,187	0.66	1.12	£244,271
tivo	£102,777	1.66	2.76	£140,982	0.69	1.19	£204,844
suni	£82,905	1.67	2.78	£160,855	0.68	1.17	£235,461
Risk population: Favourable risk							
cabo+nivo	£269,148	2.67	4.52				
pazo	£89,326	2.23	3.73	£179,822	0.44	0.78	£408,449
tivo	£119,609	2.19	3.66	£149,539	0.47	0.86	£315,998
suni	£88,737	2.20	3.68	£180,411	0.47	0.84	£385,505
Risk population: Intermediate / poor risk							
cabo+nivo	£225,867	2.16	3.65				
nivo+ipi	£155,777	1.62	2.66	£70,089	0.54	0.99	£129,331
pem+lenv	£185,897	2.23	3.62	£39,970	-0.07	0.03	Cabo+nivo dominated
pazo	£80,927	1.49	2.50	£144,940	0.68	1.15	£214,442
tivo	£95,735	1.45	2.43	£130,131	0.71	1.22	£183,820
suni	£80,234	1.46	2.45	£145,633	0.70	1.20	£207,171
cabo	£171,776	2.14	3.54	£54,090	0.02	0.10	£2,546,989

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 88: **Scenario analysis 67 pairwise comparison table**

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£213,112	1.80	2.78				
pazo	£72,106	1.45	2.28	£141,005	0.35	0.50	£401,026
tivo	£90,538	1.43	2.25	£122,574	0.37	0.54	£334,739
suni	£72,084	1.43	2.26	£141,027	0.36	0.53	£386,606
Risk population: Favourable risk							
cabo+nivo	£225,555	1.96	3.01				
pazo	£72,191	1.77	2.74	£153,364	0.19	0.28	£794,802
tivo	£98,186	1.76	2.71	£127,369	0.21	0.30	£618,862
suni	£72,286	1.76	2.72	£153,269	0.20	0.29	£747,788
Risk population: Intermediate / poor risk							
cabo+nivo	£197,458	1.67	2.60				
nivo+ipi	£114,296	1.14	1.80	£83,162	0.52	0.80	£158,676
pem+lenv	£166,998	1.84	2.82	£30,460	-0.17	-0.22	Cabo+nivo dominated
pazo	£71,563	1.30	2.07	£125,894	0.37	0.53	£341,953
tivo	£86,496	1.28	2.03	£110,962	0.38	0.56	£289,432
suni	£71,488	1.29	2.05	£125,970	0.38	0.55	£329,947
cabo	£141,614	1.70	2.65	£55,844	-0.03	-0.05	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 89: **Scenario analysis 68 pairwise comparison table**

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£231,853	2.11	3.37				
pazo	£80,672	1.63	2.64	£151,181	0.48	0.73	£316,465
tivo	£99,968	1.60	2.59	£131,884	0.50	0.78	£262,346
suni	£80,261	1.61	2.61	£151,592	0.50	0.77	£303,876
Risk population: Favourable risk							
cabo+nivo	£256,434	2.44	3.91				
pazo	£84,365	2.08	3.35	£172,069	0.36	0.56	£481,219
tivo	£113,436	2.06	3.30	£142,998	0.38	0.61	£374,466
suni	£84,069	2.06	3.31	£172,364	0.38	0.60	£455,773
Risk population: Intermediate / poor risk							
cabo+nivo	£211,019	1.91	3.06				
nivo+ipi	£122,283	1.25	2.01	£88,736	0.65	1.05	£135,853
pem+lenv	£181,878	2.14	3.39	£29,141	-0.24	-0.33	Cabo+nivo dominated
pazo	£78,467	1.43	2.34	£132,551	0.47	0.72	£280,588
tivo	£93,530	1.41	2.29	£117,488	0.50	0.77	£236,198
suni	£78,014	1.41	2.30	£133,004	0.49	0.75	£269,464
cabo	£161,559	1.99	3.21	£49,459	-0.09	-0.16	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 90: **Scenario analysis 69 pairwise comparison table**

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£235,545	2.20	3.60				
pazo	£83,011	1.68	2.78	£152,534	0.51	0.82	£297,023
tivo	£102,295	1.65	2.72	£133,250	0.54	0.88	£244,901
suni	£82,409	1.66	2.73	£153,136	0.54	0.87	£283,983
Risk population: Favourable risk							
cabo+nivo	£267,581	2.63	4.37				
pazo	£88,534	2.21	3.65	£179,047	0.42	0.72	£421,904
tivo	£118,768	2.17	3.58	£148,813	0.46	0.78	£326,932
suni	£88,019	2.18	3.60	£179,563	0.45	0.77	£398,825
Risk population: Intermediate / poor risk							
cabo+nivo	£213,589	1.98	3.24				
nivo+ipi	£123,407	1.27	2.06	£90,182	0.70	1.18	£127,926
pem+lenv	£185,372	2.22	3.57	£28,217	-0.24	-0.33	Cabo+nivo dominated
pazo	£80,399	1.47	2.45	£133,190	0.50	0.80	£264,252
tivo	£95,287	1.44	2.39	£118,301	0.53	0.86	£221,439
suni	£79,768	1.45	2.40	£133,820	0.53	0.84	£252,732
cabo	£164,432	2.05	3.38	£49,157	-0.08	-0.14	Cabo+nivo dominated

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 91: **Scenario analysis 70 pairwise comparison table**

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£210,354	1.84	2.82				
pazo	£66,216	1.56	2.39	£144,138	0.27	0.43	£527,412
tivo	£88,043	1.58	2.39	£122,310	0.26	0.43	£466,745
suni	£66,382	1.56	2.39	£143,971	0.27	0.43	£527,177
Risk population: Favourable risk							
cabo+nivo	£223,106	1.96	3.00				
pazo	£66,145	2.06	3.15	£156,961	-0.09	-0.15	Cabo+nivo dominated
tivo	£95,321	2.07	3.15	£127,785	-0.11	-0.15	Cabo+nivo dominated
suni	£66,381	2.06	3.15	£156,725	-0.09	-0.15	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£194,499	1.70	2.61				
nivo+ipi	£112,523	1.66	2.54	£81,976	0.03	0.07	£2,630,390
pem+lenv	£159,301	1.64	2.46	£35,198	0.06	0.15	£586,300
pazo	£66,305	1.33	2.03	£128,194	0.37	0.58	£348,497
tivo	£84,737	1.34	2.03	£109,762	0.36	0.58	£307,911
suni	£66,438	1.33	2.03	£128,061	0.37	0.58	£348,318
cabo	£140,937	1.55	2.33	£53,562	0.14	0.28	£371,953

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 92: Scenario analysis 71 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£225,031	2.10	3.30				
pazo	£69,872	1.79	2.81	£155,160	0.31	0.49	£500,592
tivo	£93,246	1.80	2.81	£131,786	0.30	0.49	£441,421
suni	£70,050	1.79	2.81	£154,981	0.31	0.49	£500,326
Risk population: Favourable risk							
cabo+nivo	£249,657	2.48	3.96				
pazo	£72,824	2.65	4.27	£176,833	-0.17	-0.31	Cabo+nivo dominated
tivo	£105,857	2.66	4.27	£143,800	-0.18	-0.31	Cabo+nivo dominated
suni	£73,099	2.65	4.27	£176,559	-0.17	-0.31	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£204,375	1.87	2.94				
nivo+ipi	£120,026	1.86	2.90	£84,349	0.01	0.04	£6,110,530
pem+lenv	£171,062	1.90	2.93	£33,313	-0.02	0.01	Cabo+nivo dominated
pazo	£68,487	1.45	2.25	£135,889	0.43	0.69	£318,926
tivo	£87,659	1.46	2.25	£116,716	0.41	0.69	£281,508
suni	£68,625	1.45	2.25	£135,751	0.43	0.69	£318,746
cabo	£157,827	1.80	2.78	£46,548	0.07	0.16	£630,857

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Table 93: Scenario analysis 72 pairwise comparison table

Technologies	Costs (£)	QALYs	LYs	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All risk							
cabo+nivo	£226,478	2.12	3.35				
pazo	£70,499	1.83	2.90	£155,978	0.30	0.45	£526,831
tivo	£94,141	1.84	2.90	£132,337	0.28	0.45	£464,932
suni	£70,677	1.83	2.90	£155,801	0.30	0.45	£526,572
Risk population: Favourable risk							
cabo+nivo	£258,827	2.65	4.36				
pazo	£75,340	2.88	4.82	£183,487	-0.23	-0.46	Cabo+nivo dominated
tivo	£109,896	2.89	4.82	£148,931	-0.24	-0.46	Cabo+nivo dominated
suni	£75,617	2.88	4.82	£183,210	-0.23	-0.46	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
cabo+nivo	£204,761	1.88	2.95				
nivo+ipi	£120,405	1.87	2.92	£84,356	0.01	0.03	£7,537,631
pem+lenv	£173,284	1.94	3.04	£31,477	-0.06	-0.09	Cabo+nivo dominated
pazo	£68,708	1.46	2.28	£136,053	0.42	0.67	£323,934
tivo	£87,957	1.47	2.28	£116,804	0.41	0.67	£285,920
suni	£68,846	1.46	2.28	£135,915	0.42	0.67	£323,754
cabo	£159,176	1.81	2.81	£45,585	0.07	0.14	£700,321

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

NICE National Institute for Health and Care Excellence

Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

As a stakeholder you have been invited to comment on the data and analysis included in the external assessment group (EAG) model and Final Assessment Report for this pathway pilot appraisal.

Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

Information on completing this form

We are asking for your views on data and assumptions included within the analysis model and used to form the final report that are likely to be discussed by the committee. The report provides a summary of work undertaken by the EAG developing the analysis and incorporating the data received from manufacturers, observational patient datasets and formal input from clinical experts. It outlines the analysis plan, methods used for the evaluation, as well as all identified relevant published evidence and real-world evidence (RWE) sources.

You are not expected to comment on every key topic but instead comment on the issues that are in your area of expertise.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have

to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by the end of Thursday 10 August. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during consultation, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during consultation are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Ipsen Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG. Ipsen would like to provide the following statement regarding its experience with the Pathways Pilot.

The Pathways Approach, which is being piloted as part of this appraisal, is a highly ambitious programme formed of four pillars (as stated by NICE):

- Improve efficiency, assessing multiple technologies in a disease pathway
- Inform robust decisions by building an evolving model for a disease area
- Create more cohesive guidance about treatment options in the pathway
- Provide a platform for monitoring and updating the disease pathway in the future

Ipsen has welcomed the opportunity to participate in this pilot as the appraisal of cabozantinib with nivolumab for RCC has been delayed for over three years through no fault of the company (i.e., Ipsen). It has become clear that achieving this ambitious aim is not without its considerable challenges. This includes extensive time and resource commitments from all key stakeholders: NICE, the EAG and Ipsen. As one example, for Ipsen, the data requirement demands made by the EAG for its modelling approach has been far in excess of that anticipated and significantly higher compared to the standard STA process in Ipsen's experience.

As part of the Pathways Approach, a whole disease pathway model is necessary. Although the development of a whole disease pathway model is appealing from a reimbursement body perspective, the initial model development requires substantial time and human resource investment, as evidenced by this pilot. There are key challenges from other relevant perspectives which need to be highlighted and addressed appropriately by NICE. These have been noted elsewhere but are also provided here for ease.

Firstly, the development of a model on this scale has implications for the identification, selection, and use of evidence especially given the immense data requirements of such a model. Where data gaps exist this leads to increased uncertainty in decision making thereby leading to questions regarding the validity of outputs from these models.

Additionally, given the breadth of these models, the burden of their validation is significantly increased. Ipsen have directly experienced this burden as part of this pilot; this has included the need to up-skill in R in a short time period. Whilst Ipsen understand the need to develop the RCC whole disease model in R and have greatly appreciated the EAG's assistance in helping Ipsen to run and understand the model, this has created an unnecessary burden for Ipsen. Generally, the development of models in R requires a significant level of knowledge beyond that which is possessed by most stakeholders. Of note, the running of different scenarios is time consuming (e.g., there is a running time of over ninety minutes for one scenario in the model).

A further key challenge is that Ipsen have not been able to replicate and validate the EAG results as some key information in the model is dummy data due to confidentiality restrictions (e.g., the RWE data that form the backbone of multiple model inputs).

In addition, the whole disease pathway modelling approach inevitably requires the use of specialist statistical calibration methods; these methods are complex, and there remains little consensus within the literature regarding methodologies.

The Pathways Pilot has surfaced several key issues for specific interventions, as highlighted by the EAG. The pathway model brings into focus anomalies that were apparent in TA858 and have been highlighted by the EAG in Key Issue 1 (Appendix Q) that in TA858 had ipilimumab with nivolumab been appraised in TA858 as well as lenvatinib with pembrolizumab it is likely it would not have been cost-effective versus TKI monotherapies and therefore in theory should have had its recommendation in TA780 rescinded. It is also quite possible that in this pilot pathway appraisal similar conclusions could be made from the EAG base case e.g., for ipilimumab with nivolumab versus sunitinib, as ipilimumab with nivolumab is dominated in having more costs and less QALYs compared to sunitinib (Table 21, Appendix Q).

The EAG have effectively developed two models as part of their remit: state transition and a partition survival analysis. The use of a different model structure can impact whether an intervention is deemed cost-effective and potentially leads to different results within the pathway model itself compared to previous appraisals. This may potentially mean that interventions which have been previously recommended by NICE are no longer considered cost-effective. Ipsen does not have access to the 'with PAS' ICERs for any of the comparators but judging from the results of previous appraisals this is quite possible. Thus, a key consideration is whether this pilot would lead to a reset of all past TAs in this indication.

To meet the pillars for the pathway approach, one of the most desirable aspects is consistency in the application of process, inputs, and assumptions. Some of these can be easily achieved (e.g., costs of Grade 3+ adverse events, costs and frequency of monitoring and healthcare resource use), and will be a real benefit for future appraisals. Other elements, however, are subject to much more variability. This may be due to lack of sources of information for all aspects of treatment that needs to be modelled e.g., lack of RWE for lenvatinib and pembrolizumab, absence of time-to-treatment discontinuation data for many comparators or

information not being in the public domain. This leads to additional assumptions being made in an already complex environment and introducing greater potential variation and inconsistency.

It is, of course, important from Ipsen's perspective that the Pathways Pilot does not lose its focus. Namely, the appraisal of cabozantinib with nivolumab for 1L RCC as per the decision problem and for NICE to ensure timely and fair decision making. To enable this in the context of the above, NICE's appetite with respect to decision risk and corresponding uncertainties arising from inconsistencies in modelling methods and sources that have surfaced in this pilot appraisal will be tested and it is hoped that all aspects of this are considered such that cabozantinib with nivolumab is not disadvantaged due to having been willing to participate in this pilot pathway.

Table 2: key issues

Issue		**Response**	**Does this response contain new evidence, data or analyses?**
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	Capturing and modelling the optimal treatment sequencing pathway is challenging. The choice of treatment pathway is dependent on several factors. This includes a consideration of individual patient needs and their characteristics (e.g., presence of comorbidities and receipt of concomitant medications) as well as clinician preference/experience.	No

		As new treatments become available, treatment sequences will change particularly as clinicians become more familiar with implementing novel therapies. As such, treatment sequencing pathways are based on individual patient decision making and evolve over time. The choice of treatment sequences impacts the cost-effectiveness as highlighted by the EAG which states that *"Current estimates of cost effectiveness, particularly in second line and for favourable risk patients, may evolve as this evidence develops. Optimal treatment sequencing may also impact overall estimates of OS in first line, but the direction of impact on cost-effectiveness estimates is unclear."* This is demonstrated in the heavily redacted **Appendix I – Consistency with recent previous technology appraisals by NICE in advanced renal carcinoma**, where the EAG notes that *"The distribution of patients receiving cabozantinib or nivolumab (the most expensive later line options) as sequential therapies in earlier technology assessments is shown in the following table. This proportion varies considerably across appraisals."* This variability demonstrates the difficulty in accurately defining treatment sequencing in aRCC.	
	Key Issue 2: Company's definition of relevant comparators	Ipsen understands the rationale for the removal of avelumab with axitinib as a comparator in the economic analyses, however, Ipsen still believes that this combination should be considered part of routine practice (having been in the CDF for 3 years). To add to the inconsistency of past, current and future NICE appraisals for companies, Ipsen understands that NICE stated at the ABPI and NICE Operational Effectiveness Group Meeting held on 25th January 2023	No

		that NICE's position statement for CDF medicines as comparators would be retired and that the decision as to whether CDF medicines should be comparators would in the future be made by the NICE Associate Director on a case-by-case basis depending on when the medicine is expected to exit the CDF. This more dynamic view of scoping will no doubt cause more challenges due to the lack of predictability. No further challenge will be raised by Ipsen on this matter, yet our position remains the same. Tivozanib is considered a relevant comparator in the first line setting in this appraisal, although its market share is very low as demonstrated in Ipsen's response to clarification question A1. This is at odds with the EAG assertion that tivozanib is used more frequently in first line than cabozantinib monotherapy based on the real-world UK source that the EAG has access to but is redacted. More recent sales data for tivozanib shows its market share has remained low and unchanged since the company's response to clarification question Q1 (1). The inclusion of tivozanib as a comparator leads to increased uncertainty in the network meta-analysis (NMA), specifically with the inclusion of trials that did not enrol any poor risk patients. Whilst the EAG conducted a sensitivity analysis excluding trials which did not enrol patients with poor risk, there is no explanation as to why a sensitivity analysis has not been conducted for trials that excluded patients with a favourable risk status.	
	Key Issue 3: Company's definition of relevant outcomes	It is worth noting that the data demands from the EAG to the company in this appraisal have been significantly higher than what would be expected for a Single Technology Appraisal (STA). These data demands had not been anticipated by the company at the start of this	No

		pilot pathway appraisal. It should also be noted that these data demands have implications for future pathway appraisals particularly in light of the demand placed on submitting company resources. The example of a specific data request from the EAG makes this point. The EAG clarification questions detailed the need for further information on time to next treatment (TTNT) to inform the health economic modelling. Ipsen provided the individual patient level data for time to subsequent treatment for the overall risk, favourable risk, and intermediate/poor risk populations. In the end, the use of TTNT is academic as very few trials (n=3) reported TTNT outcomes (Table 11, EAG report) TTNT was not used in the economic modelling. Indeed, data for TTNT have only been made available from two of the three trials following bespoke patient level analysis of the CheckMate 9ER and CheckMate 214 studies.	
	Key Issue 4: Company's definition of relevant subgroups	Ipsen's position remains that cabozantinib with nivolumab should be appraised in the all-risk population. Currently, there are no 1L treatment options for the all-risk population in baseline commissioning. Clinicians in England and Wales would welcome the availability of cabozantinib with nivolumab in an all-risk population, enabling them to offer as much patient choice as possible. The recommendation of axitinib with avelumab (TA645) highlights that NICE recommendations can be made for the all-risk population. Cabozantinib with nivolumab is shown to be clinically effective in the all-risk population in the CheckMate 9ER trial. Importantly, modelling the cost-effectiveness of cabozantinib with nivolumab in the all-risk population requires the fewest assumptions.	No

	Key Issue 5: CheckMate 9ER: Consistency of reporting	The 44-month data-cut required re-review and recalculation due to the study sponsor detecting an error in the blinded independent central reviewer (BICR)-related outputs (e.g., progression-free survival [PFS], objective response rates [ORR], duration of response [DOR], time to response). An erratum was published in the Journal of Clinical Oncology with the error for the 44-month data-cut as described below: *"The abstract by Burotto et al, "Nivolumab plus cabozantinib vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the phase 3 CheckMate 9 ER trial" (Journal of Clinical Oncology 41, no. 6, suppl 603), was published February 21, 2023, with errors. The Results section and the table have been updated to correct inaccurate data that was a result of a programming issue encountered while generating the data for BICR-related study endpoints."* Ipsen cannot provide any further detail regarding the error within the data, as we are not the data owners. When receiving the updated 44-month data, we identified negligible differences within the adverse event information. However, we cannot clarify the reason as we are not the study sponsor. Nonetheless, with regard to the adverse event data, the differences are very minor and the overall adverse event information is very similar to the previous data cut at 32.9 months median overall survival (OS) follow-up. These do not impact the overall conclusions and robustness of the study conclusions.	No
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice	The EAG comment on the generalisability of CheckMate 9ER to clinical practice in the United Kingdom (UK), specifically the low	No

		enrolment of UK patients and the number of patients that received treatment post-progression. The CheckMate 9ER trial was conducted in 25 countries involving 125 sites. Of these, there were three (2.4%) sites from the UK which contributed 3.2% of the 651 patients in the study. In comparison, the CLEAR study was conducted in 20 countries involving 200 sites, of which eight (4%) sites were from the UK (number of UK patients recruited not reported). The CheckMate 214 trial was conducted in 28 countries involving 175 sites, of which six (3.4%) sites were from the UK (number of UK patients recruited not reported). Therefore, the CheckMate 9ER trial is not necessarily an outlier among other recent combination therapies that have been evaluated by NICE and no issues regarding generalisability were raised in the MTA for lenvatinib with pembrolizumab (CLEAR trial) in TA858. The EAG also comment that CheckMate 9ER included very few patients who had received a prior adjuvant treatment (n=5) and that it does not align well with current and expected future practice in the UK following the recommendation of pembrolizumab in the adjuvant setting, which impacts both generalisability and achievability of the observed effect sizes. The low number of patients who received adjuvant treatment is not surprising considering the time duration in which the trial was conducted (August 2017 – February 2020), but this should not disadvantage the evaluation of cabozantinib with nivolumab. A further question will also be the sequencing of lenvatinib with pembrolizumab following adjuvant pembrolizumab treatment. Clinicians are unlikely to use the same immunotherapy i.e. pembrolizumab previously used in the sequence based in Ipsen	

		advisory board feedback, hence the need for an additional first line treatment option with other IO/TKI combinations. Additionally, the EAG expresses concern regarding the rate of patients continuing to receive treatment post-progression, which was both higher and of a longer duration than expected and not aligned with clinical treatment patterns in the UK. We believe that there has been a misunderstanding of the data request from the EAG regarding clarification question A13. *"How many patients received treatment beyond RECIST defined disease progression in each arm and what was the duration of the treatment beyond progression in these patients?"* We now see from the EAG report that the EAG were specifically requesting the numbers of patients who continued either cabozantinib with nivolumab or sunitinib in each arm beyond RECIST defined disease progression. The data we provided used a particular censoring rule in our response data for any treatment post-progression, thus those data should be disregarded. We continue to try and obtain this information but without success to date. If we do get this information ahead of the NICE committee meeting we will share it. The time to discontinuation (TTD) data used in the model should account for treatment beyond progression (the TTD curve is above PFS) and its associated costs, so the number of patients who received treatment post-progression would be captured here. The EAG comment that patients with intermediate and poor risk receiving sunitinib had higher restricted mean survival times for both OS and PFS in the CheckMate 9ER trial than the comparable real world evidence source preferred by the EAG, with a similar trend seen	

		for OS in the favourable risk group as well. Without access to the real-world evidence (RWE), this is difficult for the company to comment on. Regarding patients receiving sunitinib having comparatively lower use of nivolumab as a subsequent treatment than expected, this may be related to the availability of second-line treatments at a particular trial site or participating country.	
	Key Issue 7: CheckMate 9ER: Effect modification by risk group	The company retains its position that cabozantinib with nivolumab should be available as a 1L treatment option for the all-risk population.	No
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials	Ipsen has commented further on this issue within Table 3 (Other topics raised in the EAG report): Treatment effectiveness and extrapolation. In summary, we believe that the NMA conducted by the EAG leads to greater uncertainty for the following reasons: • the lack of data for some interventions by risk group • inconsistencies and compromises made within the NMA • the application of relative treatment efficacy across comparators and lines of therapy in an inconsistent manner	No
	Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks	We agree that capturing all the effect modifiers across the NMA was challenging especially as they are not often reported in trials. The company provided the EAG all the data for effect modifiers including sarcomatoid features.	No
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes	The EAG note that there is evidence of 'slippage' in OS and PFS hazard ratio estimates with longer follow-up, particularly for IO/TKI combinations (Figures 30 and 31 in the EAG report). This is particularly the case for lenvatinib with pembrolizumab PFS and OS	No

		results compared to cabozantinib with nivolumab, the latter of which present stable PFS and OS. Therefore, the results of the CheckMate 9ER with the 44-month follow-up data are suitable for decision making by NICE. Issues regarding inconsistencies including the application of relative efficacy, especially for lenvatinib with pembrolizumab, are discussed under the health economic key issues.	
	Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment	**Applicability to other renal cell carcinoma (RCC) histologies** The EAG notes that there are questions about the applicability of analyses to other RCC histologies. In RCC, trials are commonly restricted to patients with a clear cell histology. These patients make up the vast majority (circa. 75%) of RCC patients. It is worth noting that all histological epithelial subtypes of RCC (clear cell, papillary, chromophobe) can present with sarcomatoid differentiation, which is the most aggressive form of RCC. A high proportion of RCC patients with sarcomatoid features present with metastatic disease. These features are found in 5-8% of clear cell RCC and in the CheckMate 9ER trial 11.95% of the patients recruited had sarcomatoid features. This is similar to the IO/IO trial CheckMate 214 (ipilimumab with nivolumab) and the IO/TKI trial JAVELIN 101 (axitinib with avelumab) but higher than other IO/TKI combination trials such as CLEAR (6.8%). This helps increase the applicability of the CheckMate 9ER results to clinical practice. Further, the EMA noted that in the application for approval of cabozantinib with nivolumab non-clear cell RCC were not excluded from the sought indication, which	No

		was deemed acceptable by the EMA because cabozantinib had shown efficacy in non-clear cell RCC in a retrospective study (2). As a final note, this highlights the difference in requirements between regulatory bodies and Health Technology Assessment (HTA) organisations. This key issue demonstrates both how the two may be at odds and the inability to resolve these concerns to the satisfaction of all parties and, thus some compromises may need to be made. **Adjuvant treatment** The EAG notes that adjuvant pembrolizumab was not available as part of routine practice when any of the included trials were conducted. Ipsen appreciates that this introduces uncertainties to this appraisal, however, it should be noted that this is by no means unique to this appraisal and that HTA bodies are familiar with making decisions in the face of uncertainty.	
Cost evidence (key issues in the Economic Results Addendum document)	Key Issue 1: Inconsistency between prior appraisals	**The EAG's base case model structure and the granularity in modelling four lines of treatment deviates from precedence, creating inconsistencies in decision making for cabozantinib with nivolumab versus previous appraisals.** In the systematic literature review (SLR) conducted by the EAG to identify previous economic evaluations and technology appraisals (TAs) of treatments in advanced RCC, it was highlighted that the majority of prior appraisals and economic evaluations both for cabozantinib with nivolumab and for other therapies employed a partitioned survival analysis (PartSA) model structure, due to its reliance on clinical trial-reported outcomes, non-intensive data input requirements, and ease of interpretation. In this appraisal, the EAG	No

		employed a hybrid state transition model (STM) with the aim of constructing a whole pathway model which accommodates the exploration of treatment sequences and incorporates multiple decision nodes. The implementation of a different model structure for the appraisal of cabozantinib with nivolumab that models granularly four lines of active treatment compared to the model structure implemented for its comparators in previous STAs is in itself a source of inconsistency which contributes to uncertainty in decision making. **Unexpected discrepancies in results between model structures** Although the EAG had originally reassured the company that the two model structures produce comparable results, the results from the hybrid STM and PartSA model structure eventually appear to produce markedly different ICERs. The company would like the EAG to clarify what are the drivers of this difference, and whether clinical outcomes estimated by each model structure, and under different scenarios, have been validated by clinical experts and/or against the clinical expert elicitation exercise. **Increased uncertainty associated with modelling subsequent lines of treatment** Ipsen note that the implementation of the hybrid STM structure, and particularly the implementation of four lines of treatment informed by RWE, introduced certain challenges and potentially serves as a source of bias for the results of the cost-effectiveness analysis. First, the PFS relative treatment efficacy derived from the NMAs was used to inform treatment efficacy on TTD and time to progression (TTP),	

		due to lack of published robust comparative efficacy evidence on the latter outcomes. Although the EAG explored the level of correlation between TTD and PFS and indicated a high level of correlation between the two outcomes based on the UK RWE (Spearman's correlation coefficient of 0.83 for TTD), this assumption further contributes to the decision uncertainty. The EAG conducted a scenario analysis assuming that the TTD is equal to PFS for which evidence is available for all comparator treatments with the rationale that TTD data are sparse whilst PFS is available for all treatments (page 369 EAG report). An example of this is the lack of TTD data for Len+Pem. In TA780 the only comparator for ipilimumab with nivolumab was sunitinib and pazopanib. Here the company used its trial data for TTD for ipilimumab with nivolumab and sunitinib and assumed the TTD for pazopanib was the same as sunitinib. In TA858 TTD from the CLEAR trial for lenvatinib with pembrolizumab and sunitinib was used. For cabozantinib monotherapy the TTD was digitised from NICE TA of cabozantinib (TA542). But as ipilimumab with nivolumab TTD was not in public domain the company and EAG used the lenvatinib TTD from CLEAR trial as the ipilimumab with nivolumab TTD. In this pathway appraisal the EAG has access to the ipilimumab with nivolumab TTD which could yield quite different results compared to TA780 and TA858. **Considering the number of assumptions made to generate TTD curves for all comparators, the company considers that the more simplified assumption that TTD is equal to PFS is more appropriate and consistent.** In addition, clinical outcomes related to the reference treatment for each line of therapy were informed based	

		on the UK RWE. Despite the use of RWE to inform the baseline being a methodologically sound approach, the baseline was informed by a limited patient sample to model outcomes for 3L and relied on assumptions to inform outcomes in 4L. Furthermore, due to lack of robust published utility estimates, strong assumptions were made to inform health state utility values in subsequent lines of treatment captured by the hybrid STM. Although the EAG stresses the importance of modelling subsequent lines of treatment, results presented in Table 3 to Table 10 of Appendix Q, highlight that the majority of life years (LYs) and quality-adjusted life-years (QALYs) for all IMDC patient groups are accrued in the first two lines of treatment by cabozantinib with nivolumab ([redacted]% of LYs and [redacted]% of QALYs) and for the relevant comparator ([redacted]% of LYs and [redacted]% of QALYs). Additionally, a previous UK audit cited by the EAG reported only 34%, and 6% of RCC patients receive 3L and 4L of treatment, respectively. These results resonate with expert advice (EAG report page 41) suggesting that it is realistic to expect that most patients with RCC would receive up to three lines of treatment. Ipsen note that the largest proportion of the modelled outcomes related to this decision problem are accrued within the first two lines of treatment, and modelling beyond 2L increases uncertainty due to a combination of assumptions required to inform the hybrid STM input parameters, and limitations related to the UK RWE to inform subsequent lines of treatment. The PartSA model structure requires fewer assumptions with regards to input parameters, and overall may be associated with less	

		uncertainty compared to a hybrid STM that aims to granularly model outcomes over 4 lines of treatment. **However, considering** • **the inherent assumptions and limitations of a PartSA** • **the uncertainty that characterises outcomes on subsequent lines of treatment based on the UK RWE (e.g., sample size , uncertainty on generalisability of evidence)** • **the uncertainty in the composition of subsequent lines of treatment** • **the majority of LYs and QALYs in the model are accumulated in the first two lines of treatment** • **and the scope of this appraisal focusing on evaluating cabozantinib in combination with nivolumab as a 1L treatment** **the company recommends favouring the hybrid STM model with two lines of treatment.** In addition, as described in Table 3 below, the company has experienced many challenges in running the model, not least the model runtime with four lines of treatment of at least 90 minutes per scenario, and the inability to replicate the EAG results due to the redacted nature of the RWE data.	
	Key Issue 2: Economic implications of trial generalisability to real-world evidence	It remains uncertain whether the RWE used by the EAG to assess the applicability of trial evidence to a real-world setting is appropriate. A key reason for this is the lack of detail provided on the external validity of the RWE conducted by the EAG (was this based on clinician	No

		opinion or published, peer-reviewed UK RWE data sources?). Of note, the structured expert elicitation exercise carried out by the EAG does not align with the RWE, raising further questions regarding the generalisability of the RWE obtained by the EAG to the target population in the UK. Importantly, Ipsen is not able to make a judgement on the generalisability of the RWE as the information has been redacted from stakeholder review. Ipsen would welcome the EAG providing a comprehensive explanation of the approach used to validate the external validity of the RWE data source. This should include detail on how reflective (i.e., generalisable) the RWE data source is of UK practice. Further, the EAG note that '*it is generally the case across most treatments that RWE reflects lower survival than the corresponding trial evidence, though RDIs are also lower in RWE than the corresponding trials. This raises important questions about the generalisability of the trial evidence base as a whole as a suitable basis for understanding expected impacts in the UK population'.* The EAG raise a key point regarding the use of trial data to model cost-effectiveness and point out RWE is "considerably more mature than the corresponding trials, reducing extrapolation uncertainty". There are a few points to be made in response to this comment: • The use of trial data to model cost-effectiveness is unavoidable as at the time of appraisal it is almost always the only source of treatment effects for a new treatment. It should also be noted that for the RWE the EAG has obtained has a median follow-up of	

		16.8 months which is shorter than most combination therapy trials included in the pilot pathway appraisal. • It is beyond the scope of this appraisal to question the use of trial data to inform cost-effectiveness analyses used in decision making by NICE. • It is well known that trial patients present with an improved baseline prognosis versus real-world patients, which is not a phenomenon specific to oncology. Ipsen believe that this observation of the EAG is not considered a key issue that should be resolved to reduce decision making uncertainty for cabozantinib with nivolumab in advanced RCC. Rather, it should be noted that there is generally a difference in the long-term survival of trial versus real-world patients.	
	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness	The EAG is suggesting that a product's cost-effectiveness depends on the follow-up length of the pivotal trial source for effectiveness, where the earlier an appraisal is conducted, the more likely the product is to be cost-effective. However, most appraisals are conducted based on the regulatory dataset as aligned with the technology appraisal process timelines to ensure a timely recommendation aligns with regulatory approval. Although this point may be a relevant question, it should not be a topic addressed in this appraisal. It is relevant, however, to note that this issue is yet another example of the inconsistency with this appraisal, as cabozantinib with nivolumab is being appraised at a much later time point in its product lifecycle and, hence, longer follow-up has become available. The appraisal of	No

		cabozantinib with nivolumab may therefore be disadvantaged by the timing of this appraisal, as some trials, including CheckMate 9ER, have accrued longer follow-up while others may not have released data cuts based on longer follow-up data. The implications of this can be illustrated when one considers the EAGs base case hybrid STM structure which is driven by PFS, as post-progression survival (PPS) is driven by PFS for each line of treatment. The EAG note that use of the current hybrid STM structure likely disadvantages ipilimumab with nivolumab as the hybrid STM model relies on PFS rather than OS to drive outcomes, while trial data does show a higher-than-expected level of post-progression survival. In addition, when one looks at the lenvatinib with pembrolizumab PFS data over time it can be seen that the low hazard ratio reported for the CLEAR trial has increased from 0.41 at median 17.4 months follow-up to 0.59 at 49.8 months median follow-up and does not yet appear relatively stable unlike that of cabozantinib with nivolumab or ipilimumab with nivolumab (Figure 32, EAG report). Thus, the state transition model, where outcomes are driven by PFS, provides an advantage for lenvatinib with pembrolizumab, but results could look different versus the other comparators if a later data-cut were to be used. A similar situation emerges for OS over time (Figure 31, EAG report). **Ipsen believes the appraisal and decision making for cabozantinib with nivolumab should be mindful of the length of the follow-up data from studies and the potential impact it has on the cost-effectiveness of cabozantinib with nivolumab and therefore decision making.**	

	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and toxicity on economic case	The EAG has identified some challenges regarding whether the differences in relative dosing intensity (RDI) between the different IO/TKIs calculated are realistic and if not alternative suggested inputs. This is a long-standing issue in that RDIs are often taken from prior appraisals without fully checking that their methods of derivation are consistent. Ipsen has tried to address some of these issues below. Ipsen previously provided the EAG (in response to clarification question B13) the RDIs used in the CheckMate 9ER trial, together with the methodology used. The comparison of dose intensities from different trials is handicapped by inconsistencies in the way dose intensities have been reported/calculated and/or information has been redacted in NICE technology assessments in the past. This has particularly become apparent for the CheckMate 9ER, CheckMate 214 and CLEAR trials, as listed in Table 87 of the EAG report and in Table 1 below, which are important comparators in this appraisal. To facilitate a like-for-like comparison, Ipsen has suggested alternative dose intensities and sources of data to be applied, as shown in the last two columns of Table 1 below. All dose intensities are based on mean values instead of median values (where reported), since mean values are more appropriate in the context of health economic analyses. The EAG has also had to make assumptions for some of the medicines below for 2L and 3L in that they have the same RDI as 1L. Where possible, Ipsen has also provided alternatives to reflect the line of therapy. In the CheckMate 9ER and CLEAR trials, the PD-1 inhibitors nivolumab and pembrolizumab were administered for a fixed duration of 2 years. In both Checkmate 9ER and CLEAR, dose reductions for	Yes, please see Table 1

		nivolumab and pembrolizumab were not permitted, however, dose delays and interruptions could occur. In TA858, it was described that an administration intensity was therefore calculated to represent these delays, defined as the mean number of administrations received divided by the mean number of administrations expected during the time the patient was considered to be on pembrolizumab. The EAG used a median of 22 infusions to calculate a RDI of 62.9% based on the three-weekly administration of pembrolizumab in the trial over a 2-year period (the mean RDI is 59.9%). To enable a like-for-like comparison, Ipsen replicated this method for calculating nivolumab RDI based on the mean number of infusions nivolumab was administered twice-weekly in the trial over a 2-year period, yielding a mean RDI of [redacted]%. This replaces the method used and results provided by Ipsen for the RDI response to clarification question B13. Similarly, Ipsen followed the EAG approach for RDI of lenvatinib to calculate a mean RDI of 70.1% for cabozantinib in the CheckMate 9ER trial, replacing the method Ipsen used for the response to clarification question B13. This is to ensure a like-for-like comparison of RDI between lenvatinib and cabozantinib and implementation in the health economic analysis as both are flat priced. This would also apply to the RDI data used (93.3%) from TA542, which was a bespoke calculation for cabozantinib monotherapy; for consistency, the RDI reported in the EPAR (82.3%) should be used. Another criterion for interpretation of RDI estimates for the interventions in this appraisal is the trial follow-up duration. For example, the RDI of cabozantinib with nivolumab is based on data from a follow-up of 44 months, whilst most of the trials only report the	

		RDI from the first data cut/point of publication. In the case of lenvatinib with pembrolizumab, the RDI is based on a follow-up of 26 months (no RDI is reported for later data-cuts from the CLEAR trial). It may mean that RDI could worsen or improve over time. In the 9ER trial the mean RDI for cabozantinib with nivolumab changed over time from 49.8% (median 18.1 months of follow-up) to [redacted]% (median 44 months of follow-up) for nivolumab and from 73.9% (median 18.1 months of follow-up) to [redacted]% (median 44 months of follow-up) for cabozantinib. Anecdotal feedback from some clinicians Ipsen has spoken to suggests that when the IO pembrolizumab is used in combination with the TKI lenvatinib, and the IO nivolumab is used in combination with the TKI cabozantinib, lower dose intensities are achieved with the IOs which result in delays to treatment. The feedback from clinicians indicates that the RDIs reported in the CLEAR and CheckMate 9ER trials are in line with real world experience. The lower dose intensity achieved with the IOs is believed to be attributable to lenvatinib and cabozantinib due to being more potent multi-targeted TKIs compared to other TKIs such as axitinib. This is also reflected in the lower dose intensities also seen with lenvatinib and cabozantinib when used in combination with PD-1/PD-L1 inhibitors as opposed to monotherapy. Similarly, PD-1 inhibitors such as nivolumab seem to achieve higher RDIs when used as monotherapy (97.5% as reported in TA417). While relating to a slightly different population, the RDI for adjuvant pembrolizumab monotherapy in RCC patients at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, achieved an RDI of 98.9% in the KEYNOTE-564 trial. In addition, although not a comparator in this	

		appraisal, the combination of pembrolizumab with axitinib achieved dose intensities of 94.8% and 84.6% respectively in the KEYNOTE-426 trial, with the high RDI for pembrolizumab reflecting possibly the use of a different TKI as part of the combination. Similarly, the mean RDI seen with the PD-L1 inhibitor avelumab in combination with axitinib in the JAVELIN-101 trial is 86.8 and 84.2 respectively, which is higher than that seen with lenvatinib with pembrolizumab and cabozantinib with nivolumab. In its report, the EAG comment that based on clinical feedback that axitinib and tivozanib have similar modes of action and that tivozanib may be better tolerated compared to other TKIs. **In conclusion, the application of RDI from clinical trials in health economic analyses is important and influenced by a number of factors requiring careful understanding and interpretation to ensure reasonably fair comparisons. RWE RDI can be helpful corroboration but does require accurate records to be taken to the level that is performed in a clinical trial to be truly meaningful. In the context of a pathway appraisal, consistency in the derivation of RDI estimates is of high importance.**	
	Key Issue 5: Problems with the health-related quality of life data supplied by the company	As mentioned previously in response to B1 of the EAG clarification questions, Ipsen would like to reiterate that it is unaware of any differences in their approach to collecting and analysing this data that would account for the difference in magnitude versus the TAs in advanced RCC. **The high utility values derived from the analysis of CheckMate9ER are, however, supported by other previously published studies assessing the cost-effectiveness of treatments with similar mechanisms of action.** For example, a recent cost-	No

		effectiveness analysis of treatment sequences for intermediate to poor risk aRCC patients reported a utility for first-line nivolumab with ipilimumab of 0.83, based on an analysis of EQ-5D-5L data from Checkmate 214 (3). Additionally, a cost-effectiveness analysis of pembrolizumab with axitinib (also in aRCC) used a mixed-effects regression of EQ-5D-3L data collected from KEYNOTE-426 to estimate utility values for different patient categories defined by days until death. The estimated utility value for patients at least one year prior to death was 0.824 (4). **There is also precedence in the literature for maintaining a high post-progression utility value, which aligns with the results of the CheckMate9ER analysis**. For example, in a cost-effectiveness analysis comparing nivolumab to everolimus in aRCC, the utility values assigned to each health state were as follows: progression-free (complete response/partial response), 0.895; progression-free (stable disease), 0.846; and progressed disease, 0.817 (5). Another example, again with nivolumab, but in carcinoma of the head and neck, used utility values in the cost-effectiveness model of 0.805 for progression-free and 0.746 for progressed disease (comparator; 0.770 and 0.676 respectively) (6). This is similar to the utilities derived from the larotrectinib study: 0.81 (PF) and 0.74 (PD) (7). Ipsen suggest that the EAG perform a scenario analysis that calculates the proportional reduction from the trial and applies it to the general population utility, in addition to its planned scenario analysis using the CheckMate 9ER derived utilities in the model.	
	Key Issue 6: Outstanding uncertainties in	In the final assessment report, the EAG highlight that based on the NICE manual it is unclear as to how severity modifiers should be	No

	application of severity modifiers	applied in a multi-comparator decision space. Hence, the EAG described three potential options including: a) defining the common reference treatment to calculate severity modifiers for all treatments; b) calculating the severity modifier based upon the market shares of all comparators; and c) calculating severity modifiers for pairwise comparisons. The EAG applied the first approach and stated that the other two options are inconsistent with the approach of a fully incremental analysis. However, the EAG highlighted that the application of severity modifiers is a key uncertainty due to the lack of guidance in this area. **Please could the EAG elaborate on the application of the severity modifier and whether severity modifiers for a pairwise analysis have been performed?** **Please could the EAG also elaborate as to why consideration of market shares does not support a fully incremental approach?** **Further, it would be helpful if the EAG were to conduct a pairwise severity modifier analysis accounting for the RWE-based market shares of 1L therapies.** Ipsen agrees that whether the severity modifier should be applied in a fully incremental analysis or a pairwise analysis is ultimately an academic debate, and it is unlikely that this appraisal would reach a definitive answer to this question. **Ipsen would welcome a more comprehensive assessment from the EAG and a more prescriptive recommendation as to which option should be considered by the committee within the context of this decision**	

		problem and ultimately whether cabozantinib with nivolumab qualifies for the severity modifier by risk group.	
	Key Issue 7: Impact of model structure on results	Due to the similarity of Issue 1 and Issue 7, the response to the two issues has been consolidated under Issue 1.	No
	Key Issue 8: Subgroups in the context of changing comparators	Ipsen notes that the EAG have acknowledged that the cost-effectiveness analyses conducted for the all-risk population possesses the least uncertainty compared to the intermediate/poor and favourable risk subgroups. Ipsen reiterates its position that cabozantinib with nivolumab should be appraised in the all-risk population; cabozantinib with nivolumab is shown to be clinically effective in the all-risk population in the CheckMate 9ER trial and the modelling of cost-effectiveness of cabozantinib with nivolumab requires the fewest assumptions.	No
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population	Ipsen is aware that modelling the effectiveness of cabozantinib monotherapy based on the CABOSUN trial has shown an unusually large effect, which has been raised in previous NICE appraisals, including for axitinib with avelumab (TA645), axitinib with pembrolizumab (TA650) and most recently lenvatinib with pembrolizumab (TA858). However, this issue has never been resolved. The CABOSUN trial was a phase II study which only recruited 157 patients which may lead to statistical heterogeneity and therefore uncertainty in the NMAs of the IMDC intermediate/poor risk status population. The EAG quality assessment of CABOSUN identified the trial had a high risk of selection bias because of its deterministic, non-random approach to balance prognostic factors at baseline. CABOSUN also included patients with a performance status ECOG 2	No

		whereas these patients are generally excluded from phase 3 trials limiting comparisons. CheckMate 9ER did not collect ECOG status but it is possible to convert to it from the Karnofsky score (8). As presented below, fewer patients with ECOG 0 were included in CABOSUN than in Checkmate 9ER and this could explain the overall shorter observed PFS and OS in the sunitinib arm from CABOSUN compared to the other trials, as patients with poorer general health state may have poorer survival outcomes. **ECOG = 0 / Karnofsky = 90-100** - CheckMate 9ER (71%) - CABOSUN (46%) **ECOG = 1 / Karnofsky = 70-80** - CheckMate 9ER (28%) - CABOSUN (41%) **ECOG = 2 / Karnofsky = 50-60** - CheckMate 9ER (0%) - CABOSUN (13%) In addition, the proportion of patients with bone metastasis was 36.6% in CABOSUN versus 21.1-25.1% in other combination trials in the NMA. Finally, PFS in the CABOSUN trial was by investigator assessment compared to BICR which may also have an impact. Whilst it is not possible to confidently explain the dominance of cabozantinib	

		monotherapy in intermediate/poor risk patients seen in this appraisal and other RCC TAs, the factors provided above may explain this to a certain extent.	

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic		Response	Does this response contain new evidence, data or analyses?
Clinical effectiveness	Literature review	Section 2.4. Figure 6 describes the treatment pathway for advanced stage RCC. The figure does not clearly define the different symbols used in the diagram and the key is not obvious.	No
	Clinical input		
	Critique of included studies	**Trial characteristics** Table 9, p.70 describes the population characteristics of included trials. Ipsen would like to clarify if the column titled "% prior surgery" should be "% prior nephrectomy". Please could the EAG confirm. Table 10, p.76 describes intervention characteristics of included trials and has a column titled "any subsequent systemic tx (% of ITT)". The figures in Table 10 state 35.9% and 45.1% for cabozantinib with nivolumab and sunitinib, respectively. The company wishes to make clear that these figures are for "any subsequent therapy" whilst the figures for patients receiving "subsequent systemic therapy are 25.1% and 40.5% for cabozantinib with nivolumab and sunitinib, respectively. Please see Table 8 of the company submission	No

		(Filename: ID6186_Company updated 44-month evidence submission_AIC_CIC_12April2023_Final). **Study level risk of bias** Ipsen would like to challenge the decision that CheckMate 9ER has a high overall risk of bias as reported in Table 12, as we do not believe that the trial has a higher risk of bias than other comparator combination trials. The EAG concluded (page 94) that: *"CheckMate 9ER, the key trial of interest, was judged to have a high overall risk of bias because of a high risk of attrition bias. This includes very high, differential overall attrition (44% in the cabozantinib + nivolumab (CABO/NIV) arm and 71% in the sunitinib (SUN) arm) as well as dropouts due to discontinuation (43% CABO/NIV and 69% SUN) and disease progression (27% CABO/NIV and 46% SUN), with reporting of single imputation approaches to account for missing data."* We believe the calculation for attrition being used by the EAG uses the median of 18.1 months follow-up data and computes the percentage of patients who discontinued on the "as treated population". Given that the discontinuation is clearly linked to the primary endpoints of the study (i.e., PFS), this would explain the different attrition rates in each arm. As a parallel, using the EAG methodology, the attrition rate in CLEAR (using median 26.6 months of follow-up) would be 60% (LENVA/PEM), 68.5 % (LENVA/EVE) and 80% (SUN), which is numerically higher. The company is unclear as to which analysis the EAG is referring to regarding missing data as there are no differences in the statistical analysis plans in the CheckMate 9ER compared to the CLEAR and CheckMate-214	

		trials, for instance. Further, the CheckMate-214 trial originates from the same study sponsor. We would like to further understand the EAG's position and reasoning on the above bias matter and request that the overall study level risk of bias be marked as "Unclear" rather than "High". **Discontinuation rates** Table 19, page 114 describes the discontinuation rates due to AEs in prioritised included trials. Ipsen would like the EAG to clarify the definition used to obtain these rates, as the numbers for cabozantinib with nivolumab do not match those we presented in our submission. In our submission (Table 7), we reported 27.5% and 10.6% for cabozantinib with nivolumab and sunitinib, respectively. Table 19 in the EAG report states 36.84% and 20.43% for cabozantinib with nivolumab and sunitinib, respectively. In the submission, figures of discontinuation rates are below 30%, resulting in the following statement (on page 114) being incorrect: *"rates of discontinuation were particularly high for avelumab with axitinib, cabozantinib with nivolumab, and nivolumab with ipilimumab where the rate of discontinuation exceeded 30% of the trial arm".* Additionally, Ipsen investigated the figures reported in Table 19 for lenvatinib with pembrolizumab. We found that the latest data cut (2023) reported 19% and 12% for the intervention and control, respectively, (median follow-up of 27.7 months for PFS and 33.7 months for OS) (9). The CLEAR study describes discontinuation as "both study drugs in combination therapy", which is different to the Ipsen definition of discontinuation of "any" treatment of the cabozantinib with nivolumab combination. In the CheckMate 9ER 44-month results, discontinuation of <u>both</u> drugs is 6.6% which is lower than CLEAR. We	

		would like to make sure that the EAG have checked the definitions in the prioritised included trials and that the figures in this trial are correct as they are otherwise misleading to the reader. **Risk group** The CheckMate 9ER trial was not powered to show statistical significance in the favourable risk group and Ipsen would like to highlight this fact when reading the following statement on page 129: *"it is notable that findings for OS do not suggest a treatment effect in favourable risk patients, in contrast to findings for patients with intermediate and poor risk."* Ipsen have already described the fewer number of patients in this subgroup (23%) within the trial and the need for longer follow-up to demonstrate improved efficacy. **Baseline characteristics of RWE trials** Table 27, p.141 describes the baseline characteristics of the included RWE. The UK RWE 2022 study includes the following % for lines of treatment: 1L: 687(48%); 2L: 415 (35%); 3L: 168 (16%); 4L 42 (%); 5L: 7 (%) – the percentages for 4L and 5L are missing in Table 27. There are two discrepancies here. • First, the percentages reported do not match the numbers – by the company's calculations the percentages should be 52%, 31.5%, 12.7%, 3% and 0.5% for 1l, 2L, 3L, 4L and 5L respectively. • Second, these figures are lower than anticipated and do not align with the results reported by McGrane et al. 2023 especially for 2L and 3L therapy (10). According to McGrane et al., out of the patients that started SACT, 60.5% of eligible patients had 2L therapy, 25.3% had 3L, 7.2% received 4L therapy and only 1% had 5L line therapy. Ipsen would like to	

		understand the definition used to report these figures, as it seems that these figures are aligned with the overall aRCC population (not focusing on patients that started therapy). Additionally, it is worth noting that the UK RWE 2022 source reports lower values for percentage of prior nephrectomy (54.2%) compared to most of the pivotal combination trials (>70%).	
	Indirect treatment comparisons	Ipsen disagrees with the inclusion of CABOSUN in the overall network as the trial includes only intermediate/poor risk patients. The treatment effect is higher in intermediate/poor risk populations and the survival outcomes are poorer. The results from CABOSUN are not comparable to other trials which include favourable risk patients. This leads to an overestimation of the treatment effect versus sunitinib in the overall population, as the EAG have acknowledged in their report. To date, there is no clear guidance for conducting indirect comparisons in situations where the assumption of proportional hazards is not met. Several approaches have been recommended (19). However, each is associated with its own merits. Notably, although fractional polynomials offer considerable flexibility, they are prone to random fluctuations in the long-term and hence potentially implausible extrapolations. Therefore, the company would recommend that, for completeness, first order fractional polynomials are also attempted. If those provide an adequate fit, their reduced number of estimated parameters means there would be reduced uncertainty in long-term extrapolations which would be potentially desirable. This approach was used in the Ipsen fractional polynomials NMA analysis (which was provided to the EAG and seemingly yielding different results) which when implemented in the Ipsen Partition Survival (PartSA) cost-effectiveness model, provides more favourable ICERs for cabozantinib in combination with nivolumab compared	No

		to the EAG's PartSA model despite the Ipsen NMA not including the latest lenvatinib with pembrolizumab data-cut. As a minimum it would be helpful to examine the impact of alternative fractional polynomial models with similar fit e.g., 2nd and 3rd best fitting models, which also appears not to have been done. Additionally, the EAG prioritised fractional polynomials on the grounds that proportional hazards were shown to not be met in previous RCC appraisals ("*The first strategy used fractional polynomial analyses as, based on previous appraisals in RCC, it is expected that there may be issues in justifying proportional hazards for all endpoints.)*". However, in TA858, where both approaches were presented to the committee, the committee preferred the results of the standard NMA which assume proportional hazards as more appropriate for decision-making purposes and highlighted that fractional polynomials produce results that are unintuitive and hard to interpret (*"The EAG cautioned that the estimates from these flexible modelling techniques can be unintuitive and difficult to interpret. For example, flexible models that appear similar according to model fit statistics for the observed period may generate very different long-term survival estimates. Because of these limitations, the EAG explained that it does not consider the results of the fractional polynomial NMAs to be appropriate for clinical decision making. Although the results of proportional hazards NMAs when the proportional hazards assumption is violated are also uncertain, the EAG suggested that they are less uncertain than the results from more flexible models such as fractional polynomial NMAs"*). Also, the EAG's model uses a mixture of NMA approaches for different comparators in their base-case e.g., relative effects produced by fractional polynomials are used for most comparators, but proportional hazards NMAs	

		are used for pembrolizumab in combination with lenvatinib. The EAG made this choice because the fractional polynomials model generated unreasonably pessimistic estimates for this comparator. Results of proportional hazards NMAs are also used for treatments in second line onwards. As a result, there is inconsistency in the assumption employed by the NMA models used for the various treatments in the EAG's base-case. Overall, the company recommends favouring proportional hazards NMAs throughout to align with precedent and ensure consistency in the analyses used to produce relative effects across comparators.	
	Critique of outputs considered	The EAG state in their report on page 121 that it *"requested IPD from the company to enable the network meta-analysis and survival analysis to be run as robustly as possible, but this was not received."* The company would like to point out that it provided a large amount of individual patient data (IPD) to the EAG, including digitised plots from its NMA analysis to facilitate the EAG's work. This appraisal has demanded data requests which have far exceeded those typical of a STA and the company has done its best within the timescales and resources available to accommodate the EAG requests.	No
Cost effectiveness model development	Published cost effectiveness studies		
	Critique of outputs included in clinical review		
	Critique of real-world evidence	As noted above, it remains unclear how the EAG has validated the external validity of the RWE (and thus STM outcomes) as this has not been described. Further, the SEE does not suggest alignment with the RWE which limits its	No

		use as a source of external validity. Therefore, it remains uncertain whether the RWE is in fact generalisable to UK advanced RCC patients. The RWE data source used by the EAG does not include all relevant comparators, for example lenvatinib with pembrolizumab is not included as a 1L treatment option in this dataset. The same holds true for cabozantinib with nivolumab. This leads to questions regarding the use of this RWE and whether it is suitable for the decision problem for cabozantinib with nivolumab.	
	Indirect comparisons	Ipsen would like further specification on the fractional polynomial steps for (page 173): • The selected models with delta AIC<5 • Area under survival curve up to the horizon (which horizon?) • The predictions beyond the trial duration to inform plausibility assessment and best fit selection? Focus on trial based RMST within trial duration horizon will not be sufficient to inform long term extrapolations in the CEA model Further clarifications on the NMAs: • Why are networks not presented by risk groups? • The criteria for selection should go beyond the “model with lowest AIC” especially considering the use of these results for extrapolation beyond duration of trials (and available data to inform AIC estimates) • Please can you update the title of figure 21 to be clearer that the hazard ratios are compared to sunitinib (and in the legend)	No

		• It would be beneficial to have an additional graph in figure 22 that contains all the survival curves The company notice that there is limited discussion (section 3.7.3.6, page 199) on the poor face validity of some of the survival curves within the model and we would appreciate further presentation of alternative selections.	
	Expert elicitation	**Population seen in clinical practice** In the structured expert elicitation (SEE), clinical experts were asked to provide estimates for the advanced RCC patients population in England they see in practice. • Did the EAG obtain any information on what each expert perceived the patient population in England to be in terms of baseline patient characteristics? How did the EAG ensure consistency across experts with regard to the expert-perceived RCC population in England and the average patient in England? • For the fractional polynomial (FP) NMA model selection, the EAG used the expert elicited landmark distributions to assess which FP NMA models better align with experts' expectations for the long-term outcome predictions. However, the FP NMA is based on trial population estimates whereas the SEE considered real-world populations which may vary across experts' practice. Could the EAG comment on the potential discrepancy and extent of bias that could result from using expert-derived predictions pertaining to clinical practice patients for FP NMA model selection on data relating to clinical trials? **Structured expert elicitation methodology**	No

		Could the EAG please comment on the potential extent and direction of bias due to the following methodological choices and any measures taken to minimise such bias considerations? • Clinical experts were offered the chance to revise their responses after being provided with a visualisation and summary of their own answers. However, experts were not offered the opportunity to see other experts' responses, either individually anonymised or aggregated, and then revise their responses if they wish so. How was high performance promoted (principle 9 of MRC SEE protocol)? • Experts were not given the chance to interact with each other following the first round of elicitation. Since experts were asked to provide predictions for the average population in England without specific baseline characteristics, could interaction have provided a valuable opportunity to exchange information across experts, settle potential differences, and reduce the potential for self-serving bias? • Some questions in the SEE were answered by fewer than 5 experts. How was between-expert variation assessed and addressed in those instances?	
Economic analysis	Model structure	The EAG have made every effort to develop a comprehensive pathway for health economic model using a hybrid state transition model structure. However, it is complex and together with the use of R makes it difficult for the relative non-health economist to follow and understand the results it is generating. As described above, this model structure with the multiple lines of therapy gives different results and, in the time available to the company in this response it is difficult to unpick and understand. There have also been a few iterations and corrections to the model which has taken time to re-adjust to	No

		and understand the implications of them on each occasion. This is compounded by the very long time it takes to run just one scenario for the hybrid STM, taking approximately 90 minutes in the company experience. Therefore, to look at 72 different scenarios would take 108 hours (or over thirteen, 8-hour days) to complete. Whilst the EAG has created a feature which has a much shorter run time it is not as accurate and coupled with the fact that some key data are redacted it is very difficult for the company to interpret the results and direction of travel as small differences in costs and QALYs can have dramatically different ICER results. It is important that this appraisal as a pathway pilot does not lose focus on the need to appraise cabozantinib with nivolumab for 1L RCC as the decision problem and ensure timely and fair decision making by NICE's appetite with respect to decision risk and corresponding uncertainties arising from inconsistencies in the application of modelling methods (between comparator treatments in this appraisal, or between this pilot and prior appraisals) that have surfaced in this pilot appraisal.	
	Population		
	Treatments included	Table 32 page 162 describes the overall survival estimates from RWE. The results show average outcomes for 2L, 3L and 4L treatments, however, they do not seem to be conditional on the treatment received in prior lines. It would be expected in a sequencing model that the conditional outcomes for each defined sequence of prior therapy had been carried out – Ipsen would like to understand if this has been done. Similarly, we would anticipate the same modelling technique to have been applied for PFS.	No
	Perspective, time horizon, cycle		

	length, discounting and price year		
	Treatment effectiveness and extrapolation	**The company notes that there are inconsistencies in the application of relative efficacy between different comparators, lines of treatment, and prior appraisals** For 1L treatments in the model base case, the EAG used the results of the FP NMA to inform relative treatment efficacy, except for the case of lenvatinib with pembrolizumab where the proportional hazards (PH) NMA was used instead because the FP NMA produced implausible results against the combination treatment. We note that this inconsistency in the application of treatment efficacy evidently biases results in favour of lenvatinib with pembrolizumab due to the CLEAR trial demonstrating non-proportional hazards (incremental QALYs between cabozantinib with nivolumab and lenvatinib with pembrolizumab using the PH NMA for lenvatinib with pembrolizumab was 0.25 under scenario 13, compared to -0.23 when using a FP NMA to inform effectiveness for lenvatinib with pembrolizumab). This is acknowledged by the EAG that the difficultly making comparison to lenvatinib with pembrolizumab via FP NMA may bias results in favour of lenvatinib with pembrolizumab which is likely to impact on cost-effectiveness conclusions (page 72, Appendix Q). This is in addition to the fact that data in the intermediate/poor risk population for lenvatinib with pembrolizumab are not available in the public domain for this treatment (page 316, EAG report). Although the proportional hazards assumption was judged to be violated, the FP NMA is associated with certain limitations related to the evidence base and model choice. In addition, the choice of FP NMA is inconsistent with precedent submissions, even in the case where the PH assumption does not stand. For instance, in TA858 both approaches had been presented to the committee with the following point raised by the EAG as part of that appraisal:	No

		"The EAG cautioned that the estimates from these flexible modelling techniques can be unintuitive and difficult to interpret. For example, flexible models that appear similar according to model fit statistics for the observed period may generate very different long-term survival estimates. Because of these limitations, the EAG explained that it does not consider the results of the fractional polynomial NMAs to be appropriate for clinical decision making. Although the results of proportional hazards NMAs when the proportional hazards assumption is violated are also uncertain, the EAG suggested that they are less uncertain than the results from more flexible models such as fractional polynomial NMAs". Similar inconsistencies arise across lines of therapy; the EAG used the results of the FP NMA for 1L but the PH NMA results for subsequent lines due to sparsity of the available network and extreme results estimated by the fitted FP NMA models. The FP NMA was conducted using the clinical trial data of the comparators included in the analysis, and model selection was based on expert elicited landmark distributions. However, the SEE exercise considered the population that clinical experts see in their clinical practice. The company notes that there is a disconnect between the data used to run the FP NMAs and the elicited evidence used to inform FP model selection due to potential differences across populations enrolled in the trials and seen in clinical practice. The relative effect parameters can considerably influence the cost-effectiveness results, as evidenced by the EAG's scenario analyses. However, the company has no access to the FP NMA statistical models and programme scripts and is, therefore, not in a position to validate the code and implementation process. The magnitude of this potential issue is uncertain.	

		Finally, the EAG in their commentary (page 224) on the FP NMA conducted by the company state the EAG and the company's approach to the FP NMA differed in three ways and as a result the EAG and the company chose different fractional polynomial distributions for each outcome, limiting direct comparability of findings. This highlights that these complex modelling techniques can introduce more variability depending on the approach taken and the interpretation of the estimates can be difficult and often are not intuitive. **Considering the inconsistencies in the application of relative treatment efficacy across comparators and lines of therapy, the high uncertainty of FP NMAs due to limitations in the evidence base and model selection, the lack of transparency in the programming and implementation of FP NMAs, and the preference of PH NMAs in recent aRCC TAs (e.g., TA858) the company believes that the PH NMA should be preferred in the base case, in line with prior technology appraisals.**	
	Adverse events	**The company notes that there are inconsistencies in the application of adverse events with recent appraisals.** The EAG included in the model grade 3+ AEs occuring in more than 5% of patients in any trial arm of the model. In the base case, NMA relative effects were applied to the reference treatment in each treatment line using EAG NMA for grade 3+ AEs and all grade NMA from the Cochrane review for the 3 specified grade 1-2 AEs namely diarrhoea, fatigue and palmar-plantar erythrodysaesthesia syndrome. However, this approach is inconsistent with prior appraisals (e.g., TA645, TA650, TA780, TA858) in which treatment related AE rates for grade 3+ AEs from the intervention and comparator trials were considered in the analysis. **Hence, for consistency, Ipsen recommends that the base case is informed by treatment related naïve**	

		AE rates for grade 3+ AEs occurring in more than 5% of patients in each comparator arm.	
	Utility values	To model the health-related quality-of-life (HRQoL) impact based on progression status and line of therapy within the context of the hybrid STM, the EAG implemented utility values reported in TA645 and TA498 for 1L and 2L, respectively, as they were deemed to demonstrate face validity. The EAG noted that progression-free utility in TA498 for 2L line treatment was higher than the progressed disease utility reported in TA645 for 1L treatment and assumed that progression-free utility at 2L is equal to the utility of progressed disease patients in 1L, to prevent logical inconsistencies. Due to the lack of robust HRQoL evidence for subsequent lines of treatment, the EAG used a multiplicative approach as outlined in the NICE DSU12 guidance to estimate the utility value for the 2L progressed disease health state, and for the progression-free and progressed disease health states of subsequent lines. **Can the EAG please elaborate on the uncertainty introduced to the analysis by these assumptions that informed health state utilities from 2L and beyond?**	No
	Resource use and costs	Ipsen has received feedback from clinical experts at a recent advisory board that in reality the theorectical advantage of administering lenvatinib with pembrolizumab every 6 weeks may not be realised. The high dose of lenvatinib that is used when initiating treatment results in significant adverse events that require patients to be seen in clinic after 3 weeks. This has an impact on healthcare professional resources until a stable dose is achieved.	
	Severity		
	Uncertainty	Ipsen would like to note that there is an **unusually high number of inconsistencies in the methods and use of evidence in this appraisal**	No

		versus prior RCC TAs, which combined lead to high levels of uncertainty in the cost-effectiveness of cabozantinib with nivolumab: 1. Inconsistency with precedence with previous TAs for many of the comparators considered in this appraisal in terms of: a. Model structure (prior TAs have implemented PartSA while the EAG is implementing a STM) b. Use of the FP approach to the NMA despite limitations in the data for some comparators, which was a driving factor in prior TAs to apply the PH NMA approach. 2. Inconsistency in the EAG's modelling of outcomes using the most recent long-term data cuts from the comparator trials combined with the RDIs based on earlier regulatory data cuts. For this reason, Ipsen believes the EAG is mixing up datasets within the model. Ipsen suggests alternatively that the EAG model outcomes across comparators based on effectiveness data with a common length of follow-up or cut-off point so as to match the RDIs which are being used to calculate the costs of treatment. 3. Inconsistency between the use of an NMA based on trial patients and model selection based on an SEE exercise reflecting UK real-world patients.	
	Model validation		
Are there any scenarios that you would like to see?		1. Run the hybrid Markov model using two lines of treatment, applying costs and utilities for two lines using the same methodology as in the PartSA model	No

	2. Use RWE to model reference treatment outcomes (i.e., sunitinib) calibrated based on clinical expert opinion using both hybrid STM and PartSA 3. Scenario 22-23: Could the EAG please clarify whether these scenarios assume a gradual convergence of the hazards starting at year 5 and resulting in equal hazards at year 20? If not, could the EAG implement this scenario? 4. Conduct a pairwise severity modifier analysis accounting for the RWE-based market shares of 1L therapies using both hybrid STM and PartSA 5. Conduct a scenario analysis applying the proportional reduction in utilities derived from CheckMate9ER study to the general population as an alternative approach to using the trial data using both hybrid STM and PartSA. Please could the EAG conduct this scenario and provide the results? For the scenarios below please provide an indication whether cabo+nivo is cost-effective with PAS prices applied: 6. Hybrid STM with 2L of treatments and AEs rate informed by individual trials 7. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and PH NMA to inform 1L relative effectiveness 8. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and TTD=PFS 9. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and FP NMA to inform pem+lenv relative effectiveness	

	10. PartSA model structure, and AEs rate informed by individual trials 11. PartSA model structure, AEs rate informed by individual trials, and TTD=PFS 12. Hybrid STM with 2L of treatments and AEs rate informed by individual trials and all company alternative RDIs 13. Hybrid STM with 2L of treatments and AEs rate informed by individual trials and all company RDIs (IOs only) 14. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and PH NMA to inform 1L relative effectiveness and all company alternative RDIs 15. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and PH NMA to inform 1L relative effectiveness and all company RDIs (IOs only) 16. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and TTD=PFS all company alternative RDIs 17. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and TTD=PFS and all company RDIs (IOs only) 18. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and FP NMA to inform pem+lenv relative effectiveness and all company alternative RDIs 19. Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and FP NMA to inform pem+lenv relative effectiveness and all company RDIs (IOs only)	

	20. PartSA model structure, and AEs rate informed by individual trials and all company alternative RDIs 21. PartSA model structure, and AEs rate informed by individual trials and all company RDIs (IOs only) 22. PartSA model structure, AEs rate informed by individual trials, and TTD=PFS and all company alternative RDIs 23. PartSA model structure, AEs rate informed by individual trials, and TTD=PFS and all company RDIs (IOs only) **Please provide both pairwise comparisons for all scenarios above reporting both absolute and incremental LYs, QALYs, costs, and ICERs within a table of results for list prices and indicative results with PAS. We do not require a report.**	
Has the value of cabozantinib + nivolumab been captured appropriately?	It is impossible to answer this question due to the many inconsistencies in the methods and evidence used in this appraisal versus prior RCC TAs as noted above. Further, the RWE used within the model appears to be an important driver of the cost-effectiveness of advanced RCC treatment options, of which the external validity and generalisability to UK practice remains uncertain.	No
Are there any benefits not captured in the model?		
Are there any equality considerations?		

Table 1: Relative dose intensities of treatments considered (trial and RWE) – Ipsen alternative mean RDIs

Drug	Treatment line	EAG Relative dose intensity, % (SE where available)		Trial source/assumption	Ipsen alternative – Relative dose intensity, % (mean value unless otherwise stated in source column)	Ipsen – Trial source/assumption
		Trial	RWE		Trial	
Ave+axi	1L advanced	Ave: 91.5 Axi: 89.4	Ave: [redacted] Axi: [redacted]	Motzer et al 2019(11)	Ave: 86.8 Axi: 84.2	Ave: (EPAR, Table 5, page 68) Axi: (EPAR, Table 5, page 68)
Axi	Prior TKI or cytokine (2L)	99	[redacted]	AXIS trial: Rini et al. 2011(12)	99 (No change from EAG)	Median value – mean not reported
Axi	3L	99	[redacted]	Assumed same as 2L	99 (No change from EAG)	AXIS trial only studied 2L
Axi	4L		[redacted]		99 (No change from EAG)	AXIS trial only studied 2L
Cabo	1L advanced	93.3	[redacted]	CABOSUN Clinical study report (as reported in TA542(13))	82.3	CABOSUN (EPAR, Table 24, page 48)
Cabo	2L	93.3	[redacted]	Assumed same as 1L	75.3	METEOR (EPAR, Table 40, page 91)
Cabo	3L+	93.3	[redacted]	Assumed same as 1L	75.3	METEOR included 3L patients
Evero	Prior VEGF (2L)	84 (1.1)	[redacted]	METEOR clinical study report (as reported in TA542(13))	83.9 (No change to EAG)	METEOR (EPAR, Table 40, page 91) Everolimus not linear pricing
Evero	3L	84 (1.1)	[redacted] (assumed same as 2L)	Assumed same as 2L	83.9 (No change to EAG)	METEOR included 3L patients
Evero	4L		[redacted]		83.9	METEOR included small number of 3L+ patients
Lenv+ evero	Prior VEGF (2L)	Lenv: 70.4 Evero: 89.3	Lenv: [redacted] Evero: [redacted]	CLEAR trial: Motzer et al 2021(14)	Lenv: 73.5	To reflect trial 2L population in HOPE 205 study (EPAR, Table 38, page 107) Everolimus RDI not reported in EPAR
Lenv+ evero	3L	Lenv: 70.4 Evero: 89.3	Lenv: [redacted] Evero: [redacted]	Assumed same as 2L	Lenv: 73.5	Assumption that same as 2L – HOPE 205 only included

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Drug	Treatment line	EAG Relative dose intensity, % (SE where available)		Trial source/assumption	Ipsen alternative – Relative dose intensity, % (mean value unless otherwise stated in source column)	Ipsen – Trial source/assumption
		Trial	RWE		Trial	
						population who had 1 prior VEGF-targeted therapy
Lenv+ pem	1L advanced	Lenv: 69.6 Pem: 62.9 – median number of infusions reported as 22	[redacted]	CLEAR trial: Motzer et al 2021(14)	Lenv: 70.5 Pem: 59.1	Lenv: (EPAR, Table 35, page 101) – no data for later follow-ups reported. Pem based on mean number of infusions received at 26.6 months median follow-up from (EPAR, Table 36, page 101) – no data for later follow-ups reported
Nivo	Previously treated (2L)	97.5	[redacted]	CheckMate 025 company submission (as reported in NICE TA463(15))	97.5 (No change to EAG)	CheckMate 025 company submission (TA417) and referenced TA463. Unclear if mean or median value.
Nivo	3L	97.5	[redacted]	Assumed same as 2L	97.5 (No change to EAG)	Checkmate 025 included 3L patients also.
Nivo+ cabo	1L advanced	Nivo: [redacted] Cabo: [redacted]	[redacted]	CheckMate 9ER (clarification response; A10a)	Nivo: [redacted] (44 month follow-up) Nivo: 49.8 (18.1 month follow-up)	Nivo based on mean number of doses received (44 month follow-up data-cut) – aligns method with mean number of doses of pembrolizumab calculation. Alternative, shorter follow-up (EPAR, Table 23, page 84)

Drug	Treatment line	EAG Relative dose intensity, % (SE where available)		Trial source/assumption	Ipsen alternative – Relative dose intensity, % (mean value unless otherwise stated in source column)	Ipsen – Trial source/assumption
		Trial	RWE		Trial	
					Cabo: [redacted] (44 month follow-up) Cabo: 73.9 (18.1 month follow-up)	Cabo: aligns with same method of calculation as lenvatinib. Alternative, shorter follow-up (EPAR, Table 23, page 84)
Nivo+ ipi	1L advanced	Nivo induction: 79*; Nivo maintenance: [redacted] Ipi: 79*	[redacted]	Motzer et al 2018(16) For nivo, same RDI as cabo+nivo to be assumed for nivo mono maintenance as data not available	Nivo: 87.4 Ipi: 90 Ipi : 84.8	Nivo: CADTH report, Table 15, page 183) – separate Induction/Maintenance intensity not reported. Ipi based on mean number of infusions administered (EPAR, Table 20, page 52) CADTH report, Table 15, page 183) Unclear if mean or median values.
Pazo	1L advanced	86	[redacted]	VEG105192 trial (as reported in NICE TA215(17) and TA512(18))	86 (No change from EAG)	Unclear if mean or median value
Pazo	2L	86	[redacted]	Assumed same as 1L	86 (No change from EAG)	VEG105192 on 1L. No data for 2L
Pazo	3L		[redacted]		86 (No change from EAG)	VEG105192 on 1L. No data for 2L
Suni	1L	[redacted]	[redacted]	CheckMate 9ER (clarification response; A10a)	[redacted] (44 month follow-up)	CheckMate 9ER 44 month follow-up data cut – RDI was

Drug	Treatment line	EAG Relative dose intensity, % (SE where available)		Trial source/assumption	Ipsen alternative – Relative dose intensity, % (mean value unless otherwise stated in source column)	Ipsen – Trial source/assumption
		Trial	RWE		Trial	
					83.5% (18.1 month follow-up)	83.5% at 18.1 months follow-up) Alternative, shorter follow-up (EPAR, Table 23, page 84) Alternative 87.4% from CABOSUN 1L trial (Cabo .vs Suni) (EPAR, Table 24, page 48)
Suni	2L	[redacted]	[redacted]	Assumed same as 1L	83.9	RDI from METEOR – 2L/3L trial of Cabo vs. Suni (EPAR, Table 40 ,page 91)
Suni	3L		[redacted]		83.9	RDI from METEOR – 2L/3L trial of Cabo vs. Suni (EPAR, Table 40 ,page 91)
Tivo	1L advanced	94	[redacted]	TIVO-1 study (as reported in NICE TA512(18))	94 (No change from EAG)	Same source as EAG - TIVO-1 study (as reported in NICE TA512)
Tivo	2L	94	[redacted]	Assumed same as 1L	94	No data – unlicensed for 2L – assumption same as 1L
Tivo	3L		[redacted]		94	No data – unlicensed for 3L – assumption same as 1L

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; NICE, National Institute for Health and Care Excellence; NR, not reported; RDI, relative dose intensity; SE, standard error; TA, technology appraisal; TKI, tyrosine kinas inhibitor

*79% reported to receive all 4 doses of nivolumab and ipilimumab within the induction phase

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Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

As a stakeholder you have been invited to comment on the data and analysis included in the external assessment group (EAG) model and Final Assessment Report for the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

Information on completing this form

We are asking for your views on data and assumptions included within the analysis model and used to form the final report that are likely to be discussed by the committee. The report provides a summary of work undertaken by the EAG developing the analysis and incorporating the data received from manufacturers, observational patient datasets and formal input from clinical experts. It outlines the analysis plan, methods used for the evaluation, as well as all identified relevant published evidence and real-world evidence (RWE) sources.

You are not expected to comment on every key topic but instead comment on the issues that are in your area of expertise.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by 5pm Friday 22 September. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during consultation, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during consultation are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Action Kidney Cancer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG.

Table 2: key issues

Issue		Response	Does this response contain new evidence, data or analyses?
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	Access to systemic anti-cancer treatments in the second line and beyond is complicated and dependent on what the patient had as their first-line treatment. For example, nivolumab can only be given to patients as a second- or third-line treatment if they have not previously been treated with a PD-1 or PD-L1 inhibitor (nivolumab, pembrolizumab or avelumab), and a first line VEGFR inhibitor can be given to patients in the second line if they have previously been treated with nivolumab plus ipilimumab. This requires careful planning on behalf of the medical oncologist with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatment for advanced/metastatic RCC. This situation is often not adequately explained to patients before they start first-line treatment with systemic anti-cancer treatments. Lack of information prevents patients from making informed decisions about their treatment options from the outset.	

		many patients are unaware of the treatment options available to them when they start first-line treatment. Informed shared decision-making with their clinician would help make patients more aware of the treatment options available to them and enable the patient and clinician to work in partnership to make the best possible decisions for the patient. Informed decision-making brings together the clinician's expertise, treatment options, evidence, risks, and benefits with the patient's individual preferences, personal circumstances, goals, values, and beliefs. Patient decision aids should be made available to patients to help them make informed decisions about their treatment. The RCC pathway should include the use of patient decision aids at key decision points throughout the kidney cancer pathway, including when, where, and how decision aids are made available to patients. The choice of systemic anti-cancer treatments at first line is so complex that patients are not able to contribute to the treatment decision-making process in a meaningful way. The health technology appraisal process does not compare new first-line treatments with existing comparable treatments (i.e., a new combination treatment compared with an existing combination treatment). Therefore, patients have no way of knowing which treatment option is best suited and most clinically effective for their personal situation. Because of the complexity of the	

		sequencing of systemic anti-cancer treatments and the lack of comparative data, it is difficult for patients to engage in meaningful shared decision making with their clinicians.	
	Key Issue 2: Company's definition of relevant comparators	We feel that the cabozantinib plus nivolumab combination should be compared with an alternative immunotherapy/TKI combination in the first line, not monotherapy with a TKI (i.e., tivozanib). This could be pembrolizumab plus lenvatinib or avelumab plus axitinib (using data collected from the CDF). We, therefore, disagree with the alternative approach as suggested by the EAG i.e., tivozanib as a relevant comparator, and not avelumab plus axitinib.	
	Key Issue 3: Company's definition of relevant outcomes	The most important outcomes of treatment for both the patient, family members and carers are living for as long as possible with a good quality of life. Being able to go back to doing the things that they could do before their diagnosis, such as working, enjoying holidays, and socialising with family and friends, without the constant worry of the cancer returning or progressing. We agree with the EAG's alternative approach in defining time to next treatment. We would welcome quality of life and patient reported outcomes being of equal importance as quantity of life and cost-effectiveness.	
	Key Issue 4: Company's definition of relevant subgroups	We agree with the EAG's alternative approach to include cost effectiveness in all risk populations, as well as intermediate/poor risk and favourable risk populations separately.	

	Key Issue 5: CheckMate 9ER: Consistency of reporting		
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice		
	Key Issue 7: CheckMate 9ER: Effect modification by risk group		
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials		
	Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks		
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes		
	Key Issue 11: Evidence base: unanswered questions relating to		

	applicability across histologies and in a context of adjuvant treatment		
Cost evidence (key issues in the Economic Results Addendum document)	Key Issue 1: Inconsistency between prior appraisals		
	Key Issue 2: Economic implications of trial generalisability to real-world evidence		
	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness		
	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and toxicity on economic case		
	Key Issue 5: Problems with the health-related quality of life data		

	supplied by the company		
	Key Issue 6: Outstanding uncertainties in application of severity modifiers		
	Key Issue 7: Impact of model structure on results		
	Key Issue 8: Subgroups in the context of changing comparators		
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population		

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic	Response	EAG response

Clinical effectiveness	Literature review		
	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons		
	Critique of outputs considered		
Cost effectiveness model development	Published cost effectiveness studies		
	Critique of outputs included in clinical review		
	Critique of real-world evidence		
	Indirect comparisons		
	Expert elicitation		
Economic analysis	Model structure		
	Population		
	Treatments included		
	Perspective, time horizon, cycle length,		

	discounting and price year		
	Treatment effectiveness and extrapolation		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
	Model validation		
Are there any scenarios that you would like to see?			
Has the value of cabozantinib + nivolumab been captured appropriately?			
Are there any benefits not captured in the model?			
Are there any equality considerations?			
Other notes			

NICE National Institute for Health and Care Excellence

Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

As a stakeholder you have been invited to comment on the data and analysis included in the external assessment group (EAG) model and Final Assessment Report for the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

Information on completing this form

We are asking for your views on data and assumptions included within the analysis model and used to form the final report that are likely to be discussed by the committee. The report provides a summary of work undertaken by the EAG developing the analysis and incorporating the data received from manufacturers, observational patient datasets and formal input from clinical experts. It outlines the analysis plan, methods used for the evaluation, as well as all identified relevant published evidence and real-world evidence (RWE) sources.

You are not expected to comment on every key topic but instead comment on the issues that are in your area of expertise.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by 5pm Friday 22 September. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during consultation, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during consultation are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Kidney Cancer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG.

Table 2: key issues

Issue		**Response**	**Does this response contain new evidence, data or analyses?**
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	An overall optimal sequencing of treatments for all patients is unlikely to be achievable. Patient response varies considerably, and the selection and sequence of treatment needs to be tailored to the individual. Data from the 2022 Kidney Cancer UK Patient Survey show that when asked what medicines they had taken for kidney cancer, patients mentioned more than 14 agents or combinations, none of which exceeded 9% of all mentions. For this reason, it is crucial that prescribers have access to the full range of treatments, so that they are able to optimise the sequence individually and without restriction. In terms of interpreting current real life prescribing, it is not only the individual patient's response that determines the sequence of treatments, the prescriber's preference and experience is also likely to be an important factor.	Yes. Data from the 2022 Kidney Cancer UK National Patient Survey.

		Finally, even if it is possible to make recommendations on an optimal sequence, this is likely to change relatively frequently as new treatments become available or new data about existing treatments are published.	
	Key Issue 2: Company's definition of relevant comparators	Our latest annual patient survey received 652 responses, of which 542 were completed surveys (field work carried out in September/October 2022). The results show that no patients mentioned tivozanib as a first line treatment. This leads us to question the inclusion of tivozanib in first line analyses. In the survey, avelumab plus axitinib was mentioned by about 4% of patients.	Yes. Data from the 2022 Kidney Cancer UK National Patient Survey.
	Key Issue 3: Company's definition of relevant outcomes	The potential data source to be used by the EAG does not seem to be clear. If the data come from real world practice, the decision to switch to a second treatment may be influenced by the experience and preference	None
	Key Issue 4: Company's definition of relevant subgroups	We believe that cabozantinib plus nivolumab should be assessed in the all-risk group. Whether this are another future agent or combination, it will be a major step forward to identify an all-risk treatment that can be commissioned in such a role.	None
	Key Issue 5: CheckMate 9ER: Consistency of reporting	No comment to make	None
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice	No comment to make	None

	Key Issue 7: CheckMate 9ER: Effect modification by risk group	Whilst appreciating the argument for measuring cost-effectiveness by risk group, we would not want to see this used as a means of narrowing choice by excluding some agents from some risk groups. Doing so could restrict the ability of clinicians to optimise treatment sequence on an individual patient basis.	None
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials	No comment to make.	None
	Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks	The EAG comments to this and the next two issues seem to highlight the difficulties in attempting to produce an optimal treatment sequence across all available agents using data from clinical trials that were not designed for this purpose. Added to this, the difference in the extent of experience of different agents or combinations make it difficult to contemplate using real world data at this point. Although it might seem a reasonable approach to focus on those agents or combinations with more and better quality data, we would urge the EAG not to do this as it is the effectiveness of the treatment and not the quality of the trials that must be considered here.	None
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes	See comments on Key issue 9 above.	None
	Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment	See comments on Key issue 9 above.	None

Cost evidence (key issues in the Economic Results Addendum document)	Key Issue 1: Inconsistency between prior appraisals	We are concerned that the attempts to overcome difficulties in comparing different modelling methods by using further modelling in the form of a state transition model, risk introducing further decision risk, rather than overcoming it. We would need to be convinced of the modelling technique itself before applying it to kidney cancer treatments as a basis of decision making.	None
	Key Issue 2: Economic implications of trial generalisability to real-world evidence	In our opinion, the difficulties in generalisability of clinical trial data to real world evidence have been known for many years. The purpose of a clinical trial being to establish the efficacy and/or safety of a medicine excluding other factors, their design is not likely to mirror real clinical practice. With reference to our comments to the previous key issue above, we urge extreme caution in attempting to overcome these difficulties through additional modelling, even with the benefit of a robust real world dataset.	None
	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness	No comment to make	None
	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and toxicity on economic case	We would like to register a simple point here, which is that given the alternative, kidney cancer patients (like all cancer patients) are likely to endure relatively serious side effects. We would be grateful for an explanation of how, and to what extent, this point is being incorporated into the overall assessment and scenario exploration.	None
	Key Issue 5: Problems with the health-related	No comment to make	None

	quality of life data supplied by the company		
	Key Issue 6: Outstanding uncertainties in application of severity modifiers	In our view the correct application of severity modifiers is crucial to the estimation of quality of life in cancers of all types. We appreciate that this process is a pilot and that consequently, issues such as this must be tackled. However, given the concerns on this raised by the EAG, we would simply like to comment that, when drawing conclusions and making recommendations on treatments that will impact people with kidney cancer, it should be borne in mind that it is not only the treatments that are under appraisal but the pathway development process itself and its methodology.	None
	Key Issue 7: Impact of model structure on results	We agree with the course of action proposed by the EAG	None
	Key Issue 8: Subgroups in the context of changing comparators	Please refer to our comments to key issue 4 in the key clinical issues above.	None
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population	No comment to make	None

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic		Response	EAG response
Clinical effectiveness	Literature review		
	Clinical input		
	Critique of included studies	As part of the output of this important pilot, we would be interested in any recommendations made by the EAG or the Committee on the design of trials and/or the type of data needed to provide an optimum input into future processes of this kind carried out by NICE. In most cases, these processes will have to deal with studies retrospectively (i.e. that were not design for use in such a process), but it would be important to have a set of future recommendations setting out the type of trials that would most closely match the needs of this type of process.	
	Indirect treatment comparisons	Whilst we accept that indirect treatment comparisons are inevitable in a process like this, we would welcome guidance setting out the extent to which such indirect comparisons would be acceptable. We would also like to see such recommendations subjected to peer review.	
	Critique of		

	outputs considered		
Cost effectiveness model development	Published cost effectiveness studies	With the potential introduction of a new process of appraisal such as this being piloted, we would welcome guidance on suitable cost effectiveness studies. The guidance would need to distinguish between studies designed for single or multiple technology appraisals and treatment pathway processes. A crucial element of this would be to indicate well in advance the approach being planned by NICE, i.e. in particular when NICE would consider a treatment pathway approach. This would need to be flagged a long time in advance. In addition, there will need to be guidance produced as to how NICE will deal with a new treatment that is being introduced to therapy area which already has a treatment pathway. For example, if a treatment pathway is eventually published for kidney cancer, how will NICE deal with new treatments being subsequently introduced?	
	Critique of outputs included in clinical review		
	Critique of real-world evidence	Whilst we understand the attraction of using a robust real world evidence database, we have some concerns over the way and the extent to which these are used to extrapolate on clinical trial results.	

	Indirect comparisons	See comments under clinical effectiveness above.	
	Expert elicitation		
Economic analysis	Model structure		
	Population		
	Treatments included		
	Perspective, time horizon, cycle length, discounting and price year		
	Treatment effectiveness and extrapolation		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty	Once again a comment to note our concern over the extent to which modelling s being used. Our fundamental concern is the extent to which modelling is being used to adapt existing modelling, instead of going back to hard data. Whilst the use of such modelling might be a short term solution, we remain concerned that it introduces too much decision uncertainty.	

	Model validation		
Are there any scenarios that you would like to see?		We would like to see cabozantinib plus nivolumab assessed in the all-risk group.	
Has the value of cabozantinib + nivolumab been captured appropriately?		See comment above	
Are there any benefits not captured in the model?			
Are there any equality considerations?			
Other notes		We would like to draw attention to the fact that Kidney Cancer UK did not appear to have received a notification from NICE regarding the republication of the pathway EAG report etc. Consequently, we have had to produce comments on the EAG report at very short notice (within 5 days). Under these circumstances and not having been granted an extension to the time allowed for our comments to be formulated, we regard these comments as preliminary and we reserve the right to produce additional comments when we have had time to consider all of the information, with the expectation that such comments will be fully considered.	

NICE National Institute for Health and Care Excellence

Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

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Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

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You are not expected to comment on every key topic but instead comment on the issues that are in your area of expertise.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bristol Myers Squibb
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG.

Table 2: key issues

Issue		Response	Does this response contain new evidence, data or analyses?
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments		
	Key Issue 2: Company's definition of relevant comparators	BMS are concerned with the consistent inclusion of the ITT(all-risk) population data from CheckMate 214 trial despite the fact that the final scope for this appraisal included nivolumab with ipilimumab(NIVO+IPI) only for the intermediate or poor (I/P) risk disease as defined in the IMDC criteria which is in line with both the licensed indication as well as the NICE guidance.[1] This raises potential issues of data interpretation and confusion as the document lacks clear differentiation between the ITT(all-risk) and I/P risk population and the former should not be used to support or validate model inputs. BMS suggest the exclusion of the CheckMate 214 all-risk population where relevant.	None
	Key Issue 3: Company's		

	definition of relevant outcomes		
	Key Issue 4: Company's definition of relevant subgroups		
	Key Issue 5: CheckMate 9ER: Consistency of reporting		
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice	In section 4.3.2 of the Final EAR, it was noted by the EAG that patient characteristics were similar between the CheckMate 9ER trial and the UK RWE data, except for age, where the UK RWE patients were older (See Final EAR; section 4.3.2; table 61). Given the comparable baseline characteristics and the longer-term follow-up observed in the CheckMate 9ER trial, the justification for extrapolating survival outcomes from the UK RWE cohort for sunitinib (SUNI) is considered unwarranted. Furthermore, such extrapolation would introduce additional bias and uncertainty, particularly given the shorter follow-up period, with a median follow-up of 16.8 months (95% CI: 15.8, 17.6) from the UK RWE data compared with the median follow-up of 44 months in the CheckMate 9ER trial and should be explored further in the scenario analysis. In section 4.3.5.1 for the EAR, it was reported by the EAG that longer-term data from CheckMate 214 and KEYNOTE 564 were employed to evaluate the alignment of results from the UK RWE data with extended survival trends. However, neither of these data sources are considered suitable for this purpose. KEYNOTE 564 is a clinical trial in the adjuvant setting, an area which had been	

		previously identified by the EAG as a significant source of uncertainty and key issue to be considered (clinical evidence key issue 11). In contrast, the sunitinib curve from CheckMate 214, as illustrated in the Final EAR (refer to section 3.7.2.2; figure 18), demonstrated an anomalously high survival rate, thereby diverging from the observed survival outcomes in previous clinical trials which include the SUNI treatment arm. In light of these uncertainties, both CheckMate 214 and KEYNOTE 564 should not be used to assess the consistency of clinical outcomes for SUNI in the UK RWE all-risk population. Given the similar baseline characteristics with the UK RWE data, BMS suggest the EAG explore scenario analysis involving the CheckMate 9ER SUNI arm, given its alignment with the UK RWE data's baseline characteristics, to address the identified uncertainties in assessing clinical outcomes.	
	Key Issue 7: CheckMate 9ER: Effect modification by risk group	Given the EAG's acknowledgement that risk group is a known prognostic factor, and an important effect modifier, the EAG should not assume that model inputs such as curve selection for the I/P risk group and favourable risk group to be consistent with the curve selections for the all-risk population (see Final EAR; section 4.3.5.1; table 70).	
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials		
	Key Issue 9: Evidence base: distribution of effect		

	modifiers across evidence networks		
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes	The inconsistent approach to applying relative treatment effects in the cost-effectiveness model as shown in Table 71 of the Final EAR (section 4.3.5.2) raises concerns. In the first line setting, the EAG applies relative effects from the Fractional Polynomial Network Meta-Analysis (FP NMA) for most treatments except pembrolizumab with lenvatinib (PEMBRO+LENVA), where the Proportional Hazards Network Meta-Analysis (PH NMA) is used. Notably, PFS data in the I/P risk population are unavailable for PEMBRO+LENVA, and the FP NMA results for OS produced irregular outcomes. This inconsistency is likely to bias the results of the cost-effectiveness model in favour of PEMBRO+LENVA and should be explored further by assuming a similar efficacy to immuno-oncology with tyrosine kinase inhibitors (IO+TKIs) given the similar mechanism of action, reserving the result for the PH NMA for the PH NMA specific scenario analysis. As stated by the EAG within the FAD for PEMBRO+LENVA in renal cell carcinoma "the uncertainty in extrapolating survival using fractional polynomial NMAs is greater than the uncertainty associated with using a proportional hazards approach that assumes a constant hazard ratio, even if the proportional hazards assumption may be violated." (TA858 FAD section 3.10).[2] The inconsistent application of relative treatment effects in the cost-effectiveness model, particularly involving PEMBRO+LENVA, and the potential bias introduced, as shown in Table 71 of the Final EAR report, necessitates further investigation and consideration, with implications for the overall model's credibility.	
	Key Issue 11: Evidence base: unanswered		

	questions relating to applicability across histologies and in a context of adjuvant treatment		
Cost evidence (key issues in the Economic Results Addendum document)	Key Issue 1: Inconsistency between prior appraisals		
	Key Issue 2: Economic implications of trial generalisability to real-world evidence		
	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness	Results of the expert elicitation demonstrate that the type of prior treatment received by a patient may influence outcomes with Dr. Larkin suggesting that the efficacy of cabozantinib (CABO) may diminish after prior treatment with specific TKIs due to shared mechanisms of action. Surprisingly, this insight does not appear to have been fully considered by the EAG, potentially influencing results in favour of TKI monotherapy and IO+TKI combinations. The expected attenuation of effectiveness of TKI treatments across treatment lines should be explored through scenario analysis particularly given the lack of adjustment for PFS and OS hazard ratio slippage for the IO+TKI combinations.	
	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and	None	

	toxicity on economic case		
	Key Issue 5: Problems with the health-related quality of life data supplied by the company		
	Key Issue 6: Outstanding uncertainties in application of severity modifiers		
	Key Issue 7: Impact of model structure on results		
	Key Issue 8: Subgroups in the context of changing comparators		
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population	Given the inconclusive results of the I/P NMA and the fact that less than 9% in the UK RWE dataset use 1L CABO where it is predominantly used 2L setting (38.8% of the UK RWE dataset), exclusion of cabozantinib (via CABOSUN) from the modelling of 1L treatments is advised as a scenario analysis. This is further supported by the fact that the model output results from the previous PEMBRO+LENVA NICE appraisal demonstrated an improvement in life years (LYs) with both PEMBRO+LENVA and NIVO+IPI over CABO.[2] The PartSA model outputs in this appraisal were consistent with the previous PEMBRO+LENVA submission,	

		despite producing LYs 79% lower than the previous NICE submission when comparing NIVO+IPI with CABO (see Table 6). In contrast, the base case sequence model produced more LYs for CABO over NIVO+IPI, resulting in a 368% difference between the LYs produced by the previous PEMBRO+LENVA NICE appraisal and the base case sequence model (see Table 5).[2] The contrasting results seen in the base case sequence model and previous NICE appraisal further support the exclusion of cabozantinib from the modelling of 1L treatments is advised as a scenario.	

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic		Response	EAG response
Clinical effectiveness	Literature review		
	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons	BMS are concerned there is a lack of clinical validity and plausibility with the FP NMA results particularly in the I/P population which informs the relative efficacy of comparators in the model.	

		Whilst the EAG aimed to achieve a good match between the results of the FP NMA and expert elicitation by ensuring that the point estimate for FP NMA conditional survival fell within the 95% confidence interval of the expert elicitation result for each treatment, this approach has resulted in models which do not fit the clinical trial data (Final EAR; section 3.7.1). The selected models do not accurately capture the underlying PFS pattern for NIVO+IPI as the survival probabilities from the first-line PFS (Final EAR Report, Section 3.7.3.3, Figure 28) for the I/P risk patients are notably lower than those observed in the CheckMate 214 clinical trial with a minimum 60-month follow-up. Specifically, in Figure 28 of the Final EAR, the PFS probability for NIVO+IPI after approximately 38 months is 25%. In contrast, the CheckMate 214 PFS KM curve for NIVO+IPI (see Figure 1 below) indicates the formation of a plateau at approximately 2 years, resulting in a PFS of 31% at 60 months (see Table 3). However, in Figure 28, at approximately 63 months, the PFS probability drops to 19%.[3] The same can be see with the OS survival probabilities produced from the FP NMA where Figure 30 (Final EAR Report; page 215) shows that at approximately 63 months, the OS	

		survival probability is 38%, where the trial data (see Table 4) is 43% at 60 months.[3] A balance in model selection should be sought, ensuring that clinical expert opinion is integrated while also guaranteeing that the models accurately reflect the trial data, alternatively this could be explored further with the appropriate scenario analysis.	
	Critique of outputs considered		
Cost effectiveness model development	Published cost effectiveness studies		
	Critique of outputs included in clinical review		
	Critique of real-world evidence	BMS are concerned that there is a lack of transparency for stakeholders to review and comment on the UK RWE dataset which underpins the EAGs modelling. The UK RWE dataset included 1,319 metastatic renal cell carcinoma patients who commenced 1st line systemic therapies between June 2018 and August 2022 across 15 UK centres with median follow up of 16.8 months (95% CI 158, 17.6), which is considerably shorter when compared with data from the clinical trials for the comparators included in this appraisal. During this period clinical outcomes and patient	

		characteristics in RWE data may have been influenced by the coronavirus disease 2019 (COVID-19) pandemic, particularly during the data collection period. The short length of follow-up of the RWE dataset would not adequately capture the longer term changes as seen in some of the clinical trials such as the slippage in PFS and OS estimates as well as the maintenance of OS benefit with NIVO+IPI or the improvements in PFS for patients treated with NIVO+IPI over time and where a clear and defined plateau has been observed from year 2 which is seen in the CheckMate 214 trial in Figure 1 below. This is particularly evident when comparing survival outcome extrapolations between CheckMate 9ER, UK RWE and CheckMate 214. In light of the considerations regarding the long-term extrapolations of survival curves, it is important to highlight that the change in the most appropriate extrapolation choice between the 30-months minimum follow-up CDF entry for NIVO+IPI and the 60-month CDF exit. With 30-months minimum follow-up on CDF entry for NIVO+IPI, the committee considered both the log-normal, and Kaplan–Meier with exponential extrapolation curves as clinically plausible. With 60-months minimum follow-up the exponential extrapolation was judged as inappropriate due to the poor predictive performance with 60-month CheckMate 214	

		data, poor goodness of fit statistics and poor visual fit of the exponential hazard to hazards for either treatment arm (see Figure 2 and Table 1 below). Based on the OS model fit statistics for sunitinib from the CheckMate 214 trial I/P risk patients (60-month data cut), the log-normal and gen-gamma are the best fitting extrapolations whilst exponential extrapolation was judged to be the poorest fitting (see Figure 2 and Table 1), this is closely aligned with the OS model fit statistics seen with sunitinib from CheckMate 9ER I/P risk population with log-normal fitting best. When compared with the extrapolations which offer a statistically good fit for UK RWE 1L sunitinib in the I/P risk population (Appendix K; section K2.2.2, table 86), the exponential curve as see as the best fitting will the remaining 6 standard parametric models being considered good statistical fit (AIC within 5 of best fitting curve), it suggests that none of the models provides a significantly better fit to the data compared to the others which indicate that the data may be inherently volatile or that the models you're considering are not able to capture all the underlying patterns in the data. The goodness of fit statistics for PFS for sunitinib in the I/P risk subgroup from CheckMate 9ER closely match the ranks for those seen with CheckMate 214 which include log-normal followed by Gen. Gamma and Log-	

		logistics (see Appendix K; section K.1.2.1 table 33 and Table 2 below). As stated in section 4.3.5.1 (Extrapolation of survival curves) “Input from clinical experts was that the hazard function PFS would be expected to initially rise as those who are not sensitive to treatment progress early (first 1-2 years) followed by a slowing in the hazard function as those patients remaining are those who experienced initial disease control.” Given this expected change in hazard functions, standard parametric models would not adequately capture the shape of the hazard functions and flexible parametric models should be explored to provide a better fit to the observed data, which as demonstrated in the PFS model fit statistics for sunitinib (see Table 2 below) offer better fitting curves than the standard parametric models. Given the uncertainty surrounding the RWE extrapolations when compared with trial data such as CheckMate 9ER, BMS suggest validating and adjusting the RWE extrapolations with clinical trial data and exploring flexible parametric models.	
	Indirect comparisons	See above	
	Expert elicitation	BMS are concerned with the level of reliance on expert elicitations to inform long term estimates and FP NMA model selections. A large portion of treatments included within the expert elicitation involved only three clinical experts,	

		and there are noteworthy issues surrounding their contributions. Specifically, three responses were excluded from one clinician as they had not understood the question, and responses from three clinicians required reformatting because of incorrect survey completion. Furthermore, upon closer examination of the expert opinions, it becomes evident that almost half of the expert elicitation results (30 out of 66 treatments) were based on existing data rather than clinical experience or expectations which introduces potential bias into the overall findings. Additionally, in the case where RWE data was available, clinicians' estimates consistently exceeded the observed outcomes. For example, when analysing sunitinib, clinicians' estimates from the expert survey consistently exceeded the trial Kaplan-Meier curves. To help reduce some of the potential biases associate with expert elicitation, these biases in expert elicitation, clinical trial data can be used to validate and calibrate inputs.	
Economic analysis	Model structure	In the preliminary EAR consultation, it was previously mentioned that BMS is concerned about the inconsistency of the base case model structure (treatment sequencing approach) with other appraisals used in 1L RCC. The combination of multiple treatment sequence lines has resulted in a highly complex model, necessitating numerous simplifying assumptions across these sequences. This complexity has reduced the scientific credibility and clinical	

		validity of the model outputs, which do not align with the clinical trial data from the phase 3 randomized clinical trial of CheckMate 214 and are inconsistent with previous NICE appraisal outputs.	
	Population		
	Treatments included		
	Perspective, time horizon, cycle length, discounting and price year		
	Treatment effectiveness and extrapolation		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
	Model validation	BMS are concerned by the inconsistencies in the model results stemming from both the EAG sequencing base case model and PartSA, as they deviate significantly from the findings in previous NICE appraisals and fail to align with clinical trial data. This misalignment challenges the overall validity of the modelling approach	

		and, in turn, has the potential to undermine the credibility of prior NICE conclusions and pose a substantial risk of establishing an adverse precedent for future renal cell carcinoma appraisals, where comparators within scope may be reimbursed based on different methodologies. **Base case model** Within Table 5 below you can see the life (LYs) years and quality adjusted life years (QALYs) from previous NICE appraisals (where available) compared with those from the EAG base case model which demonstrate between a 81% to 349% difference between the model outputs seen in previous NICE appraisals compared with the EAG base case model outputs. In the I/P poor risk group, the EAG base case model produced 2.45 life years gained (LYG) for sunitinib compared with 2.09 for NIVO+IPI (see Appendix Q; Section Q.2.1; table 1). These results are at odds with the results of the CheckMate 214 trial which demonstrated a significant improvement in OS for patients receiving NIVO+IPI compared to those receiving sunitinib (hazard ratio 60-month data-cut (HR: 0.68 [95% CI: 0.58, 0.81]). The results from the clinical trial which fed into the CDF review model for NIVO+IPI resulted in greater incremental LYGs and QALYs when compared with sunitinib, however this is not the case with the EAG base case model where patients are	

		expected to experience a loss in life years and QALYs (see Table 5). Interestingly, the EAG base case model also highlights the extent to which the benefits for PEMBRO+LENVA are over overestimated versus NIVO+IPI when compared with the NICE appraisal for the same indication, resulting in a 349% increase in LYGs compared with the previous NICE appraisal for PEMBRO+LENVA. **PartSA** The differences between the previous NICE appraisals and EAG PartSA model are less pronounced when compared with the base case EAG model (see Table 6 below) with NIVO+IPI demonstrating an improvement in LYs and QALYs when compared with sunitinib, however there is still between 2% - 77% difference between the LYs and QALYs seen between the previous NICE appraisals and EAG PartSA model. For the CDF exit for NIVO+IPI it can be seen that regardless of the company or EAG model scenarios, which the committee felt the ICER fell between, both substantially are substantially underpredicted when compared with the PartSA put forth by the EAG. When compared to the clinical trial data, the PartSA analysis for NIVO+IPI generates a mean 2.92 life years (e.g. 35 months) over a 40-year time horizon, despite the clinical trial data from CheckMate 214 demonstrating a median overall survival of 47 months for NIVO+IPI at 60 months	

		minimum follow-up. Of note, the PFS on treatment for I/P risk patients treated with NIVO+IPI is 0.98 years (11.8 months) despite a median of 11.6 months, and 31% of patients being progression free with 60-months minimum follow-up observed in CM-214. Failing to address these inconsistencies between the model outputs, previous NICE appraisal outputs and the clinical trial data could undermine the validity of the model for decision making leading to misinformed decisions regarding treatment choices. It is essential for the committee to address these discrepancies to ensure the model outputs do not lack face validity resulting in scientifically implausible results.	
Are there any scenarios that you would like to see?		• See Clinical evidence key issue 6: Sunitinib RWE extrapolations • See Clinical evidence key issue 10: Preferred 1st line NMA FP NMA for PEMBRO+LENVA. • See cost evidence key issue 3: attenuation of CABO and other TKIs across treatment lines given shared mechanism of action • See cost evidence key issue 9: Exclusion of CABO in the first line treatment setting. • Balancing model selection and FP NMA results with clinical expert opinion and clinical trial data	

Has the value of cabozantinib + nivolumab been captured appropriately?		
Are there any benefits not captured in the model?	As previously mentioned, BMS are concerned that the long term PFS benefits for NIVO+IPI are not appropriately captured in the EAG base case model as the short follow-up with the RWE data does not capture the plateau which appears to be forming from approximately 2 years for NIVO+IPI, which is not observed for sunitinib (see Figure 1). Additionally, the models do not capture the durability of treatment benefit with NIVO+IPI beyond progression as patients treated with NIVO+IPI experience a significantly longer time from randomisation to first subsequent therapy and time from randomisation to second subsequent therapy or death, than patients treated with sunitinib demonstrating the positive benefits of NIVO+IPI beyond the first line setting.	
Are there any equality considerations?		
Other notes		

Figure 1 KM curve of PFS by treatment arm - CheckMate 214 intermediate-/poor-risk patients (60-month data cut; IRRC primary definition)[3]

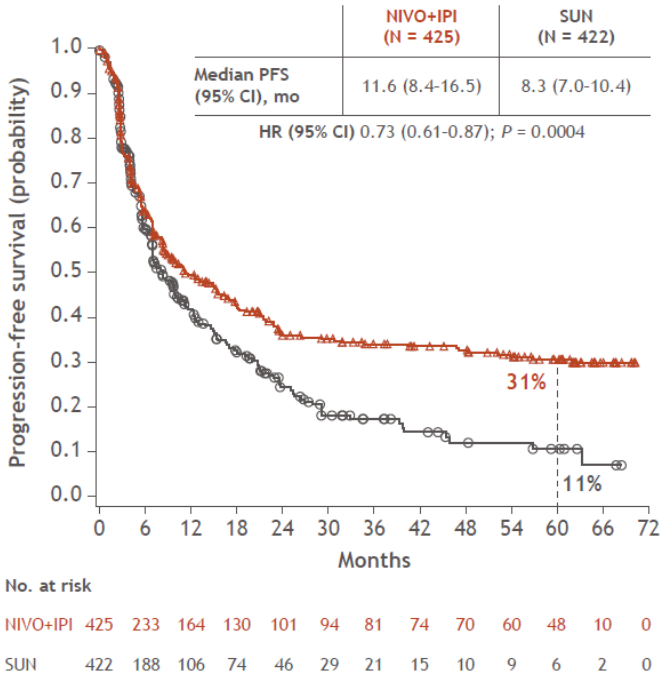

Figure 2 OS extrapolations based on 30-month CheckMate 214 (KM + exponential, log-logistic, and log-normal) versus OS 60-month CheckMate 214 KM data – intermediate-/poor-risk patients (Reproduced from NIVO+IPI CDF Review, A.7.2 page 33 figure 5)[1]

Table 1 OS independent model fit statistics – CheckMate 214 intermediate/poor risk patients (60-month data cut;

Reproduced from NIVO+IPI CDF Review, Section A15.2.2, page 66; table 19)[1]

Model	NIVO+IPI				Sunitinib				Overall			
	AIC	AIC rank	BIC	BIC rank	AIC	AIC rank	BIC	BIC rank	AIC	AIC rank	BIC	BIC rank
Log-normal	**2522.5**	**1**	**2530.6**	**1**	2709.4	2	**2717.5**	**1**	**5231.9**	**1**	**5248.1**	**1**
Gen. gamma	2524.4	2	2536.6	4	**2708.1**	**1**	2720.2	2	5232.5	2	5256.8	2
Log-logistic	2526.5	3	2534.6	2	2718.6	3	2726.7	3	5245.1	3	5261.3	3
Gompertz	2528.1	4	2536.2	3	2725.4	4	2733.5	4	5253.5	4	5269.7	4
Weibull (AFT)	2534.6	5	2542.7	6	2743.0	5	2751.1	6	5277.6	5	5293.8	6
Gamma	2536.1	6	2544.3	7	2746.1	6	2754.2	7	5282.2	6	5298.4	7
Exponential	2536.9	7	2540.9	5	2746.2	7	2750.3	5	5283.1	7	5291.2	5

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Notes: Models sorted by overall AIC score. Best fitting curve by AIC/BIC rank highlighted in bold and green; worst fitting curve highlighted in orange

Table 2 PFS independent model fit statistics – CheckMate 214 intermediate/poor risk patients (60-month data cut; Reproduced from NIVO+IPI CDF Review, Section A15.3.2, page 77; table 21)[1]

Model	NIVO+IPI				Sunitinib				Overall			
	AIC	AIC rank	BIC	BIC rank	AIC	AIC rank	BIC	BIC rank	AIC	AIC rank	BIC	BIC rank
Hazard (2 knot)	2382.3	1	2398.6	1	2636.7	1	2652.9	1	5019.1	1	5051.5	1
Odds (2 knot)	2382.9	2	2399.1	2	2642.7	2	2658.9	3	5025.6	2	5058.0	2
Normal (1 knot)	2388.1	4	2400.3	3	2647.4	4	2659.6	5	5035.5	3	5059.8	3
Normal (2 knot)	2387.3	3	2403.5	4	2648.9	6	2665.0	7	5036.2	4	5068.6	5
Gen. gamma	2391.9	5	2404.1	5	2649.1	7	2661.2	6	5041.0	5	5065.3	4
Hazard (1 knot)	2399.0	7	2411.1	7	2647.2	3	2659.3	4	5046.2	6	5070.5	6
Odds (1 knot)	2394.1	6	2406.3	6	2653.1	8	2665.3	8	5047.2	7	5071.5	7
log-normal	2441.5	8	2449.6	8	2648.2	5	2656.3	2	5089.7	8	5105.9	8
Log-logistic	2458.8	10	2466.9	10	2659.6	9	2667.7	9	5118.4	9	5134.6	9
Gompertz	2450.2	9	2458.3	9	2684.0	10	2692.1	10	5134.2	10	5150.3	10
Weibull (AFT)	2513.3	11	2521.4	11	2697.3	11	2705.4	12	5210.6	11	5226.8	11
Gamma	2533.4	12	2541.5	12	2700.5	13	2708.6	13	5233.9	12	5250.1	12
Exponential	2574.6	13	2578.7	13	2698.9	12	2702.9	11	5273.5	13	5281.6	13

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Notes: Models sorted by overall AIC score. Best fitting curve by AIC/BIC rank highlighted in green; worst fitting curve highlighted in orange

Table 3: PFS rates by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut, IRRC primary definition)

Timepoint in months	PFS rates by treatment, %	
	NIVO+IPI	Sunitinib
24[4]	36	25
48[4]	33	12
60[3]	31	11

Table 4 OS rates by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)

Timepoint in months	OS rates by treatment, %	
	NIVO+IPI	Sunitinib
12[5]	80	72
24[4]	66.4	52.4
36	[redacted]	[redacted]
48[4]	50	35.8
60[3]	43	31.3

Table 5 Difference in LYs and QALYs from previous NICE TAs versus LYs and QALYs from the EAG base case model (Sequence)

NICE TA	Treatment	NICE TA assessment				EAG model (Base case sequencing model)				Difference (EAG Sequence model - TA)	
		LYs	QALYs	Inc LYs	Inc QALYs	LYs	QALYs	Inc LYs	Inc QALYs	Inc LYs	Inc QALYs
Intermediate/Poor risk											
TA780 (Company base case)[1]	**NIVO+IPI**	8.083	4.62	2.734	1.489	2.09	1.28	-0.36	-0.18	3.094 (113%)	1.669 (112%)
	SUNI	5.349	3.131			2.45	1.46				
TA780 (EAG scenario S1)[1]	**NIVO+IPI**	6.896	4.132	1.547	1.001	2.09	1.28	-0.36	-0.18	1.907 (123%)	1.181 (118%)
	SUNI	5.349	3.131			2.45	1.46				
TA780 (EAG scenario S2)[1]	**NIVO+IPI**	8.083	4.62	1.884	1.146	2.09	1.28	-0.36	-0.18	2.244 (119%)	1.326 (116%)
	SUNI	6.199	3.474			2.45	1.46				
TA858 (AG revised base case)[2]	**PEMBRO+LENVA**	4.933	NR	0.341	NR	3.62	2.23	1.53	NR	-1.189 (-349%)	N/A
	NIVO+IPI	4.592	NR			2.09	1.28				
TA858 (AG revised base case)[2]	**PEMBRO+LENVA**	4.933	NR	0.853	NR	3.62	1.46	0.16	-0.61	0.693 (81%)	N/A
	CABO	4.080	NR			3.46	2.07				
TA858 (AG revised base case)[2]	**NIVO+IPI**	4.592	NR	0.512	NR	2.09	1.28	-1.37	-0.79	1.882 (368%)	N/A
	CABO	4.080	NR			3.46	2.07				
TA542 (Revised company base case)[6]	**CABO**	NR	NR	NR	0.342	NR	2.07	NR	-0.38	N/A	0.722 (211%)
	SUNI	NR	NR			NR	2.45				

NR: Not reported; N/A not applicable.

Table 6 Difference in LYs and QALYs from previous NICE TAs versus LYs and QALYs from the EAG model (PartSA)

NICE TA	Treatment	NICE TA assessment				EAG model (PartSA; corrected values shared via email on 13/9/23)				Difference (EAG PartSA - TA)	
		LYs	QALYs	Inc LYs	Inc QALYs	LYs	QALYs	Inc LYs	Inc QALYs	Inc LYs	Inc QALYs
Intermediate/Poor risk											
TA780 (Company base case)[1]	**NIVO+IPI**	8.083	4.62	2.734	1.489	2.92	1.87	0.64	0.41	-2.094 (-77%)	-1.079 (-72%)
	SUNI/PAZO	5.349	3.131			2.28	1.46				
TA780 (EAG scenario S1)[1]	**NIVO+IPI**	6.896	4.132	1.547	1.001	2.92	1.87	0.64	0.41	-0.907 (-59%)	-0.591 (-59%)
	SUNI/ PAZO	5.349	3.131			2.28	1.46				
TA780 (EAG scenario S2)[1]	**NIVO+IPI**	8.083	4.62	1.884	1.146	2.92	1.87	0.64	0.41	-1.244 (-66%)	(-0.736 (-64%)
	SUNI/ PAZO	6.199	3.474			2.28	1.46				
TA858 (AG revised base case)[2]	**PEMBRO+LENVA**	4.933	NR	0.341	NR	3.04	1.94	0.12	0.07	0.221 (65%)	N/A
	NIVO+IPI	4.592	NR			2.92	1.87				
TA858 (AG revised base case)[2]	**PEMBRO+LENVA**	4.933	NR	0.853	NR	3.04	1.94	0.23	0.13	0.623 (73%)	N/A
	CABO	4.080	NR			2.81	1.81				
TA858 (AG revised base case)[2]	**NIVO+IPI**	4.592	NR	0.512	NR	2.92	1.87	0.11	0.06	0.402 (79%)	N/A
	CABO	4.080	NR			2.81	1.81				
TA542 (Revised company base case)[6]	**CABO**	NR	NR	NR	0.342	NR	1.81	NR	0.35	N/A	-0.008 (-2%)
	SUNI	NR	NR			NR	1.46				

NR: Not reported; N/A not applicable.

[1] National Institute for Health and Care Excellence (NICE). TA780: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. 2022 Available at: https://www.nice.org.uk/guidance/ta780. Accessed: September 2023.
[2] National Institute for Health and Care Excellence (NICE). TA858: Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma. 2023. Available at: https://www.nice.org.uk/guidance/ta858/. Accessed September 2023
[3] Motzer, R. J., Tannir, N. M., McDermott, D. F., et al. Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma. Presented at the ESMO Virtual Congress 2021; 2021
[4] Albiges, L., Tannir, N. M., Burotto, M., et al. (2020). Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO open, 5(6), e001079. https://doi.org/10.1136/esmoopen-2020-001079
[5] Motzer, R. J., Rini, B. I., McDermott, D. F., et al.(2019). Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. The Lancet. Oncology, 20(10), 1370–1385. https://doi.org/10.1016/S1470-2045(19)30413-9
[6] National Institute for Health and Care Excellence (NICE). TA542: Cabozantinib for untreated advanced renal cell carcinoma. 2018. Available at: https://www.nice.org.uk/guidance/ta542. Accessed September 2023

NICE National Institute for Health and Care Excellence

Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

As a stakeholder you have been invited to comment on the data and analysis included in the external assessment group (EAG) model and Final Assessment Report for the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

Information on completing this form

We are asking for your views on data and assumptions included within the analysis model and used to form the final report that are likely to be discussed by the committee. The report provides a summary of work undertaken by the EAG developing the analysis and incorporating the data received from manufacturers, observational patient datasets and formal input from clinical experts. It outlines the analysis plan, methods used for the evaluation, as well as all identified relevant published evidence and real-world evidence (RWE) sources.

You are not expected to comment on every key topic but instead comment on the issues that are in your area of expertise.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by 5pm Friday 22 September. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during consultation, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during consultation are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Eisai Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG.

Table 2: key issues

Issue		Response	Does this response contain new evidence, data or analyses?
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments		
	Key Issue 2: Company's definition of relevant comparators		
	Key Issue 3: Company's definition of relevant outcomes		
	Key Issue 4: Company's definition of relevant subgroups		
	Key Issue 5: CheckMate 9ER:		

	Consistency of reporting		
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice		
	Key Issue 7: CheckMate 9ER: Effect modification by risk group		
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials		
	Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks		
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes		
	Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a		

	context of adjuvant treatment		
Cost evidence (key issues in the Economic Results Addendum document)	Key Issue 1: Inconsistency between prior appraisals		
	Key Issue 2: Economic implications of trial generalisability to real-world evidence		
	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness		
	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and toxicity on economic case		
	Key Issue 5: Problems with the health-related quality of life data supplied by the company		

	Key Issue 6: Outstanding uncertainties in application of severity modifiers		
	Key Issue 7: Impact of model structure on results		
	Key Issue 8: Subgroups in the context of changing comparators		
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population		

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic		Response	EAG response
	Literature review		

Clinical effectiveness	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons		
	Critique of outputs considered		
Cost effectiveness model development	Published cost effectiveness studies		
	Critique of outputs included in clinical review		
	Critique of real-world evidence		
	Indirect comparisons		
	Expert elicitation		
Economic analysis	Model structure		
	Population		
	Treatments included		
	Perspective, time horizon, cycle length,		

	discounting and price year		
	Treatment effectiveness and extrapolation		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
	Model validation		
Are there any scenarios that you would like to see?			
Has the value of cabozantinib + nivolumab been captured appropriately?			
Are there any benefits not captured in the model?			
Are there any equality considerations?			
Other notes		*Table 55, Summary of previous technology appraisals, TA858, p254 of 394.* For consistency with the rest of the External Assessment report, please amend trial name to CLEAR under the 'Source of HRQoL data' header.	

NICE National Institute for Health and Care Excellence

Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

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Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

Information on completing this form

We are asking for your views on data and assumptions included within the analysis model and used to form the final report that are likely to be discussed by the committee. The report provides a summary of work undertaken by the EAG developing the analysis and incorporating the data received from manufacturers, observational patient datasets and formal input from clinical experts. It outlines the analysis plan, methods used for the evaluation, as well as all identified relevant published evidence and real-world evidence (RWE) sources.

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	MSD UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG.

Table 2: key issues

Issue		Response	Does this response contain new evidence, data or analyses?
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments		
	Key Issue 2: Company's definition of relevant comparators		
	Key Issue 3: Company's definition of relevant outcomes		
	Key Issue 4: Company's definition of relevant subgroups		
	Key Issue 5: CheckMate 9ER:		

	Consistency of reporting		
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice		
	Key Issue 7: CheckMate 9ER: Effect modification by risk group		
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials		
	Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks		
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes		
	Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a	MSD note that the exploratory analyses from the SEE exercise examining the proportion of patients “alive and progression free” who were previously treated with adjuvant pembrolizumab after at certain landmark timepoints are based on pooled responses from 2 or 3 clinical experts. The MRC protocol recommends that “at least five experts should be included in the SEE.” Therefore, the results of this analysis should be interpreted with caution.	No

	context of adjuvant treatment		
Cost evidence (key issues in the Economic Results Addendum document)	Key Issue 1: Inconsistency between prior appraisals		
	Key Issue 2: Economic implications of trial generalisability to real-world evidence		
	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness		
	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and toxicity on economic case		
	Key Issue 5: Problems with the health-related quality of life data supplied by the company		

	Key Issue 6: Outstanding uncertainties in application of severity modifiers	The EAG note that “in probabilistic analysis it is highly likely that a number of scenarios would result in application of the modifier, it is not clear how the modifier should be handled in such analyses).” MSD would also welcome clarity on how the severity modifier should be handled in this situation.	No
	Key Issue 7: Impact of model structure on results		
	Key Issue 8: Subgroups in the context of changing comparators		
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population		

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic		Response	EAG response
	Literature review		

Clinical effectiveness	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons		
	Critique of outputs considered		
Cost effectiveness model development	Published cost effectiveness studies		
	Critique of outputs included in clinical review		
	Critique of real-world evidence	Due to extensive redaction it is difficult to comment fully on the RWE included. MSD notes that the UK RWE data used in the model comprises of data from 15 centres. It is unclear from the EAG report whether these centres provide a geographically representative reflection of UK clinical practice. MSD acknowledges that the EAG was unable to access data from CPRD and HES but notes that that using data from these sources may have several benefits, most notably a larger sample size. This may help to reduce uncertainty in effectiveness estimates at later lines of therapy, where sample sizes in the UK RWE were small.	

	Indirect comparisons		
	Expert elicitation	As noted above some of the results in the SEE were based on responses from a lower number of experts than recommended in the MRC protocol. While this is understandable as a pragmatic choice to prevent response fatigue, the limited number of responses introduces additional uncertainty to the results where a smaller number of experts have responded.	
Economic analysis	Model structure		
	Population		
	Treatments included		
	Perspective, time horizon, cycle length, discounting and price year		
	Treatment effectiveness and extrapolation		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		

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	Model validation	The EAG notes that “Given the proposed primary model structure (state transition), calibration to expected OS estimates was considered as an option. In the end this was not considered necessary as the PartSA analyses were available to cross-check against. This may be further explored in Phase 2.” Given the discrepancy in life years gained between the two modelling approaches (state transition and PartSA) MSD notes that further exploration of this may be appropriate.	
Are there any scenarios that you would like to see?			
Has the value of cabozantinib + nivolumab been captured appropriately?			
Are there any benefits not captured in the model?			
Are there any equality considerations?			
Other notes			

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Renal cell carcinoma: Pathways Pilot [ID6186]

Patient expert statement and response form

Thank you for agreeing to give us your views on the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with renal cell carcinoma or caring for a patient with renal cell carcinoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

You are also not expected to comment on every key message, again we have given guidance on the key messages that you might have insight to share, but don't worry if not.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **22 September.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with renal cell carcinoma

Table 1 About you, renal cell carcinoma, current treatments and equality

1. Your name	Geraldine Fox
2. Are you (please tick all that apply)	A patient with renal cell carcinoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with renal cell carcinoma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	I am drawing from personal experience I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Listening and reading about other patients and carers experience at all stages of the pathway over 8 years I have completed part 2 of the statement **after attending** the expert engagement teleconference

Patient expert statement

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with renal cell carcinoma? **If you are a carer (for someone with renal cell carcinoma) please share your experience of caring for them**	I was diagnosed in 2014 with stage 3 intermediate risk kidney cancer. Since then I have undergone a nephrectomy and 10 years of follow-up scanning which will end in 2024.
7a. What do you think of the current treatments and care available for renal cell carcinoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a: Treatments for stages 1-3 could be better targeted to ensure that patients are not over or under treated more consistently across England.. Stage 4 treatments can be confusing and don't appear to be consistently applied either. Care generally can be inconsistent, with some patients experiencing difficulty with getting a diagnosis, lack of communication, no CNS/key worker, slow scan results and months waiting for treatment. Recently I was contacted by a patient who needed adjuvant treatment after nephrectomy but was not able to get access to an oncologist within 90 days and therefore was unable to have treatment. This suggests a lack of communication/co-ordination to ensure these patients have the best chance of no recurrence, or if unavoidable at least explain the reason for the inability to have treatment. Care after nephrectomy for stages 1-3 patients is almost non-existent and many patients feel abandoned during follow-up because they have very little contact with clinicians even though they are still technically under the care of the hospital. Most patients have varying amounts of emotional and mental issues connected with fear of recurrence/progression, what future they might have, and how they will cope with family responsibilities, yet very few are offered mental health support. Greater and more effective communication at the appropriate time is needed with patients and their families to ensure they can make decisions based on the information they need, ensuring that their understanding is sufficient to lead to informed decisions. Information and support for patients on systemic treatment about side effects and their mitigating treatment does not always seem to be consistent. Clinical trials do not always get offered to suitable patients and therefore those patients could miss out on treatments for which they

	could be suitable, not to mention the loss of the opportunities for the trials to produce better results.. 7b) My experience of treatment is now 9 years old, and not much has changed. After hearing many other experiences my views may be broader than other patients, also my contact with clinicians as part of my role with Kidney Cancer UK and in kidney cancer research has given me an insight into the issues clinicians face, so I probably have a better idea of the "Big Picture" than most patients. But, I have no personal experience of metastatic cancer or systemic treatments.
8. If there are disadvantages for patients of current NHS treatments for renal cell carcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Patients with a suspected diagnosis who do not have a biopsy can be given a nephrectomy unnecessarily if the subsequent pathology indicates it is benign. Inconsistencies in the use of nephron sparing treatments for small masses in favour of the more traditional nephrectomy can result in over treatment. Poor communication with patients for decision making can lead to poor decision making. Lack of mental health support during the pathway can make the patient experience very challenging. Metastatic patients, often in poor health, having to attend hospital regularly for access to medication can mean long journeys and related expenditure. Side effects from treatments can result in the development of other serious conditions such as osteoporosis and diabetes, impacting both the patients quality of life and workload for the NHS having to manage potentially avoidable long term conditions.
9a. If there are advantages of cabozantinib plus nivolumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does cabozantinib plus nivolumab help to overcome or address any of the listed disadvantages**	9a) If the combination brings patients the advantages of both without the side effects of both that is great. The greatest advantages would be quality of life and overall survival if it could be proved that the combination provides better results than they do separately. 9b) Quality of life. While overall survival is obviously something to aim for, quality of life is more important - there is no point in extending life if that life is being bed bound or suffering other serious long term conditions from treatment side effects..

of current treatment that you have described in question 8? If so, please describe these	9c) I don't know - until the combination is approved we won't know if patients find them better in combination than separately.
10. If there are disadvantages of cabozantinib plus nivolumab over current treatments on the NHS please describe these. For example, are there any risks with cabozantinib with nivolumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Currently it appears that those on Nivolumab often progress to Cabozntinib so if the advantages of both independently aren't replicated when combined, does that mean that if the combination doesn't work, patients have one less 2nd line treatment available because they couldn't then have either of them separately, which might give them better results than the combination? There must be concern that combining the two medications could result in some patients suffering the worst side effects of both. As with other treatments, ensuring that the patients given the combined treatment are carefully chosen and limited to those who are expected to have the best results, might reduce the potential for serious side effects which would have considerable impact on quality of life.
11. Are there any groups of patients who might benefit more from cabozantinib with nivolumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who are frail or in poor health generally might not benefit, indeed being put on the combination might worsen their health. Patients unable to understand the implications of the combination, such as those with dementia, might not be suitable.
12. Are there any potential equality issues that should be taken into account when considering renal cell carcinoma and cabozantinib with nivolumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	I don't think there are any equality issues specifically in relation to the combination that wouldn't equally apply to other similar treatments for renal cell carcinoma as both elements are already in use for metastatic kidney cancer patients.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	I am concerned that the current treatment appraisal focus detracts from the equal need to consider the wider RCC pathway's issues as a whole. I did not receive the original notification that the documentation had been reissued, and was only aware of it 4 days before the deadline. I have therefore made my comments as best I can at such short notice. I sincerely hope there will be additional opportunities in future to make further comments, and that future requests for responses allow for reasonable response times. I would also like to make the point that the Lay Summary, while useful, does not go into enough detail to help me really understand the report.

Part 2: Technical engagement questions for patient experts

Issues and topics arising from external assessment report

The key issues and topics covered in the external assessment report (EAR) are listed in table 2 and table 3. We welcome your comments on these, but you do not have to provide a response to every issue or topic, such as the ones that are technical. We have flagged the issues where we consider a patient perspective may be most relevant and valuable in **bold**. If you think anything that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Key issues

	Additional information and questions	Response
Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	One of the aims of the pathway approach is to provide more information on the optimal treatment choices following initial treatment. Can you provide any information on the pathway of care you have received?	Optimal sequencing of treatments is only useful if they are adopted in clinics and patients are told what that optimal sequence is in their particular circumstances..
Key Issue 2: Company's definition of relevant comparators	Are you aware what treatments you could have received in place of the pathway of care you received?	N/A - no personal experience of systemic treatment

Key Issue 3: Company's definition of relevant outcomes	What outcomes are most important to you? Have any important outcomes that have been missed in the report?	Quality of life allied with overall survival, not one or the other. Preservation of optimal mental health is an important outcome - outcomes aren't just about the physical aspects.
Key Issue 4: Company's definition of relevant subgroups	Cabozatinib with nivolumab is indicated for patients of all risk types. The external assessment group have investigated the cost-effectiveness of cabozantinib with nivolumab in intermediate-/poor-risk and favourable-risk groups as advice to them is that NHS practice also follows these risk groups. Are you aware if your treatment been informed by risk status? If so, did available treatments change due to your risk status?	I am aware that risk status informs treatment recommendations, and that therefore the importance of ensuring patients' risk is properly assessed is extremely important.
Key Issue 5: CheckMate 9ER: Consistency of reporting		
Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice		
Key Issue 7: CheckMate 9ER: Effect modification by risk group		
Key Issue 8: Evidence base: quality and sufficiency		The perceived quality of the trials does not necessarily mean that the results

Patient expert statement

of included randomised trials		will not be meaningful. Also, if that is the only evidence available it would seem sensible to include it but note where and why there might be reason for doubt.
Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks		See comment in Key Issue 8 above.
Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes		This is one of many issues around the constantly changing landscape of available treatments. The Pathways Pilot will no doubt have processes for ensuring that evolving treatments and outcomes are reviewed and included where appropriate on a regular basis?
Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment		See comment in Key Issue 10 above.
Other issues not captured in the External Assessment Report.		All the Key Issues relate to the treatment appraisal and not the patient pathway element. This concerns me greatly - there is a danger that the focus will remain only on the treatment appraisal and the pathway issues (of which there are many) will not be

		given the same focus. Similarly, if the treatment appraisal is considered in isolation from the pathway, is it possible that the appraisal itself needs to be reviewed once a pathway has been established.

Table 3 Key topics

Topic		Additional information and questions	Response
Pathways appraisal process			
Condition specific information	**Treatment pathway**	Is there anything missing from the treatment pathway diagrams in Figure 5, Figure 6 and Figure 7?	Figure 5 - Not everyone who has a nephrectomy goes on to have adjuvant treatment. The note at the bottom of Figure 6 suggests that Unresectable Stage 3 (in the heading) is spread outside Gerota's fascia, whereas Stage 3 is usually described as spread inside Gerota's fascia. What happens to patients on active surveillance?
	Risk status	As above in Table 2	Table 2 is headed Untreated aRCC, but it refers to 2nd line treatments.

Patient expert statement

	Decision problem	The decision problem highlights everything that should be included in the cost-effectiveness analysis. Is there anything that is missing in Table 3?	
Clinical effectiveness	Literature review		
	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons		
Cost effectiveness model development	Published cost effectiveness studies		
	Expert elicitation		
Economic analysis	Model structure		
	Population		
	Treatments included		

Patient expert statement

	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
Model validation			
Benefits not captured		Is there anything that the external assessment group hasn't captured in their analysis that is important to you?	That patients across the country have equal access to all relevant treatments regardless of where they live.
Equality considerations		Do you believe there are any equality considerations to account for in our guidance?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The Treatment Appraisal is just one element in the Pathways Pilot.
- Quality of Life and Overall Survival is not just about the physical, don't forget patients' mental health.
- The importance of more effective communication with patients cannot be underestimated.
- Concerns over the quality of trial processes don't necessarily mean the results are worthless.
- Patients need consistency of treatment opportunities regardless of where they live.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Renal cell carcinoma: Pathways Pilot [ID6186]

Patient expert statement and response form

Thank you for agreeing to give us your views on the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with renal cell carcinoma or caring for a patient with renal cell carcinoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

You are also not expected to comment on every key message, again we have given guidance on the key messages that you might have insight to share, but don't worry if not.

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **22 September.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Living with this condition or caring for a patient with renal cell carcinoma

Table 1 About you, renal cell carcinoma, current treatments and equality

1. Your name	Steve Pointon
2. Are you (please tick all that apply)	☒ A patient with renal cell carcinoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with renal cell carcinoma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Action Kidney Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with renal cell carcinoma? **If you are a carer (for someone with renal cell carcinoma) please share your experience of caring for them**	Metastatic RCC is a devastating disease with currently no known cure. I was very fortunate to be accepted for high dose interleukin 2 (HD IL 2) treatment and it worked for me, but as I have found out recently that does not necessarily put you free from the condition. I have received news of a recurrence and so the fear and worries start again after 5 years. The mental side of knowing the disease cannot be cured is especially tough with a very young family. Whilst for me there has never been a period where I have been ill due to the disease, the toxicity of the treatment has left its scars many years on.
7a. What do you think of the current treatments and care available for renal cell carcinoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I think the treatments have improved over the 7 years since I have been diagnosed. However, this condition is still clearly well behind other cancer treatments and more needs to be done.
8. If there are disadvantages for patients of current NHS treatments for renal cell carcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I think the mental wellbeing of cancer patients in general is not considered enough when a diagnosis and treatment are given. Charities and patient organisations are left to pick up the pieces. This is intensified with RCC as it is a less common cancer, there is not as much peer support. The toxicity of the treatments is hard to cope with physically and mentally and can affect us as patients in many ways, from our work and therefore financial situations to everyday family life.
9a. If there are advantages of cabozantinib plus nivolumab over current treatments on the NHS please	

describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does cabozantinib plus nivolumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of cabozantinib plus nivolumab over current treatments on the NHS please describe these. For example, are there any risks with cabozantinib with nivolumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	One of the side effects of cabozantinib is loss of appetite due to dysgeusia leading to severe weight loss. We know of several patients who have experienced severe weight loss as a result of dysgeusia while taking cabozantinib for advanced/metastatic RCC.
11. Are there any groups of patients who might benefit more from cabozantinib with nivolumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering renal cell carcinoma and cabozantinib with nivolumab? Please explain if you think any groups of people with this condition are particularly disadvantaged	

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues and topics arising from external assessment report

The key issues and topics covered in the external assessment report (EAR) are listed in table 2 and table 3. We welcome your comments on these, but you do not have to provide a response to every issue or topic, such as the ones that are technical. We have flagged the issues where we consider a patient perspective may be most relevant and valuable in **bold**. If you think anything that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Key issues

	Additional information and questions	Response
Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	One of the aims of the pathway approach is to provide more information on the optimal treatment choices following initial treatment. Can you provide any information on the pathway of care you have received?	Access to systemic anti-cancer treatments in the second line and beyond is complicated and dependent on what the patient had as their first-line treatment. For example, nivolumab can only be given to patients as a second- or third-line treatment if they have not previously been treated with a PD-1 or PD-L1 inhibitor (nivolumab, pembrolizumab or avelumab), and a first line VEGFR inhibitor can be

		given to patients in the second line if they have previously been treated with nivolumab plus ipilimumab. This requires careful planning on behalf of the medical oncologist with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatment for advanced/metastatic RCC. This situation is often not adequately explained to patients before they start first-line treatment with systemic anti-cancer treatments. Lack of information prevents patients from making informed decisions about their treatment options from the outset. There are multiple treatments for advanced RCC throughout the treatment pathway. However, none of the systemic anti-cancer treatment combinations have been compared to one another resulting in a lack of information/data about comparable treatments, e.g., ipilimumab plus nivolumab has not been compared to an equivalent

		combination in the first line resulting in a lack of information/data for patients. This makes it impossible for patients to make a meaningful informed decision about their treatment options.
Key Issue 2: Company's definition of relevant comparators	Are you aware what treatments you could have received in place of the pathway of care you received?	As mentioned above, many patients are unaware of the treatment options available to them when they start first-line treatment. Informed shared decision-making with their clinician would help make patients more aware of the treatment options available to them and enable the patient and clinician to work in partnership to make the best possible decisions for the patient. Informed decision-making brings together the clinician's expertise, treatment options, evidence, risks, and benefits with the patient's individual preferences, personal circumstances, goals, values, and beliefs.

Key Issue 3: Company's definition of relevant outcomes	What outcomes are most important to you? Have any important outcomes that have been missed in the report?	The most important outcomes of treatment for both the patient, family members and carers are living for as long as possible with a good quality of life. Being able to go back to doing the things that they could do before their diagnosis, such as working, enjoying holidays, and socialising with family and friends, without the constant worry of the cancer returning or progressing. To minimise anxiety and depression resulting from a diagnosis of advanced/metastatic RCC and to improve quality of life, patients would benefit from psychosocial support following a diagnosis of kidney cancer.
Key Issue 4: Company's definition of relevant subgroups	Cabozantinib with nivolumab is indicated for patients of all risk types. The external assessment group have investigated the cost-effectiveness of cabozantinib with nivolumab in intermediate-/poor-risk and favourable-risk groups as advice to them is that NHS practice also follows these risk groups.	The choice of systemic anti-cancer treatments at first line is so complex that patients are not able to contribute to the treatment decision-making process in a meaningful way. The health technology appraisal process does not compare new first-line

	Are you aware if your treatment been informed by risk status? If so, did available treatments change due to your risk status?	treatments with existing comparable treatments (i.e., a new combination treatment compared with an existing combination treatment). Therefore, patients have no way of knowing which treatment option is best suited and most clinically effective for their personal situation. Because of the complexity of the sequencing of systemic anti-cancer treatments and the lack of comparative data, it is difficult for patients to engage in meaningful shared decision making with their clinicians.
Key Issue 5: CheckMate 9ER: Consistency of reporting		
Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice		
Key Issue 7: CheckMate 9ER: Effect modification by risk group		
Key Issue 8: Evidence base: quality and sufficiency of included randomised trials		

Patient expert statement

Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks		
Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes		
Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment		
Other issues not captured in the External Assessment Report.		

Table 3 Key topics

Topic		**Additional information and questions**	**Response**
Pathways appraisal process			
Condition specific information	**Treatment pathway**	Is there anything missing from the treatment pathway diagrams in Figure 5, Figure 6 and Figure 7?	Figure 5: A biopsy should be taken before surgery to determine malignancy, grade, and subtype of the primary tumour to inform future treatment options. For example, benign
Patient expert statement			

			tumours would be actively surveyed, whereas high grade malignant tumours would require surgery and adjuvant therapy. Young adults (<45 years) presenting with kidney cancer should have genetic screening for hereditary/familial subtypes of kidney cancer. Figures 6 and 7: We know of several patients who are on neoadjuvant treatment. We realise that this is off-label use, however we feel strongly that neoadjuvant treatment is a viable treatment option for some patients. We know of several patients who have been successfully treated with high dose interleukin 2 (HD IL 2) as part of a research programme at the Christie Hospital in Manchester. HD IL 2 used to be a treatment option for advanced/metastatic RCC before the availability of targeted

			therapies. It is an outlier, since it has marketing authorisation, but is being used off-label and does not have NICE recommendation for the treatment of advanced/metastatic RCC. Although, we feel it deserves a mention as a potential treatment option for a select group of patients. Belzutifan is currently undergoing NICE appraisal as a first-line treatment for VHL-associated RCC, with a decision expected in January 2024. If cabozantinib plus nivolumab is shown as first-line treatment for advanced RCC in figures 6 and 7 as 'appraisal in progress', surely, belzutifan should also be included in these figures as 'appraisal in progress'. Likewise, belzutifan for previously treated advanced RCC, which is also 'appraisal in progress'. Denosumab is recommended for the treatment of skeletal-related

			events in adults with bone metastases from solid tumours, including RCC [TA265]. This should this be included as a treatment option for RCC patients with bone metastases in Figures 6 and 7.
	Risk status	As above in Table 2	
	Decision problem	The decision problem highlights everything that should be included in the cost-effectiveness analysis. Is there anything that is missing in Table 3?	As already mentioned above, health related quality of life (HRQoL) is of prime importance to patients faced with a life-limiting condition, such as advanced/metastatic RCC. We feel strongly that HRQoL should be considered as one of the primary outcome measures of this treatment pathway.
Clinical effectiveness	Literature review		
	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons		

Patient expert statement

Cost effectiveness model development	Published cost effectiveness studies		
	Expert elicitation		
Economic analysis	Model structure		
	Population		
	Treatments included		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
Model validation			
Benefits not captured		Is there anything that the external assessment group hasn't captured in their analysis that is important to you?	
Equality considerations		Do you believe there are any equality considerations to account for in our guidance?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Access to systemic anti-cancer treatments in the second line and beyond is complicated and requires careful planning with respect to the ordering of drugs to get the most benefit from systemic anti-cancer treatments for advanced/metastatic RCC. This situation is often not adequately explained to patients before they start first-line treatment with systemic anti-cancer treatments.
- Informed shared decision-making with their clinician would help make patients more aware of the treatment options available to them and enable the patient and clinician to work in partnership to make the best possible decisions for the patient.
- The most important outcomes of treatment for both the patient, family members and carers are living for as long as possible with a good quality of life.
- High dose interleukin 2 is not mentioned as a potential treatment option for a select group of patients.
- Belzutifan is undergoing appraisal as a first-line treatment for VHL-associated RCC and for previously treated patients with advanced RCC. Belzutifan should be included as a potential treatment in figures 6 and 7.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Renal cell carcinoma: Pathways Pilot [ID6186]

Patient expert statement and response form

Thank you for agreeing to give us your views on the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with renal cell carcinoma or caring for a patient with renal cell carcinoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

You are also not expected to comment on every key message, again we have given guidance on the key messages that you might have insight to share, but don't worry if not.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **22 September.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with renal cell carcinoma

Table 1 About you, renal cell carcinoma, current treatments and equality

1. Your name	Sophie Scott
2. Are you (please tick all that apply)	☐ A patient with renal cell carcinoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with renal cell carcinoma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Drawing on patient's experiences ☒ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with renal cell carcinoma? **If you are a carer (for someone with renal cell carcinoma) please share your experience of caring for them**	I work as a nurse for kidney cancer UK and I speak to many patients with kidney cancer on our online support groups and telephone line and offer advice and support to them. Being diagnosed with kidney cancer can be incredibly stressful for patients and their families, and the challenges they face greatly depend on the stage of their disease. Most people with kidney cancer will receive surgery at some point, which will require a period of recovery. There will be times when the patient and family/carers will be worried about the future and require information and guidance. Waiting for news, scans and procedures can be emotionally draining. Knowledge that there are a variety of treatment options available to them will give them some comfort. Dealing with side effects of drugs can be equally exhausting as the symptoms of the cancer, so finding the balance of treatment and quality of life that is right for each patient is important. According to our last annual survey patients with kidney cancer reported feeling anxious, emotionally low, abandoned after surgery and scared about their cancer returning. Knowledge that there are a variety of treatment options available to them will give patients and their carers some hope and comfort. Patients reported having a range of symptoms from their cancer including fatigue, haematuria, depression, weight loss, anorexia, anaemia and pain which varies in severity according to the stage of their disease, which can be disabling for many and distressing for both patients and carers. This can affect their life in many ways, they may need to take regular pain medication to control their pain, many people report having less energy to carry out their activities of daily living and have needed to take time off work or take early retirement. The psychological effects of cancer are a big issue and many patients reported feeling depressed, alone and unable to cope emotionally following their diagnosis. Many patients reached out to the charity for more emotional support and counselling.

	Side effects from cancer treatment patients experience include extreme fatigue, mouth ulcers, GI disturbances, sore hands and feet, night sweats and rashes, and in severe cases some patients reported being hospitalised with colitis or pneumonitis. The side effects can be very difficult to deal with and some patients find relief when taking a temporary break from their treatment under supervision from their consultant. Many other patients report that they are able to tolerate their treatment with few side effects, and have reduced spread of disease which helps to improve their mental health and quality of life. Several patients reported that if they experienced side effects their doctor was able to titrate their dose of medication which helped to alleviate their symptoms but in some cases patients had to be taken off treatment and switched to another line of treatment. Some patients were too unwell to begin treatment and were made palliative. Other patients I spoke to were already on their last line of treatment so it was devastating for them when they were told that their treatment had failed. More new treatment options and clinical trials give these patients and their families hope. Finding the balance of treatment and quality of life that is right for each patient is vital.
7a. What do you think of the current treatments and care available for renal cell carcinoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The treatment and outcome are very much dependant on how early the kidney cancer has been caught. Ideally the tumour is of an early stage and is removed by surgery or cryotherapy and the patient enjoys a life after cancer. This would always be the preferred treatment. However, if the tumour has spread patients will rely on targeted therapies and immunotherapy treatments. Current drug treatments for kidney cancer are growing in number but still have plenty of side effects. Kidney Cancer UK feel that there are significant improvements that could be made in this area. A wider range of options with improved efficacy and fewer side effects are needed. Commonly used Tyrosine kinase inhibitors such as cabozantanib, sunitinib and pazopanib act to extend life and in some cases they work very well and extend life for many years. For others, the extension of life is a matter of months. However, those months can be invaluable for individuals and their families.

	Immunotherapy has tremendously changed the landscape and overall survival of patients with metastatic kidney cancer and now new treatments and combinations are becoming available for patients bringing hope. The introduction of nivolumab as a NICE recommended drug was well received by patients and their families. Patients have reported back on how effective this drug has been for them, especially on how it improves their quality of life. I think that having combinations of treatments may give alternate options and even better results as a first line treatment. Giving alternate treatment options for patients can be invaluable. It may be found that Nivolumab and Cabozantanib works for a set of patients where other treatments may fail. A multitude of treatment options is always desirable.
8. If there are disadvantages for patients of current NHS treatments for renal cell carcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Disadvantages of current treatments patients reported include: • Poor disease control and metastatic progression • No difference in survival rate • Side effects such as fatigue, low mood, weight loss, poor appetite, urticaria, bone pain, elevated liver enzymes, and in rarer cases colitis and pneumonitis as reported by patients • The patients may have to travel far to the hospital to receive their treatment • Difficulties in taking or using the treatment (for example, receiving IV medication) • Difficult for carers watching loved ones suffer from side effects of the treatment
9a. If there are advantages of cabozantinib plus nivolumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	Potential advantages of the treatment: • Better disease control with no metastatic progression • Prolonged survival rate • Reduction in cancer pain and other cancer symptoms • Improvement in their mental health knowing that their treatment is working • Quality of life- living longer and having more time with family and friends • Family and friends feel reassured that their loved one's treatment is working • Patients felt more in control of their lives on treatment

9c. Does cabozantinib plus nivolumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of cabozantinib plus nivolumab over current treatments on the NHS please describe these. For example, are there any risks with cabozantinib with nivolumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Patients reported that they were worried about potential side effects such as adrenal insufficiency, thyroid problems, extreme fatigue or extreme reactions requiring hospitalisation or stopping the medication.
11. Are there any groups of patients who might benefit more from cabozantinib with nivolumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with advanced (stage 3 or 4) disease are likely to require medication to extend their life. People who have failed prior systemic treatment are likely to need another treatment option, which introducing cabozantanib and Nivolumab will provide.
12. Are there any potential equality issues that should be taken into account when considering renal cell carcinoma and cabozantinib with nivolumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	Elderly patients may face difficulties in accessing healthcare due to frailty and reliance on carers to assist them and may struggle to travel to hospital for regular Nivolumab infusions. Patients with disabilities may require additional support during their treatment for kidney cancer. They may require accessible formats of information regarding their treatments and people with dementia and learning difficulties may require extra support to understand their treatment options. Advocates, family members and carers may be needed to support their decision making on their behalf where legally allowed. Patients with limited English proficiency may have barriers to accessing treatments and need support with translation.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	People from lower income families may find it harder to take time off work to travel to appointments for infusions. Treatments would be delayed in women who were pregnant. Most systemic anticancer drugs would mean breastfeeding would need to be avoided.
13. Are there any other issues that you would like the committee to consider?	N/A

Part 2: Technical engagement questions for patient experts

Issues and topics arising from external assessment report

The key issues and topics covered in the external assessment report (EAR) are listed in table 2 and table 3. We welcome your comments on these, but you do not have to provide a response to every issue or topic, such as the ones that are technical. We have flagged the issues where we consider a patient perspective may be most relevant and valuable in **bold**. If you think anything that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Key issues

	Additional information and questions	Response
Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	One of the aims of the pathway approach is to provide more information on the optimal treatment choices following initial treatment. Can you provide any information on the pathway of care you have received?	
Key Issue 2: Company's definition of relevant comparators	Are you aware what treatments you could have received in place of the pathway of care you received?	
Key Issue 3: Company's definition of relevant outcomes	What outcomes are most important to you? Have any important outcomes that have been missed in the report?	Equal access to treatments and care for all patients in a quicker time frame.

Patient expert statement

Key Issue 4: Company's definition of relevant subgroups	Cabozatinib with nivolumab is indicated for patients of all risk types. The external assessment group have investigated the cost-effectiveness of cabozantinib with nivolumab in intermediate-/poor-risk and favourable-risk groups as advice to them is that NHS practice also follows these risk groups. Are you aware if your treatment been informed by risk status? If so, did available treatments change due to your risk status?	It is great that the appraised treatment will be offered to all patients irregardless of their risk type. Many patients I spoke to did have available treatments changed due to their risk status.
Key Issue 5: CheckMate 9ER: Consistency of reporting		
Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice		
Key Issue 7: CheckMate 9ER: Effect modification by risk group		
Key Issue 8: Evidence base: quality and sufficiency of included randomised trials		
Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks		
Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes		

Patient expert statement

Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment		
Other issues not captured in the External Assessment Report.		

Table 3 Key topics

Topic		**Additional information and questions**	**Response**
Pathways appraisal process			
Condition specific information	**Treatment pathway**	Is there anything missing from the treatment pathway diagrams in Figure 5, Figure 6 and Figure 7?	
	Risk status	As above in Table 2	
	Decision problem	The decision problem highlights everything that should be included in the cost-effectiveness analysis. Is there anything that is missing in Table 3?	
Clinical effectiveness	Literature review		
	Clinical input		
	Critique of included studies		

Patient expert statement

	Indirect treatment comparisons		
Cost effectiveness model development	Published cost effectiveness studies		
	Expert elicitation		
Economic analysis	Model structure		
	Population		
	Treatments included		
	Adverse events		
	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
Model validation			
Benefits not captured		Is there anything that the external assessment group hasn't captured in their analysis that is important to you?	
Equality considerations		Do you believe there are any equality considerations to account for in our guidance?	All patients require equal access to health care, regardless of their age, socio economic background, if they have disabilities or language barriers.

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Focusing on streamlined care, equal access for all patients
- Faster waiting times for treatments and procedures
- Better communication between health professionals and patients
- New treatment options bringing hope
- Tackling inequalities in healthcare

Thank you for your time.

Your privacy

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Stakeholder response form

Treatments for renal cell carcinoma [ID6186]

As a stakeholder you have been invited to comment on the data and analysis included in the external assessment group (EAG) model and Final Assessment Report for the renal cell carcinoma pathway and the treatment cabozantinib with nivolumab and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. The EAG's reports and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting on both the pathway and specific technologies being evaluated.

Information on completing this form

We are asking for your views on data and assumptions included within the analysis model and used to form the final report that are likely to be discussed by the committee. The report provides a summary of work undertaken by the EAG developing the analysis and incorporating the data received from manufacturers, observational patient datasets and formal input from clinical experts. It outlines the analysis plan, methods used for the evaluation, as well as all identified relevant published evidence and real-world evidence (RWE) sources.

You are not expected to comment on every key topic but instead comment on the issues that are in your area of expertise.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by 5pm Friday 22 September. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during consultation, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during consultation are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Dr BALAJI VENUGOPAL
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil from tobacco industry**

NICE National Institute for Health and Care Excellence

Stakeholder comments on the EAG report for the appraisal of treatments for renal cell carcinoma

All: Please use table 2 below to respond to the key clinical and economic issues raised by the EAG.

Table 2: key issues

Issue		Response	Does this response contain new evidence, data or analyses?
Clinical evidence	Key Issue 1: Optimal sequencing of treatments, including after novel first-line treatments	This is a pauci-evidence domain where the practice is driven by consensus and guidelines rather than robust randomised clinical trials. I would agree with EAG's conclusion that this is an area of uncertainty.	No
	Key Issue 2: Company's definition of relevant comparators	It is appropriate to include avelumab plus axitinib as a comparator as this is a standard practice in NHS England, and this provides a comparison against similar technology i.e., comparing different combinations of i/o-tki.	No
	Key Issue 3: Company's definition of relevant outcomes	Time to next treatment is not, in my opinion, reliable clinical outcome as, with the availability of subsequent lines of therapy, and the known attrition when patients move between lines of therapy, clinicians do not treat patients beyond disease progression.	No
	Key Issue 4: Company's definition of relevant subgroups	Checkmate 9ER included mRCC patients with all risk groups and the distribution of the same largely aligns with the real-world evidence. As the study was not powered a priori to show	No

		differential response in these risk group and since this was an intention to treat analysis, I would support the option of using cabozantinib plus nivolumab in all risk groups.	
	Key Issue 5: CheckMate 9ER: Consistency of reporting	No additional comments. Agree with EAG position.	No
	Key Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice	The trial population is very much generalisable to the U.K population notwithstanding the minimal representation of U.K patients in the checkmate 9ER study. This minimal representation could have been due to the other competing industry sponsored trials that were ongoing (CLEAR/JAVELIN101) during the time of active enrolment. The demographics and patients' predisposition in Checkmate 9ER largely aligns with the real-world population with the caveats that all these pivotal trials exclude patients with non-clear cell histology and brain metastases. Whilst there is no clear data on patients with post progression treatment in real life, on my personal experience and from peer-peer discussion, I am unable to relate to the figures in Checkmate 9ER. The lower use of nivolumab in sunitinib treated patients could be attributed to the larger proportion of patients (in both arms) who were treated beyond disease progression.	No
	Key Issue 7: CheckMate 9ER: Effect modification by risk group	As per my response to key issue 4.	No
	Key Issue 8: Evidence base: quality and sufficiency of included randomised trials	This is a limitation of the available evidence base as most of the newer combination drugs are based on single but large randomised control trial. EAG has captured all the available RCT data here.	No

	Key Issue 9: Evidence base: distribution of effect modifiers across evidence networks	The inter trial heterogeneity of patient characteristics makes it harder for any meaningful analyses. Whilst certain variables like present of sarcomatoid features, prior nephrectomy is accepted as a prognostic variable, I am unable to comment on the cost effectiveness analyses of these variable.	
	Key Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes	On the basis of the OS updates of other TKI-I/O based trials namely Keynote 426 (although this was not reviwed by EAG) and CLEAR trials, it is evident that there is convergence of survival curves in KM plot. It is therefore plausible that with longer follow up, there could be reduction in the magnitude of benefit in OS that is demonstrated with cabozantinib plus nivolumab.	
	Key Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment	Yes, these are unmet needs in such that all the pivotal trials include clear cell histology alone. However cabozantinib as a multitargeted tyrosine kinase inhibitor that has demonstrated meaningful clinical benefit in non-clear cell histology as a monotherapy in 2nd line and beyond therapy, and accepted in international guidelines, could be expected to have similar if not enhanced benefit in combination with nivolumab. The question of SACT for mRCC post failure of adjuvant treatment is an evidence free domain. It is likely that patients will still be given i/o in mRCC even if they had received adjuvant i/o and this would depend on the disease free interval.	
Cost evidence (key issues in the Economic Results	Key Issue 1: Inconsistency between prior appraisals	I am not an expert in cost effectiveness analyses and therefore not able to comment on this section.	
	Key Issue 2: Economic implications of trial generalisability to real-world evidence		

Addendum document)	Key Issue 3: Maturing data relating to immune-oncology (IO)/ Tyrosine Kinase Inhibitor (TKI) combinations have magnified uncertainties relating to their long-term effectiveness		
	Key Issue 4: Impact of Relative Dosing Intensity (RDI) and toxicity on economic case		
	Key Issue 5: Problems with the health-related quality of life data supplied by the company		
	Key Issue 6: Outstanding uncertainties in application of severity modifiers		
	Key Issue 7: Impact of model structure on results		

	Key Issue 8: Subgroups in the context of changing comparators		
	Key Issue 9: Dominance of cabozantinib in the intermediate/poor risk population		

All: Please use table 3 to add any further responses to topics raised in any other sections of the EAG report. In particular, please consider the questions at the end of the table asking whether the value of cabozantinib + nivolumab has been captured appropriately, and whether there are any key scenarios that you would like to see.

Table 3: other topics raised in EAG report

Topic		Response	EAG response
Clinical effectiveness	Literature review	This is comprehensive	
	Clinical input		
	Critique of included studies		
	Indirect treatment comparisons		
	Critique of		

	outputs considered		
Cost effectiveness model development	Published cost effectiveness studies	I am not an expert in cost effectiveness analyses and therefore not able to comment on this section.	
	Critique of outputs included in clinical review		
	Critique of real-world evidence		
	Indirect comparisons		
	Expert elicitation		
Economic analysis	Model structure	I am not an expert in cost effectiveness analyses and therefore not able to comment on this section.	
	Population		
	Treatments included		
	Perspective, time horizon, cycle length, discounting and price year		
	Treatment effectiveness and extrapolation		
	Adverse events		

	Utility values		
	Resource use and costs		
	Severity		
	Uncertainty		
	Model validation		
Are there any scenarios that you would like to see?			
Has the value of cabozantinib + nivolumab been captured appropriately?			
Are there any benefits not captured in the model?			
Are there any equality considerations?			
Other notes			

Treatments for renal cell carcinoma [ID6186]

A Pathways Pilot Appraisal

EAG Review of Company's Response to Technical Engagement

Produced by

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None, however, Professor Larkin also provided clinical input to NICE during the scoping stages of the appraisal.

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Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This TE response is linked to EAG report

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All CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all AIC (academic in confidence) data is highlighted in yellow and underlined, all [redacted] is highlighted in green and underlined

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List of abbreviations

Acronym	Definition
1L / 2L / 3L / 4L	1st line / 2nd line / 3rd line / 4th line
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
AIC	Akaike information criterion
AUC	area under the curve
BNF	British National Formulary
BSC	Best supportive care
cabo	cabozantinib
CDF	Cancer Drugs Fund
CI	Confidence interval
DSU	Decision Support Unit
EAG	External assessment group
ECOG PS	Eastern Cooperative Oncology Group performance status
eMIT	Electronic market information tool
FP	Fractional polynomials
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IMDC	International Metastatic RCC Database Consortium
IO	Immuno-oncology
ipi	ipilimumab
KM	Kaplan Meier
lenv	lenvatinib
LY	life years
LYG	life years gained
MIMS	Monthly Index of Medical Specialties
MRC	Medical Research Council
MTA	Multiple technology appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nivo	nivolumab
NMA	Network meta-analysis

ORR	Overall response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
pazo	pazopanib
PD	Progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
pem	pembrolizumab
PFS	Progression free survival
PH	Proportional hazards
PPS	Post progression survival
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QC	Quality control
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dosing intensity
RWE	Real-world evidence
SE	Standard error
SEE	structured expert elicitation
STA	Single technology appraisal
STM	state transition model
suni	sunitinib
TA	Technology appraisal
tivo	tivozanib
TKI	Tyrosine kinase inhibitor
TSD	Technical support document
TTD	Time to treatment discontinuation
TTP	Time to progression
TTNT	Time to next treatment
UK	United Kingdom

1. INTRODUCTION

This document provides the External Assessment Group's (EAG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of treatments for renal cell carcinoma (RCC) [ID6186].

ID6186 is the first pilot topic for NICE's 'pathways' process to increase the efficiency of some of its assessments of clinical and cost-effectiveness for reimbursement decisions on the NHS in England and Wales. This pilot is designed to address a broader decision problem than is considered within a standard Single Technology Appraisal (STA). The platform model to be developed encompasses all stages of the treatment pathway for RCC, including all treatments within the treatment pathway for 1st and subsequent line systemic treatment. Within the pilot and summarised in this report, the EAG appraised the clinical and cost effectiveness of one new treatment: cabozantinib + nivolumab for untreated advanced or metastatic RCC.

The objectives of this specific analysis were to estimate the costs, effects and cost-effectiveness of:

- cabozantinib + nivolumab vs pazopanib vs tivozanib vs sunitinib as 1st line systemic therapy in people with untreated advanced or metastatic RCC with International mRCC Database Consortium (IMDC)-defined all-risk disease.
- cabozantinib + nivolumab vs pazopanib vs tivozanib vs sunitinib as 1st line systemic therapy in people with untreated advanced or metastatic RCC with IMDC-defined favourable-risk disease.
- cabozantinib + nivolumab vs pazopanib vs tivozanib vs sunitinib vs cabozantinib vs nivolumab+ ipilimumab vs pembrolizumab + lenvatinib as 1st line systemic therapy in people with untreated advanced or metastatic RCC with IMDC-defined intermediate- or poor-risk disease.

This is in addition to analyses of existing 2nd-line treatment options, and future planned work on treatment sequences.

The evidence package available to address the decision problem includes:

- The CheckMate 9ER trial for cabozantinib + nivolumab versus sunitinib, a single-blind parallel group, randomised controlled trial (RCT) of cabozantinib + nivolumab comparing cabozantinib + nivolumab (n=323) against sunitinib (n=328) with median follow-up of 44 months at the time of reporting
- 23 additional RCTs of treatments for RCC across all lines of treatment. Sample sizes varied between 22 and 1,110 participants.

- A total of four databases, 12 publications and five stakeholder submissions which provided information on relevant real-world evidence sources. Data extracted included treatment patterns, overall survival (OS), progression free survival (PFS), time to next treatment (TTNT) and discontinuation. This included the EAG obtaining access to a large, recent, representative and rich database of United Kingdom (UK) real-world evidence (RWE) (n=1,319)
- A structured expert elicitation exercise to provide additional information on expected longer-term PFS for the treatments used in practice.

This evidence package is considerably richer than considered in a typical STA, or even a multiple technology appraisal (MTA), and thus access to a rich source of real-world evidence is seen by the EAG as a key strength of this appraisal.

Each of the issues outlined in the EAG assessment report are discussed in further detail in Sections 1 (decision problem), Section 4 (clinical effectiveness evidence) and Section 5 (economic evidence).

In response to the technical engagement report, the company presented updated analyses for their and comparators relative dosing intensity (RDI), the EAG conducted their internal quality control (QC) checks, the DSU's external quality control comments were received, comments were received from a number of stakeholders (Ipsen, BMS, MSD, Eisai, Action Kidney Cancer, Kidney Cancer UK and two individual patients), finally comments were received from the NICE lead team.

The additional information provided by the company led to an updated base case which was included in the information sent to other stakeholders in August 2023 along with correction of issues identified during the EAG QC. This is presented in Section 2.

2. UPDATED EAG BASE CASE ANALYSES

2.1. Changes made following the first round of technical engagement

After receipt of initial company comments and conduct of internal QC the EAG made a number of updates to its base case analysis. These are detailed below.

2.1.1. Network-meta analysis

The EAG updated its fractional polynomial (FP) network meta-analysis (NMA) for OS in the all-risk outcome to include updated data for CLEAR, in which intermediate and poor risk group data had previously been included. Analyses have been corrected in the report, with amendments to model diagnostics and plots. This did not meaningfully impact interpretation of results.

2.1.2. Economic analysis

The EAG further updated its NMA of discontinuation due to adverse events (AEs) in response to the company's comments, including updating data for the CLEAR trial. This also did not meaningfully impact interpretation of results.

The key changes made to the Excel inputs file that had tangible impact on the model results/interpretation are as follows:

1. 'Effectiveness settings' sheet:
    i. 4th line pooled post-progression survival (PPS) survival curve selection based on RWE in the base case (Columns DK and DL) was corrected to Log-normal (previously it was Exponential)
    ii. Hazard ratios (HRs) for prior adjuvant impact were added (Cells I384:J397).
    iii. Axitinib 2nd line and 3rd line effectiveness source was updated to "PH_NMA" instead of "FP_NMA" (Columns FX, FY and FZ)
    iv. Amended formulae for cabozanitinib + nivolumab and pembrolizumab + lenvatinib survival outcomes for scenario analysis following QC check (Columns FY and GC)
2. "Treatment sequence" sheet (Columns DJ: DQ): Calculations were updated to consider the RDI values (previously RDI values were not included in the calculation). Also, corrections were made in the formula to look up correct RDI adjusted subsequent drug and admin costs for lenvatinib + everolimus, everolimus, axitinib, cabozantinib and tivozanib (previously the costs were either zero or not the respective costs for these treatments). These calculations are used in the partitioned survival analysis (PartSA) only.

3. “Scenario controls” sheet (the following new scenarios were added to the existing list of scenarios):
    i. Time on treatment data taken from time to treatment discontinuation (TTD) equal to PFS, PartSA
    ii. PartSA analysis with efficacy using the proportional hazards (PH) NMA
    iii. Apply all alternative RDI (state transition and PartSA)
    iv. Apply alternative RDI for immune-oncology (IO) combinations (state transition and PartSA)
    v. CheckMate 9ER for all lines (PartSA)
    vi. CheckMate 9ER for all lines with no age adjustment (state transition and PartSA)
    vii. Time horizon = five years (state transition and PartSA)
    viii. Time horizon = 10 years (state transition and PartSA)
    ix. Time horizon = 20 years (state transition and PartSA)

The following changes were made to the existing scenarios:

    i. Discount rate applied to quality adjusted life years (QALYs) (previously it was only applied to costs)
    ii. Trial-based analyses (state transition and PartSA): “dd_cabo_nivo_outcome_from” dropdown value was changed to Trial survival analysis from FP_NMA and an error in the formula in Column FY of the “Effectiveness settings” sheet was corrected.
    iii. Double AE impact and Assume AE impact of axitinib same as tivozanib: changes were made in the “Safety parameters” sheet and the “Utilities” sheet for the scenario settings to feed into calculations (previously the scenario settings were not feeding into the calculations and in turn into the R model).

Other minor changes which had little or no impact on the model results:

4. ‘Patient characteristics’ sheet: 3rd line and 4th line mean age values were updated for RWE data and 4th line mean age values and 3rd line/ 4th line standard error (SE) values for starting % female was updated for trial data. In additions, sources/assumptions were also updated to reflect the changes.
5. “Resource use and costs” sheet: lenvatinib cost as part of pembrolizumab + lenvatinib combination was corrected (however, this did not have any impact on the results as it was not feeding into the calculations and in turn to the R model). Also, the drug costs weighted by RDI values to feed into the treatment sequence calculations were added (Cells CJ10:CO49) and the RDI values for the additional scenarios have also been added to this sheet (Cells DG11:DL82).
6. Macros added: Restore default base case values, Apply scenario settings for each scenario.

The changes made to the R model were:

- Incorporation of functionality for probabilistic analysis.
- Incorporation of functionality to run scenarios around the impact of adjuvant treatment on effectiveness.
- Incorporation of functionality to automate model reporting into Word.
- Amendment to the code to process the transitions for the state transition matrix following issues spotted during quality control.
- Amendment to the code to allow different lengths of time horizon to be handled for scenario analysis.
- Amendment to the code to allow the use of cabozantinib as reference treatment in 3rd line for the FP NMA for scenario analysis.

2.2. Changes made following the second round of technical engagement

Following the second round of technical engagement five changes were made to the EAGs economic analysis:

- Cabozantinib was included as an allowed 2nd line treatment after nivolumab plus ipilimumab in response to company clarification questions
- The application of the dosing of lenvatinib was amended to better reflect clinical practice following additional clinical consultation (see Section 6.3.8)
- Following provision of additional details relating to the new RDI information supplied by the company this was incorporated into the EAG base case (see Economic Key Issue 4)
- The application of the hazard ratio for nivo+ipi TTD relative to PFS used in Scenario 20 was corrected in response to company clarification questions
- Scenario analysis has been presented using TTNT as a proxy for PFS within CheckMate 214 in order to explore the issue around poor surrogacy between PFS and OS for nivo+ipi – this is described in Appendix B
- Added a switch to allow the costs and QALY impact of 3rd and 4th line treatments to be removed from the PartSA and within this fixed a minor issue with the lookups for AE costs and QALY impacts from subsequent therapies

No issues were flagged by the NICE DSU during their external QC which impacted on the calculated ICERs.

All new analyses were run probabilistically given the small amount of time available to the EAG to run new scenarios and the previous analyses demonstrating that the probabilistic and deterministic base case results were similar.

2.3. Updated EAG base case

Table 1 provides the updated EAG base case list price base case results, both as fully incremental analysis and as pairwise analysis. The results presented are deterministic as previous probabilistic analysis using the lambda approximation method to reduce the run speed showed consistent results with the deterministic analysis using the lambda approximation method (see Appendix R of the main EAG report).

As would be expected the life years (LYs) and QALYs for the three tyrosine kinase inhibitor (TKI) monotherapies remain similar (these are set to have the same 1st line effectiveness in the model base case). The results differ slightly as the types of 2nd line therapies used differ across the treatments in line with the UK RWE and the AE impacts also differ across treatments. In all risk groups tivozanib was the least effective of the three TKI monotherapies with sunitinib being the most effective.

The majority of the time spent in state for all treatments is still in 1st and 2nd line. For example, in the all-risk population 83% of time in state is spent in 1st and 2nd line for cabozantinib + nivolumab and 69% is spent in 1st and 2nd line for pazopanib with 17% spent in 3rd line and 12% spent in best supportive care (BSC).

There is little change in the ICERs in the all-risk and favourable risk populations (the only change relevant to this being the updated RDI for cabozantinib as part of the combination supplied by the company). In the intermediate / poor risk population larger changes can be ssen firstly in the life years predicted for nivolumab plus ipilimumab (increase from 2.09 to 2.44 life years following the allowance of cabozantinib as a 2nd line treatment) and in the cost associated with pembrolizumab plus lenvatinib (increase from £185,897 at list price to £229,649 at list price driven by the new information gathered by the EAG around the dosing of this treatment).; there is also a minor reduction in the cost associated with cabozantinib plus nivolumab based upon the updated RDI for cabozantinib as part of the combination supplied by the company.

The conclusions from the analysis in the all-risk and favourable risk populations remain the same: cabozantinib plus nivolumab is not cost-effective at list price.

In the intermediate / poor risk population cabozantinib plus nivolumab is dominated by cabozantinib monotherapy. This is driven by the unexpectedly good performance of cabozantinib observed relative to sunitinib in the CABOSUN trial raised previously by the EAG

in Economic Key Issue 9. Neither pembrolizumab plus lenvatinib nor nivolumab plus ipilimumab are cost-effective in comparison to cabozantinib monotherapy and other TKIs which aligns with the conclusion of TA858. Sunitinib monotherapy is the most cost-effective treatment at list price when considering a £30,000 per QALY threshold.

When comparing to the two other novel combinations cabozantinib plus nivolumab is less effective and less expective than pembrolizumab plus lenvatinib (SW quadrant ICER of £110,498). This is by the higher effectiveness of pembrolizumab plus lenvatinib predicted from the proportional hazards NMA (HR = 0.767 (0.562,1.049) vs cabozantinib plus nivolumab) and the increased cost associated with reduced doses of pembrolizumab plus lenvatinib relative to cabozantinib plus nivolumab due to lenvatinib pills being priced at the same cost rather than reduced linearly with the reduced dosing; it is acknowledged that due to redacting of the PFS Kaplan Meier for pembrolizumab plus lenvatinib the EAGs analysis had to use the PH NMA for this treatment which likely biases towards pembrolizumab plus lenvatinib.

In the intermediate / poor risk population qualification for the severity modifier remains dependent on which treatment is considered representative of current practice with a modifier of 1.2 applying versus sunitinib, pazopanib and tivozanib but not the other more recent treatment options.

In the all- and favourable risk populations the severity modifier does not apply regardless of the comparator. As within the previous report the QALY shortfall-related modifier has not been directly incorporated within the calculations provided given the uncertainty around which, if any, modifier to apply. A modifier of 1.2 equates to a willingness to pay threshold of £24,000 - £36,000 using the standard NICE thresholds.

Appendix D presents the detailed breakdown for the PartSA results using the EAG base case settings at list price. Focusing on the QALY gains the three novel therapies have relatively similar predicted QALY gains in the base case (1.86 for nivo+ipi, 1.91 for cabo+nivo, 1.96 for pem+lenv) with results being similar to the previous EAG base case (the only minor amendment being in the QALYs associated with adverse events for subsequent treatments).

Table 2 to Table 4 present scenario analysis for each of the risk populations. Results in the all-risk and favourable risk populations are broadly consistent with the previous EAG analysis in that cabo+nivo is not cost-effective at list price compared to TKI monotherapies and when the

PartSA model is used is less effective than TKI monotherapies in the favourable risk population due to the OS HR in CheckMate 9ER being > 1.

Notable results include:

- Nivo+ipi dominates nivo+cabo in the intermediate / poor risk population when trial data is used in the PartSA model
- When the PH NMA is used within the state transition structure the most effective treatment in the intermediate / poor risk population is pem+lenv (2.23 QALYs) followed by cabo+nivo (2.16 QALYs) and then followed by nivo+ipi (1.82 QALYs)
- When the PH NMA is used within the PartSA structure the most effective treatment in the intermediate / poor risk population is cabo+nivo (2.17 QALYs) followed by nivo+ipi (2.09 QALYs) and then pem+lenv (1.96 QALYs)
- When TTNT is used instead of PFS from CheckMate 214 within the FP NMA nivo+ipi remains predicted to be of lower effectiveness than cabo+nivo; this is due to the hazard ratio predicted being higher in the first year (Figure 10) during which time a large number of events have already occurred within the sunitinib RWE reference curve
- If all RDIs are set to 100% the costs associated with cabozantinib plus nivolumab substantially increase and at list price it is dominated by pem+lenv

The difference in ordering of the treatments when the PH NMA is used across the two different structures should be interpreted with the following caveats:

- The base case state transition structure likely underestimates the effectiveness of nivo+ipi due to poor surrogacy between PFS and OS
- The PH NMA likely overestimates the effectiveness of both IO+TKI combinations as it does not account for slippage in the HRs seen in the data; this is not fully mitigated by assumptions applied for TE waning as hazards are expected to cross in the long-term between IO+TKI combinations and TKI monotherapy
- The FP NMA results for pem+lenv are not considered reliable due to a combination of redaction of Kaplan Meier data in TA858, meaning that ITT data had to be used, and lack of events in the placebo arm in the initial part of the CLEAR trial (both PFS and OS) making it difficult for the fractional polynomial method to produce a plausible output; for the reasons noted in the bullet above the base case (using the FP NMA for all other treatments and the PH NMA for pem+lenv) is likely to bias in favour of pem+lenv

The Committee should pay particular attention to analyses around the RDIs included in the model. The EAG base case includes RDIs provided by the company for cabozantinib which are likely to somewhat underestimate the cost of this combination as although the EAG model costs treatment per pack rather than per pill the information presented assumes that all patients come

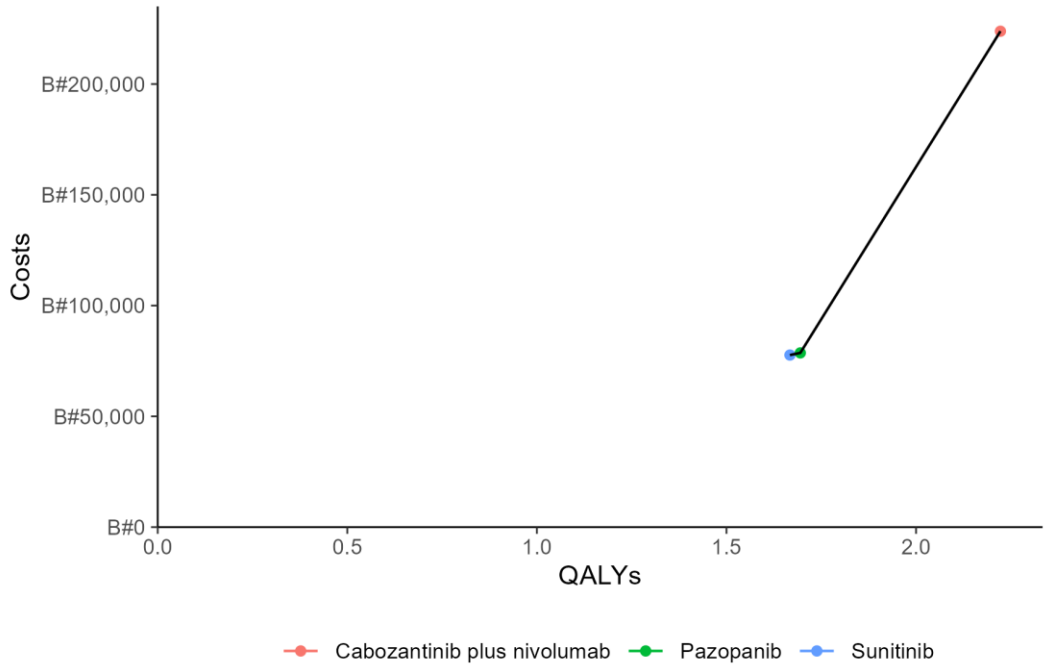
off treatment in the CheckMate 9ER trial due to either progression or unacceptable toxicity. This is not the case, as some patients were observed to discontinue for other reasons (e.g. participant request, participant withdrawing consent).

Table 1: Updated EAG base case (list price)

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER cabo + nivo vs comparator	ICER incremental	Severity modifier
Risk population: All-risk									
Suni	£77,675	2.78	1.67	-	-	-	£263,297	-	1
Pazo	£78,649	2.84	1.69	£974	0.06	0.03	£275,106	£35,580	1
Tivo	£98,517	2.76	1.66				£223,701	(dominated)	1
Cab+nivo	£223,847	3.71	2.22	£145,198	0.88	0.53		£275,106	-
Risk population: Favourable risk									
Suni	£83,420	3.68	2.20	-	-	-	£358,676	-	1
Pazo	£84,321	3.73	2.23	£900	0.06	0.03	£379,222	£32,471	1
Tivo	£115,279	3.66	2.19				£287,383	(dominated)	1
Cabo+nivo	£251,276	4.52	2.67	£166,955	0.78	0.44		£379,222	-
Risk population: Intermediate / poor risk									
Suni	£75,069	2.45	1.46	-	-	-	£237,872	-	1.2
Pazo	£76,064	2.50	1.49	£995	0.05	0.03	£248,380	£36,780	1.2
Tivo	£91,528	2.43	1.45				£205,798	(dominated)	1.2
Nivo+ipi	£137,774	2.44	1.46				£123,562	(dominated)	1
Cabo	£158,308	3.46	2.07	£82,243	0.96	0.59	Cabo+nivo dominated	£140,523	1
Cabo+nivo	£204,721	3.36	2.00					(dominated)	-
Pem+lenv	£229,649	3.62	2.23	£71,341	0.15	0.16	SW quadrant £110,498	£450,638	1

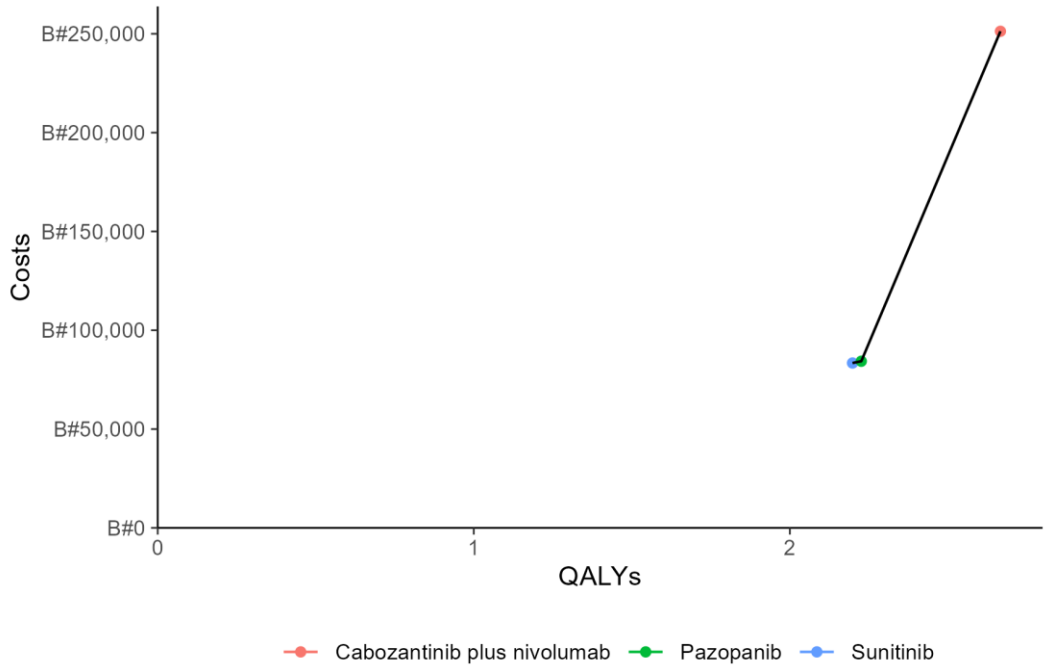
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year

Figure 1: Cost-effectiveness acceptability frontier – all-risk



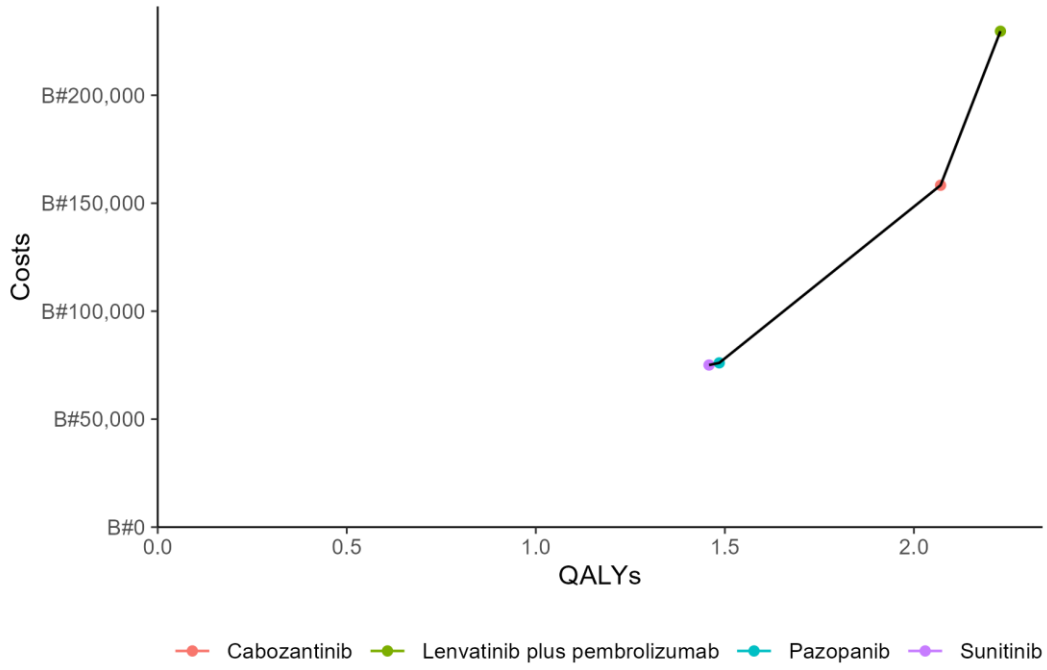
Abbreviations: QALYs, quality-adjusted life-years

Figure 2: Cost-effectiveness acceptability frontier – favourable risk



Abbreviations: QALYs, quality-adjusted life-years

Figure 3: Cost-effectiveness acceptability frontier – intermediate / poor risk



Abbreviations: QALYs, quality-adjusted life-years

2.3.1. Scenario analyses

Table 2: Scenario analyses (All-risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				Pazo	£145,198	0.528	£275,106
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Suni	£142,265	0.319	£445,511
		3	State transition 2 lines	Pazo	£159,026	0.695	£228,912
Primary data source							
Data source for baseline risk and patient characteristics	UK RWE, state transition model	6	Trial-based analyses, state transition model	Suni	£153,199	0.431	£355,214
	UK RWE, state transition model	7	Trial-based analyses, PartSA	Pazo	£148,612	0.286	£519,752
Effectiveness							
Preferred 1st line NMA	FP NMA	11	PH NMA	Pazo	£150,768	0.656	£229,908
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Suni	£148,284	0.535	£277,106
Preferred NMA for pem+lenv	PH NMA	13	FP NMA	Pazo	£145,198	0.528	£275,106
Surrogate outcome for nivo+ipi	PFS	73	Using TTNT data as a proxy for PFS for nivo+ipi	Pazo	£145,198	0.528	£275,106

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Surrogate outcome for nivo+ipi	PFS	74	Using TTNT data as a proxy for PFS for nivo+ipi, PH NMA	Pazo	£150,768	0.656	£229,908
TTD data source	TTD	18	TTD equal to PFS	Pazo	£149,924	0.515	£290,923
	Relative effectiveness for nivo + ipi from PFS consistent with other treatments	20	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	Pazo	£145,198	0.528	£275,106
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints, based on hazards	24	Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	Pazo	£144,690	0.519	£278,645
		26	No treatment effect waning	Pazo	£144,630	0.518	£279,065
Suni RWE 1L PFS	Log-logistic	29	Weibull	Pazo	£139,299	0.404	£345,056
Impact of prior TKI treatment	Not considered	76	Exploratory analysis HR1.59 applied to TKI after TKI monotherapy	Pazo	£129,002	0.609	£211,852
Costs/RDI							
RDI	Applied	41	All RDI set to 100%	Pazo	£178,604	0.528	£338,401
Lenv dosing within pem+lenv	TA858 & RDI data	75	NHSE input	Pazo	£145,198	0.528	£275,106
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same	50	CheckMate 9ER for all lines	Pazo	£145,198	0.549	£264,436

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	proportional decrease for 3L and 4L						
Adverse events							
Data source used for AEs	NMA	58	Individual trials	Pazo	£144,383	0.548	£263,634

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

*Next best comparator defined as next most efficient non-dominated comparator.

Table 3: Scenario analyses (Favourable risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				Pazo	£166,955	0.440	£379,222
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Tivo	-	-	Cabo+nivo dominated
		3	State transition 2 lines	Pazo	£181,255	0.612	£296,395
Primary data source							
Data source for baseline risk and patient characteristics	UK RWE, state transition model	6	Trial-based analyses, state transition model	Suni	£177,707	0.315	£564,209

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	UK RWE, state transition model	7	Trial-based analyses, PartSA	Tivo	-	-	Cabo+nivo dominated
Effectiveness							
Preferred 1st line NMA	FP NMA	11	PH NMA	Pazo	£166,955	0.440	£379,222
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Tivo	-	-	Cabo+nivo dominated
Preferred NMA for pem+lenv	PH NMA	13	FP NMA	Pazo	£166,955	0.440	£379,222
Surrogate outcome for nivo+ipi	PFS	73	Using TTNT data as a proxy for PFS for nivo+ipi	Pazo	£166,955	0.440	£379,222
Surrogate outcome for nivo+ipi	PFS	74	Using TTNT data as a proxy for PFS for nivo+ipi, PH NMA	Pazo	£166,955	0.440	£379,222
TTD data source	TTD	18	TTD equal to PFS	Pazo	£175,480	0.430	£408,325
	Relative effectiveness for nivo + ipi from PFS consistent with other treatments	20	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	Pazo	£166,955	0.440	£379,222
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints, based on hazards	24	Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	Pazo	£166,955	0.440	£379,222
		26	No treatment effect waning	Pazo	£166,955	0.440	£379,222

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Suni RWE 1L PFS	Log-logistic	29	Weibull	Pazo	£166,961	0.441	£378,766
Impact of prior TKI treatment	Not considered	76	Exploratory analysis HR1.59 applied to TKI after TKI monotherapy	Pazo	£139,731	0.523	£267,397
Costs/RDI							
RDI	Applied	41	All RDI set to 100%	Pazo	£209,776	0.440	£476,487
Lenv dosing within pem+lenv	TA858 & RDI data	75	NHSE input	Pazo	£166,955	0.440	£379,222
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	50	CheckMate 9ER for all lines	Pazo	£166,955	0.456	£366,224
Adverse events							
Data source used for AEs	NMA	58	Individual trials	Pazo	£166,148	0.460	£361,257

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

*Next best comparator defined as next most efficient non-dominated comparator.

Table 4: Scenario analyses (Intermediate / poor risk)

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case				Cabo	-	-	Cabo+nivo dominated
Model structure							
Overall structure	State transition 4 lines	1	PartSA 4 lines	Nivo+ipi	-	-	Cabo+nivo extendedly dominated
		3	State transition 2 lines	Cabo	-	-	Cabo+nivo dominated
Primary data source							
Data source for baseline risk and patient characteristics	UK RWE, state transition model	6	Trial-based analyses, state transition model	Cabo	-	-	Cabo+nivo dominated
	UK RWE, state transition model	7	Trial-based analyses, PartSA	Pem+lenv	-	-	Cabo+nivo extendedly dominated
Effectiveness							
Preferred 1st line NMA	FP NMA	11	PH NMA	Pem+lenv	-	-	Cabo+nivo extendedly dominated
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	21	PH NMA throughout, PartSA	Nivo+ipi	£46,097	0.084	£549,457

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Preferred NMA for pem+lenv	PH NMA	13	FP NMA	Cabo	-	-	Cabo+nivo dominated
Surrogate outcome for nivo+ipi	PFS	73	Using TTNT data as a proxy for PFS for nivo+ipi	Cabo	-	-	Cabo+nivo dominated
Surrogate outcome for nivo+ipi	PFS	74	Using TTNT data as a proxy for PFS for nivo+ipi, PH NMA	Cabo	-	-	Cabo+nivo extendedly dominated
TTD data source	TTD	18	TTD equal to PFS	Cabo	-	-	Cabo+nivo dominated
	Relative effectiveness for nivo + ipi from PFS consistent with other treatments	20	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	Cabo	-	-	Cabo+nivo dominated
Treatment effectiveness waning	5 years for IO/TKIs, all endpoints, based on hazards	24	Between 5 and 20 years all IO/TKIs, all endpoints, based on hazards	Cabo	-	-	Cabo+nivo dominated
		26	No treatment effect waning	Cabo	-	-	Cabo+nivo dominated
Suni RWE 1L PFS	Log-logistic	29	Weibull	Cabo	-	-	Cabo+nivo dominated
Impact of prior TKI treatment	Not considered	76	Exploratory analysis HR1.59 applied to TKI after TKI monotherapy	Cabo	-	-	Cabo+nivo dominated
Costs/RDI							
RDI	Applied	41	All RDI set to 100%	Pem+lenv	-	-	Cabo+nivo dominated

Parameter	Base case		Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Lenv dosing within pem+lenv	TA858 & RDI data	75	NHSE input	Cabo	-	-	Cabo+nivo dominated
Utilities							
Data source used for utilities	JAVELIN Renal 101 for 1L, AXIS trial for 2L and assumed same proportional decrease for 3L and 4L	50	CheckMate 9ER for all lines	Cabo	-	-	Cabo+nivo dominated
Adverse events							
Data source used for AEs	NMA	58	Individual trials	Cabo	-	-	Cabo+nivo dominated

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

*Next best comparator defined as next most efficient non-dominated comparator.

2.4. Company base case

Table 5 presents the company preferred base case with changes made in incremental steps from the EAG base case analysis. In the favourable and all-risk populations cabozantinib plus nivolumab is not cost-effective at list price vs TKI monotherapy in any analysis. The most impactful steps are the switch from FP to PH NMA (as this does not capture the impact of the slippage seen in the hazard ratios for cabozantinib plus nivolumab in the long-term), the assumption that TTD is equal to PFS which generally increases the ICER as TTD had been expected to be less than PFS which impacts expensive novel therapies more than cheaper TKI monotherapies, the reduction from consideration of two lines of treatment to three lines (as there are more effective options available for subsequent therapy after TKI monotherapy) and the use of the company RDIs which double counts with TTD (and therefore underestimates the cost of novel therapies) and also does not account for the non-linear pricing of lenvatinib within the pembrolizumab plus lenvatinib combination and therefore biases towards pembrolizumab plus lenvatinib.

Table 6 presents the company preferred PartSA analysis again with changes made in incremental steps from the EAG base case PartSA analysis. In the favourable risk population cabozantinib plus nivolumab is dominated at all steps. In the all-risk population cabozantinib plus nivolumab is not cost-effective at list price vs TKI monotherapy. The most impactful steps are the switch from FP to PH NMA (as this does not capture the impact of the slippage seen in the hazard ratios for cabozantinib plus nivolumab in the long-term), the assumption that TTD is equal to PFS which generally increases the ICER as TTD had been expected to be less than PFS which impacts expensive novel therapies more than cheaper TKI monotherapies and the use of the company RDIs which double counts with TTD (and therefore underestimates the cost of novel therapies) and also does not account for the non-linear pricing of lenvatinib within the pembrolizumab plus lenvatinib combination and therefore biases towards pembrolizumab plus lenvatinib.

Table 5: Company preferred base case: state transition model

Parameter	Base case	Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
All-risk population						
EAG base case			Pazo	£145,198	0.528	£275,106
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	Above + PH NMA throughout	Pazo	£150,768	0.656	£229,908
Lines of treatment	4	Above + 2 lines of treatment	Pazo	£164,674	0.823	£199,980
Time on treatment	Use TTD data	Above + TTD equal to PFS	Pazo	£175,195	0.822	£213,105
Data source used for AEs	NMA	Above + Individual trials	Pazo	£174,544	0.839	£208,158
Data source for RDI	EAG updated analysis	Above + Company analysis which double counts RDI and TTD	Pazo	£139,683	0.839	£166,584
Favourable risk population						
EAG base case			Pazo	£166,955	0.440	£379,222
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	Above + PH NMA throughout	Pazo	£166,955	0.440	£379,222
Lines of treatment	4	Above + 2 lines of treatment	Pazo	£181,255	0.612	£296,395
Time on treatment	Use TTD data	Above + TTD equal to PFS	Pazo	£194,235	0.615	£315,695
Data source used for AEs	NMA	Above + Individual trials	Pazo	£193,582	0.632	£306,453
Data source for RDI	EAG updated analysis	Above + Company analysis which double counts RDI and TTD	Pazo	£155,716	0.632	£246,507

Parameter	Base case	Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Intermediate / poor risk population						
EAG base case			Cabo	-	-	Cabo+nivo dominated
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	Above + PH NMA throughout	Cabo	-	-	Cabo+nivo extendedly dominated†
Lines of treatment	4	Above + 2 lines of treatment	Cabo	£72,649	0.348	£208,885¥
Time on treatment	Use TTD data	Above + TTD equal to PFS	Cabo	£78,392	0.348	£225,392¤
Data source used for AEs	NMA	Above + Individual trials	Cabo	£77,744	0.365	£212,829+
Data source for RDI	EAG updated analysis	Above + Company analysis which double counts RDI and TTD§	Pem+lenv	-	-	Cabo+nivo dominated

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

* Next best comparator defined as next most efficient non-dominated comparator

† List price ICER £108,292 vs nivo+ipi and SW quadrant £237,882 vs pem+lenv

¥ List price ICER £100,579 vs nivo+ipi and SW quadrant £407,623 vs pem+lenv

¤ List price ICER £104,638 vs nivo+ipi and SW quadrant £315,990 vs pem+lenv

+ List price ICER £102,094 vs nivo+ipi and SW quadrant £391,233 vs pem+lenv

§ This analysis is also biased towards pem+lenv as it fails to account for the impact of the cost being the same for different pill sizes

Table 6: Company preferred PartSA analysis

Parameter	Base case	Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
All-risk population						
EAG base case		PartSA	Suni	£142,265	0.319	£445,511
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	Above + PH NMA throughout	Suni	£148,284	0.535	£277,106
Lines of treatment	4	Above + 2 lines of treatment	Suni	£156,642	0.537	£291,900
Time on treatment	Use TTD data	Above + TTD equal to PFS	Suni	£165,557	0.537	£308,512
Data source used for AEs	NMA	Above + Individual trials	Suni	£165,099	0.551	£299,845
Data source for RDI	EAG updated analysis	Above + Company analysis which double counts RDI and TTD	Suni	£131,715	0.551	£239,214
Favourable risk population						
EAG base case		PartSA	Tivo	-	-	Cabo+nivo dominated
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	Above + PH NMA throughout	Tivo	-	-	Cabo+nivo dominated
Lines of treatment	4	Above + 2 lines of treatment	Tivo	-	-	Cabo+nivo dominated
Time on treatment	Use TTD data	Above + TTD equal to PFS	Tivo	-	-	Cabo+nivo dominated
Data source used for AEs	NMA	Above + Individual trials	Tivo	-	-	Cabo+nivo dominated
Data source for RDI	EAG updated analysis	Above + Company analysis which double counts RDI and TTD	Tivo	-	-	Cabo+nivo dominated

Parameter	Base case	Scenario	Next best comparator*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Intermediate / poor risk population						
EAG base case		PartSA	Nivo+ipi	-	-	Cabo+nivo extendedly dominated
Preferred NMA	FP NMA 1st line, PH NMA 2nd line	Above + PH NMA throughout	Nivo+ipi	£73,919	0.313	£236,369
Lines of treatment	4	Above + 2 lines of treatment	Nivo+ipi	£76,827	0.315	£244,179
Time on treatment	Use TTD data	Above + TTD equal to PFS	Nivo+ipi	£76,953	0.315	£244,580
Data source used for AEs	NMA	Above + Individual trials	Nivo+ipi	£76,493	0.328	£233,521
Data source for RDI	EAG updated analysis	Above + Company analysis which double counts RDI and TTD§	Suni	£118,807	0.722	£164,617

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; AEs, adverse events; AUC, area under the curve; axi, axitinib; BSC, best supportive care; evero, everolimus; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; IV, intravenous; KM, Kaplan-Meier; OS, overall survival; pazo, pazopanib; PD, progressed disease; PFS, progression free survival; PH, proportional hazards; PPS, pos-progression survival; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; tivo, tivozanib; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression

* Next best comparator defined as next most efficient non-dominated comparator
Note cabo+nivo is dominant or cost-effective vs pem+lenv in all scenarios except when the company RDI data is used
§ This analysis is also biased towards pem+lenv as it fails to account for the impact of the cost being the same for different pill sizes

3. EAG REVIEW OF KEY ISSUES: THE DECISION PROBLEM

The following sections provide response to company comments for each of the key issues raised in the EAG report, the original issue tables are repeated here for ease of reading.

Issue 1: Optimal sequencing of treatments, including after novel 1st-line treatments

Report sections	
Description of issue and why the EAG has identified it as important	Clinical advice to the EAG and consideration of relevant evidence highlights that optimal treatment sequencing following novel treatments at 1st-line (i.e. IO/IO or IO/TKI combinations) remains an area of uncertainty. In addition, evidence for optimal treatment choice and sequencing in favourable risk patients at 1st-line remains an area of clinical debate.
What alternative approach has the EAG suggested?	The EAG has received clinical advice as to most likely treatment sequences. However, additional clinical evidence is needed to ascertain which treatments are most likely to be received, and most effective, as novel treatments continue to emerge in 1st-line; as well as optimal treatment choice for favourable risk patients.
What is the expected effect on the cost-effectiveness estimates?	Current estimates of cost effectiveness, particularly in 2nd line and for favourable risk patients, may evolve as this evidence develops. Optimal treatment sequencing may also impact overall estimates of OS in 1st-line, but the direction of impact on cost-effectiveness estimates is unclear.

Abbreviations: EAG, External Assessment Group; IO, immune-oncology; OS, overall survival; TKI, tyrosine kinase inhibitor

Company comment:

The company agreed that treatment sequencing is a challenge in this appraisal.

Other stakeholder comments:

Kidney Cancer UK raise that an optimal sequencing of treatments for all patients is unlikely to be achievable due to: the need to tailor treatment individually, prescriber preference and experience, and frequent changes to optimal practice arising from new data and treatments. They also highlight considerable variation in current practice.

Action Kidney Cancer raise the careful planning required for oncologists due to existing restrictions on the order in which treatments can be used. Action Kidney Cancer also note that patients are often not informed about the restrictions and therefore not able to make an informed decision. They suggest that patient decision aids should be made available to patients to help them make informed decisions at key points throughout the pathway.

EAG response:

No response required. Comment from Action Kidney Cancer relating to materials has been flagged to the NICE guidelines team.

Issue 2: Company's definition of relevant comparators

Report sections	
Description of issue and why the EAG has identified it as important	The company argued that, at 1st line, ave+axi is a relevant comparator, and excluded tivo. The EAG disagrees with this position as ave+axi is not considered to be routinely commissioned while it is accessed through the CDF; further, tivo is a relevant treatment at 1st line.
What alternative approach has the EAG suggested?	The EAG has included ave+axi in clinical effectiveness analyses for completeness in line with the scope of the pathways decision problem (rather than the decision problem specific to cabo+nivo), but has not included this treatment in economic analyses for cabo+nivo in keeping with NICE guidance. The EAG has also included tivo where possible in 1st-line analyses acknowledging limitations in the ability to conduct indirect treatment comparisons.
What is the expected effect on the cost-effectiveness estimates?	The EAG's cost-effectiveness estimates will more closely reflect NICE guidance.

Abbreviations: ave, avelumab; axi, axitinib; cabo, cabozantinib; CDF, Cancer Drugs Fund; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; IO, immune-oncology; OS, overall survival; TKI, tyrosine kinase inhibitor

Company comment:

The company reiterated the value of avelumab + axitinib, citing evidence from the Association of British Pharmaceutical Industry (ABPI) and NICE Operational Effectiveness Group Meeting on 25 January 2023, but noted that there was no intent to pursue this key issue.

The company also disagreed with the EAG's assertion that tivozanib is frequently used in 1st-line and is thus a relevant comparator, reiterating evidence it presented in response to clarification questions. The company also commented that including tivozanib in the NMAs exacerbates uncertainty due to the need to include trials that did not include any poor risk patients, and queried why the EAG did not undertake a sensitivity analysis for trials that excluded patients with favourable risk status.

Other stakeholder comments:

Kidney Cancer UK provide information from their latest patient survey that 4% of patients received avelumab plus axitinib as a 1st line treatment and none received tivozanib as a first line

treatment (542 completed surveys, Sept / Oct 2022). Action Kidney Cancer raise the importance of comparing nivolumab plus cabozantinib to other IO / TKI combinations.

BMS raise issues with inclusion of data from the all-risk population from CheckMate 214 in the analysis, given that nivolumab plus ipilimumab is only licensed in the intermediate / poor risk population.

EAG response:

The EAG agrees with Action Kidney Cancer that providing comparison to another IO / TKI combination is important. Comparison is provided to pembrolizumab plus lenvatinib which is the only combination available within routine commissioning.

The EAG notes the company's comments regarding avelumab plus axitinib and levels of current usage based on the Kidney Cancer UK survey and regards that any further decisions on this point are proper to NICE.

The EAG disagrees that the evidence for comparatively low use of tivozanib is as straightforward as presented by the company, i.e. that cabozantinib monotherapy is more frequently used than tivozanib. The EAG notes that the company's original source for this assertion relied on total pack sales, which is misleading as cabozantinib, to a greater degree than tivozanib, is used over multiple lines. The EAG acknowledges that its source for RWE is redacted, principally because alternative sources did not materialise. However, the EAG reiterates that Figure 8 in the EAG report provides visual evidence that tivozanib is used to a reasonable degree in first line. We also note that data provided by the company in clarification question A23 indicates their own budget impact assessment assumes a 9% market share for tivozanib (only 4% lower than sunitinib and cabozantinib). The EAG thanks Kidney Cancer UK for the provision of data from their survey conducted last year, however, the EAG note that the sample size of this data set is less than half the size of UK RWE registry available to the EAG and that, as Kidney Cancer UK note in their response to Key Issue 1, it is important to consider all possible options given the variation in patient response and physician prescribing practice.

Finally, the EAG disagrees that introducing tivozanib into the NMA generates additional uncertainty, as the alternative—excluding a known comparator with meaningful use in first line—would have generated even higher levels of uncertainty; i.e. the absence of a comparative effectiveness estimate. The EAG acknowledges the point raised by BMS that data for treatments only licenced in the intermediate/poor risk population were included in the all-comers

NMA. However, these trials provide relevant data relating to sunitinib, and inclusion is consistent with the EAG's general approach of including relevant evidence from 'in-line' treatments in NMAs without specific regard to risk group. As is clear, the EAG did not carry through treatments licenced for intermediate/poor risk into the all-risk cost-effectiveness analyses.

The EAG also is surprised to note the company's observation that a sensitivity analysis excluding trials without favourable risk patients was not undertaken, as NMAs restricted to patients in intermediate and poor risk subgroups formed a core part of the EAG's analytic strategy, and were presented for OS, PFS, and overall response rate (ORR) outcomes.

Issue 3: Company's definition of relevant outcomes

Report sections	
Description of issue and why the EAG has identified it as important	The company argued in its original submission that TTNT was not a relevant outcome. When these data were provided, the definition used was non-standard, precluding meaningful comparisons to other studies.
What alternative approach has the EAG suggested?	The EAG has suggested defining time to next treatment in a way similar to other studies; i.e. considering the time from initiation of 1st-line treatment to the first of uptake of a second systemic treatment where this has been recorded, death or loss to follow-up. These data are not yet available.
What is the expected effect on the cost-effectiveness estimates?	The EAG's economic modelling will be able to draw on data for this outcome to produce more consistent and high-fidelity cost-effectiveness estimates.

Abbreviations: EAG, External Assessment Group; TTNT< time to next treatment

Company comment:

The company asserted that data requirements for this appraisal were considerably higher than in STAs, and that the relatively few studies reporting TTNT meant that the value of this outcome was minimal.

Other stakeholder responses:

Action Kidney Cancer highlight that the most important outcome of treatment is living for as long as possible with a good quality life. They also consider time to next treatment an important outcome as part of this. They state that they would welcome quality of life and patient report outcomes being given equal importance to quantity of life in cost-effectiveness analysis.

EAG response:

The EAG communicated early in the appraisal as to the data requirements needed to provide the highest-fidelity model possible. The data requirements were specified in the user guide provided to the company as an advance version on 17th February and as final on 23rd March 2023. These sorts of data have been previously, and are frequently, requested in STAs by other EAGs, for example TA627 (see clarification question A13[1]).

While it is true that other evidence for time to next treatment was sparse, that does not obviate that this was a scoped outcome. Ultimately, the EAG was unable to include time to next treatment in its analysis, but this is not to say that this evidence is not probative for Committee. It remains that the definition used by the company to provide evidence against this outcome was non-standard. The EAG welcomes the statement of Action Kidney Cancer that this outcome is of relevance and value to patients.

Issue 4: Company's definition of relevant subgroups

Report sections	
Description of issue and why the EAG has identified it as important	The company argued in its original submission that cabo+nivo should be assessed in the all-risk group. The EAG notes that risk group is known to be an important prognostic factor, an important effect modifier across a range of RCC treatments, and a key factor in previous NICE appraisals, as well as a salient factor in clinical decision-making. As a result, subgroup-specific evidence is highly probative. Moreover, in subgroup-specific NMAs, the EAG found that patterns of effect were different by risk group.
What alternative approach has the EAG suggested?	The EAG has considered cost-effectiveness both in an all-risk population as well as in intermediate/poor risk populations and favourable risk populations separately, reflecting practice in prior appraisals for RCC.
What is the expected effect on the cost-effectiveness estimates?	The EAG expects that cost-effectiveness estimates will more closely reflect clinical realities and the existing treatment pathway, supporting more robust decision-making.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; NMA, network meta-analysis; RCC, renal cell carcinoma

Company comment:

The company reiterates its point that cabozantinib + nivolumab should be appraised in the all-risk population, particularly given no novel therapies are available in all-risk populations in 1st-line (with the exception of avelumab + axitinib, which is not available in routine commissioning). The company also asserts that modelling in an all-risk population requires the fewest assumptions.

Other stakeholder comments:

Kidney Cancer UK highlight that the identification and commissioning of an all-risk treatment would be a major step forward. Action Kidney Cancer state that they agree with the EAG approach.

EAG response:

The EAG acknowledges that there is evidence for effectiveness of cabozantinib + nivolumab in the pooled population but observes that prior NICE appraisals have also sought to make subgroup-specific combinations including the most recent appraisal in RCC (TA858). In addition, as the majority of patients in UK clinical practice fall into the intermediate and poor risk categories, an all-risk comparison would exclude all other novel therapies, which could be misleading. This is because, in reality, these novel therapies represent a substantial amount of all treatment provided to patients at 1st line. Nevertheless, the EAG has presented cost-effectiveness estimates for an all-risk group alongside for an intermediate and poor risk group and a favourable risk group.

4. EAG REVIEW OF KEY ISSUES: THE CLINICAL EFFECTIVENESS EVIDENCE

Issue 5: CheckMate 9ER: Consistency of reporting

Report sections	
Description of issue and why the EAG has identified it as important	The company submitted an interim report of clinical effectiveness, with a subsequent update provided due to data quality issues. However, the EAG did not find that the explanation of changes provided was sufficiently comprehensive to provide confidence in the data quality. For example, data relating to AEs had minor changes that were not explicitly described as updated.
What alternative approach has the EAG suggested?	It was not possible for the EAG to resolve this issue within its appraisal using the available data. A clear explanation of all changes made between data cuts provided would increase confidence in the analyses provided.
What is the expected effect on the cost-effectiveness estimates?	It is unclear if an explanation would impact data inputs to the EAG's economic model; however, confidence in data quality is essential to minimise decision risk.

Abbreviations: AE, adverse events; EAG, External Assessment Group

Company comment:

The company acknowledged that no further detail relating to the error could be provided, but that any errors did not impact overall conclusions.

EAG response:

No response required.

Issue 6: CheckMate 9ER: Generalisability of the trial to UK practice

Report sections	
Description of issue and why the EAG has identified it as important	The EAG's inspection of the company's trial data found that the trial enrolled a relatively small number of UK patients, and that the rate of patients continuing to receive treatment post-progression was both higher than expected and not in keeping with clinical treatment patterns in the UK. In addition, patients with intermediate and poor risk receiving suni had higher restricted mean survival times for both OS and PFS in the CheckMate 9ER trial than the comparable RWE source preferred by the EAG, with a similar trend seen for OS in the favourable risk group as well. Patients receiving suni also had comparatively lower use of nivo as a subsequent treatment than expected.
What alternative approach has the EAG suggested?	It was not possible for the EAG to resolve this issue within its appraisal using the available data. A clearer justification of why post-progression treatment rates were higher than expected would contextualise concerns

Report sections	
	about generalisability. Analyses accounting for post-progression treatment would be valuable to better understand the impact of post-progression treatment rates and mix of post-progression treatments.
What is the expected effect on the cost-effectiveness estimates?	Clearer understanding of time on treatment post-progression would impact treatment costs estimated in an economic model. The direction of this impact is unclear pending an explanation from the company.

Abbreviations: EAG, External Assessment Group; nivo, nivolumab; OS, overall survival; PFS, progression free survival; RWE, real-world evidence; suni, sunitinib; UK, United Kingdom

Company comment:

The company noted that the proportion of UK patients in CheckMate 9ER was similar to the CLEAR trial, which was included in TA858. The company also raised broader questions relating to the appropriateness of other treatments in the context of adjuvant pembrolizumab.

In addition, the company notes that the data provided in response to the EAG's request for information on patients continuing treatment post-progression relied on a misapprehension of the EAG's request.

Finally, the company notes that nivolumab use lower than expected after progression may be due to availability of treatments in study sites.

Other stakeholder comments:

BMS note that, given the comparability of baseline characteristics between CheckMate 9ER and the UK RWE outside of age, that use of the RWE to inform the reference curve is unwarranted given the longer follow-up available for CheckMate 9ER.

BMS also note that CheckMate 214 and KEYNOTE 564 may not be useful sources to validate long-term extrapolations due in the former case to the anomalously good performance of sunitinib for PFS and KEYNOTE 564 being a trial in the adjuvant setting.

An additional comment was provided separately by BMS in relation to a request to provide any explanation known to them for the anomalously good performance of sunitinib for PFS in CheckMate 214. The following response was received which is replicated verbatim below:

There is no clinical rationale or explanation for the overperformance of sunitinib in the CheckMate 214 ITT population. However, BMS believes that several factors may have contributed to this phenomenon and it is not known to what extent these factors interact:

- [redacted] randomised to sunitinib crossed over to NIVO+IPI during the CheckMate 214 trial.
- In the original CDF entry (Section B.2.7, page 39) for NIVO+IPI it was stated during the clinical consultation that the favorable-risk group may exhibit distinct antigenic signatures in tumors compared to intermediate-/poor-risk patients. Favorable-risk patients were suggested to have relatively 'pure' tumours predominantly driven by VEGF, whereas tumors in intermediate-/poor-risk patients were characterized as more complex with multiple mutational drivers. This led to the hypothesis that intermediate-/poor-risk tumors might develop resistance to VEGFR TKIs more rapidly but respond better to immune checkpoint inhibitor therapy compared to tumors from favorable-risk patients.
    - This statement finds support in Escudier 2020 […]. This study demonstrated that the ORR for NIVO+IPI remained consistent across the six IMDC risk factors. In contrast, the ORR for sunitinib showed a decreasing trend as the number of risk factors increased. Additionally, sunitinib exhibited decreasing median OS and median PFS with increasing risk factors.
    - Notably, when examining median PFS in the intermediate/poor-risk group, the differences observed with sunitinib were less pronounced:

	CheckMate 214	KEYNOTE 426	CheckMate 9ER	CLEAR	JAVELIN
Median follow-up	67.7	67	44	49.8	NR (42-NR)
Suni mPFS	8.3	8.3	7.1	5.9	8.2

Abbreviations: PFS, progression free survival; suni, sunitinib

- The multivariable model (Motzer 2019 with supplementary materials attached) used to assess the impact of baseline characteristics on OS demonstrated that haemoglobin, PD-L1 expression and prior nephrectomy significantly impacted OS in the CheckMate 214 sunitinib arm.
    - Supplementary Table 2 also includes the univariable analysis of the effect of baseline clinical features as a single coefficient on the probability of OS in the ITT population in the NIVO+IPI and SUN arms.

- Within CheckMate 214 trial 95% of patients with a favourable risk in the sunitinib arm received prior nephrectomy (80% in the CheckMate 214 ITT population versus 70% in CheckMate 9ER).
- In the original CDF entry submission, BMS also presented some exploratory analysis on PD-L1 subgroups which impact both the performance of sunitinib and nivolumab + ipilimumab which you might find interesting though as stated in in the ERG report that "Clinical advice to the ERG is that advanced RCC patients would not be treated differently depending on PD-L1 status. I have attached the PFS data KM curves which were presented at ESMO 2017 as well as the data which was shared in the original CDF entry submission below:

	Intermediate/Poor Risk population		Intention-to-treat population (All-risk)	
	PD-L1 <1%	PD-L1 ≥1%	PD-L1 <1%	PD-L1 ≥1%
Nivo+ipi	11.0m	22.8m	[redacted]	[redacted]
Suni	10.4m	5.85	[redacted]	[redacted]

Abbreviations: ipi, ipilimumab; nivo, nivolumab; suni, sunitinib"

EAG response:

The EAG acknowledges the company's comments regarding CLEAR, which the committee in TA858 concluded was a "well-designed trial and results are generalisable to NHS clinical practice", and subsequent use of nivolumab. Ultimately, the EAG regards the magnitude of uncertainty introduced by these points as for the Committee to determine.

The EAG addresses the point about adjuvant pembrolizumab in Key Issue 11 below.

The EAG acknowledges BMS's point in relation to the use of PFS data for sunitinib in CheckMate 214 for validation and would like to correct a typographical error in the report in relation to the additional trial used for validation. This was in fact KeyNote 426 (rather than 564), which is a trial comparing pembrolizumab plus axitinib and sunitinib in the advanced RCC setting. As noted below Table 65 in the EAG report, long-term trial data played only a limited role in the validation process: "Given differences in populations included (RWE vs trials) curves were only ruled out if no patients remained in PFS at a timepoint clinical trial data indicated there should be patients remaining".

In addition, the EAG note with thanks the reply of BMS to queries relating to the anomalous performance of sunitinib on PFS in CheckMate 214. The EAG have considered the different factors raised by BMS, and regard that the totality of BMS's observations relate to: a) crossover, b) performance profiles in the favourable risk group, and c) the impact of baseline factors relating to prior nephrectomy and PD-L1 status. In respect of point a), the EAG note that crossover would be unlikely to impact PFS especially as this is more likely to have occurred after progression. In respect of point b), the EAG note that the intermediate/poor risk group also experienced anomalously good PFS outcomes in CheckMate 214 (a point addressed below and reflected in Figure 7, where differences are especially pronounced after 9 months of follow-up). In respect of point c), the EAG note that prior nephrectomy rates are consistently high in modern trials, but also acknowledge that distribution of PD-L1 status is a potentially useful factor, though one that is inconsistently reported in trials. The EAG consider that on balance differences in PD-L1 distribution compared to prior trials may explain part of the anomalous performance but is unlikely to explain the totality of the outcome pattern seen.

The EAG consider the key difference in patient characteristics between CheckMate 9ER and the UK RWE to be prior nephrectomy status rather than age (54% in the UK RWE versus ~70% in CheckMate 9ER), which is known to be highly prognostic. The UK RWE dataholders considered that this was due to artificial inflation of nephrectomy rates in trials compared to general practice as this is required in order to be able to gain a complete response. Relatedly, the EAG do not regard that the longer follow-up of CheckMate 9ER is itself dispositive for choice of reference curve. The EAG considers that the source of RWE identified ensures better generalisability of the model to UK practice, includes mature data relating to PFS in terms of events accrued and follow-up (though specific curves remain redacted), and more closely reflects treatment decisions and prognosis in a UK context.

Finally, the EAG would welcome correct data relating to its original request if Ipsen are able to obtain it; we note that the company states that considerable efforts to obtain these data have been made. While the company notes that the difference between TTD and PFS curves is an estimate of post-progression treatment, formal estimates of this difference would be valuable.

Issue 7: CheckMate 9ER: Effect modification by risk group

Report sections	
Description of issue and why the EAG has	The EAG's inspection of the company's trial data found that there was some evidence of effect modification by risk group for OS and PFS; for example, the HR for OS comparing cabo+nivo against suni in

Report sections	
identified it as important	favourable-risk patients (HR=1.07) is more than twice as high as for patients with poor risk (HR=0.46), with a similar trend in evidence for PFS (HR=0.72 vs HR=0.37). This is important because it reinforces the value of risk group as a key consideration in this appraisal and its salience in clinical and cost-effectiveness decision-making.
What alternative approach has the EAG suggested?	The EAG reiterates that cost-effectiveness modelling should also consider risk group as a key factor, including production of cost-effectiveness estimates by risk group.
What is the expected effect on the cost-effectiveness estimates?	Estimates for the cost-effectiveness of cabo+nivo are likely to be very different by risk group.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; HR, hazard ratio; nivo, nivolumab; OS, overall survival; PFS, progression free survival; sunitinib

Company comment:

The company reiterates its view that cabozantinib + nivolumab is best appraised in an all-risk population.

Other stakeholder responses:

Kidney Cancer UK note that whilst they appreciate the rationale for measuring cost-effectiveness by risk group, producing recommendations by risk group restricts the ability of clinicians to optimise treatment sequences on an individual patient basis.

BMS note that because risk group is an important prognostic factor and effect modifier, the EAG should not assume that model inputs such as curve selection for the intermediate/poor and favourable risk group are consistent with the all-risk population in survival curve selection.

EAG response:

The EAG do not regard that further response is required to points around optimisation of recommendations by risk group. Consistency of curve selection across risk groups was not used as a criterion for curve selection (see the list of criteria used in Section 4.3.5.1). The survival curves selected in the end were largely consistent across risk groups when using the UK RWE as the selected fits were considered to be most appropriate based upon the stated criteria. The EAG also presented appropriate scenario analyses for curve selections. The level of completeness of the Kaplan Meier data for the UK RWE should also be noted (in all populations), meaning that uncertainty stemming from survival curve selection for PFS and other endpoints used in the state transition model is limited. This was not the case for

CheckMate 9ER data (see original EAG report Appendix K) where the survival curves selected generally differed between the intermediate / poor risk and favourable risk groups.

Issue 8: Evidence base: quality and sufficiency of included randomised trials

Report sections	
Description of issue and why the EAG has identified it as important	The EAG's appraisal of the RCTs included in its syntheses identified significant limitations in the quality of included trials, including CheckMate 9ER; of the 17 prioritised trials, nine were appraised as being at high risk of bias and eight were appraised as being at an unclear risk of bias. The majority of comparisons in 1st-line and 2nd-line networks were informed by only one trial, meaning that many comparisons between novel treatments were based on indirect evidence only, and inconsistency in networks could not be assessed. Moreover, risk group-specific analyses drew on comparatively sparse data, which were often unevenly presented; in particular, pem+lenv could not be included in risk group-specific FP NMAs for PFS due to redacting of data in TA858.
What alternative approach has the EAG suggested?	The EAG has used parallel analysis methods for survival outcomes, including FP NMA and PH NMA, to test the robustness of analyses to different assumptions where possible. However, only PH NMAs are available for survival outcomes in the favourable risk group patients in 1st line. However, this does not address the challenges relating to risk of bias.
What is the expected effect on the cost-effectiveness estimates?	Estimates for the cost-effectiveness of cabo+nivo are increased in their statistical uncertainty due to limitations and sparseness in the underpinning evidence base; in addition, it is impossible to quantify the impact of trial-level bias on cost-effectiveness estimates.

Abbreviations: FP, fractional polynomial; lenv, lenvatinib; NMA, network meta-analysis; pem, pembrolizumab; PH, proportional hazards; RCTs, randomised controlled trials; TA, technology appraisal

Company comment:

The company presents a separate table of queries relating to the EAG's NMA; in short, these boil down to the lack of availability of data for some treatments and risk groups, the need for simplifying assumptions, and the application of relative treatment efficacy across comparators and lines of therapies.

EAG response:

The EAG has addressed the company's points below. In short, decisions taken by the EAG for curve selection were based on a range of criteria, as for any other extrapolation undertaken in a NICE appraisal. Any other decisions taken were explained in the context in which they were made. The EAG disagrees that these "inconsistencies" are anything except the careful consideration of evidence to minimise uncertainty in analysis. To the extent that the company's

comments relate to the tension between FP and PH NMAs, the EAG reiterates that both sets of results are provided. The EAG agrees with the company about the broader limitations in the evidence base for this appraisal and has presented these extensively in the primary report. Scenario analysis is presented within the economic results using PH NMAs.

Issue 9: Evidence base: distribution of effect modifiers across evidence networks

Report sections	
Description of issue and why the EAG has identified it as important	While the EAG did not regard that distribution of effect modifiers across the network precluded the feasibility of NMAs, it remains that differences between trials in risk group distribution, histological features, proportion with prior nephrectomy, proportion with sarcomatoid features and, to a possibly lesser degree, age could not be meaningfully addressed in NMAs. This was both because of the sparseness of networks and because of poor reporting of several of these characteristics (particularly proportion with sarcomatoid features). More generally, observational evidence suggests that over time and in the last 15 years, patients have experienced better outcomes regardless of treatment. Trials included draw from a wide range of timeframes and follow-up lengths, adding another challenge to interpretation.
What alternative approach has the EAG suggested?	The EAG used a random effects term when appropriate in its FP NMAs, which accounted for some heterogeneity in baseline risk. However, a network meta-regression with a less sparse evidence network would have provided greater confidence in findings.
What is the expected effect on the cost-effectiveness estimates?	The direction of travel of cost-effectiveness estimates as a result of this uncertainty is difficult to quantify, as it in part depends on the age of the trial and trial-specific distribution of effect modifiers. However, given lower numbers of poor risk patients in trials linking tivo in 1st-line networks, estimates may be biased in favour of tivo.

Abbreviations: EAG, External Assessment Group; FP, fractional polynomial; NMA, network meta-analysis; tivo, tivozanib

Company comment:

The company agreed that reporting of effect modifiers is a challenge in this evidence base.

Other stakeholder comments:

Kidney Cancer UK note that these difficulties (and those in the next two issues) highlight the challenges in attempting to produce an optimal treatment sequence across all available agents using data from clinical trials that were not designed for this purpose. They also highlight difficulties using real-world data due to differences in the extent of experience with different treatments. They urge against focussing on treatments with more or better quality data.

EAG response:

The EAG acknowledges that the company provided all relevant effect modification data for CheckMate 9ER.

Issue 10: Evidence base: non-proportional hazards and evolution over time in survival outcomes

Report sections	
Description of issue and why the EAG has identified it as important	Many of the prioritised trials exhibited violations of the PH assumptions, based either on statistical tests or on visual inspection. In addition, time-to-event data were drawn from the last available data cut given difficulties in identifying 'most similar' time points for analysis and to avoid discarding collected data. However, differential trial maturity is a challenge for interpretation given evidence of 'slippage' in HRs towards the null, particularly for IO/TKI combinations, over sequential follow-ups.
What alternative approach has the EAG suggested?	As above, the EAG has used parallel analysis methods for survival outcomes, including FP NMA and PH NMA, to test the robustness of analyses to different assumptions. However, challenges in estimating hazard functions generated some inconsistencies between both analysis strategies, particularly for pem+lenv in 1st-line, and generated estimates for 2nd-line FP NMAs that were inconsistent between outcomes. It is likely that the EAG's analyses should be revisited when all trials have reached maturity.
What is the expected effect on the cost-effectiveness estimates?	Based on evidence of slippage, it is likely that cost-effectiveness estimates for novel treatments drawing on comparatively less mature trials may be unduly optimistic.

Abbreviations: EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio; IO, immuno-oncology; lenv, lenvatinib; NMA, network meta-analysis; pem, pembrolizumab; PH, proportional hazards; TKI, tyrosine kinase inhibitor

Company comment:

The company agreed that slippage in OS and PFS was in evidence but asserted that this was not the case for cabozantinib + nivolumab.

Other stakeholder comments:

BMS notes the inconsistency in approach to the NMA between pembrolizumab plus lenvatinib and other treatments due to redaction of PFS data in the intermediate / poor risk population and request scenarios to be presented assuming equal effectiveness to other IO / TKI treatments.

EAG response:

The EAG disagrees that there is no slippage in OS estimates for cabozantinib + nivolumab. However, this is less pronounced for cabozantinib + nivolumab than for other novel therapies

(see Figures 30 and 31 in the EAG report), and the EAG acknowledges that there is no formal statistical test of this.

The EAG currently note in the report that it "[…]is acknowledged that use of the PH NMA will bias towards pem+lenv as the CLEAR trial demonstrated non-proportional hazards (curves coming together), the extent of bias is, however, expected to be mitigated by the application of treatment-effectiveness waning in the model base case." The EAG also reiterates that the redaction of PFS curves for the intermediate/poor risk population is an insurmountable issue to the inclusion of FP NMA results for this group.

Scenario analysis has already been presented assuming equal effectiveness between pembrolizumab plus lenvatinib and nivolumab plus cabozantinib (Scenarios 43 and 44; the former uses newer RDI data supplied by the company in addition). The total discounted QALYs predicted for pembrolizumab plus lenvatinib reduce to 1.91 from 2.23 relative to 2.00 for nivolumab plus cabozantinib with the slight reduction due to differences in subsequent treatments. The Committee have been presented with the impact of this on the ICER including commercial in confidence discounts.

Additional plots requested by the lead team member for the survivor functions resulting from the FP NMA are provided in Appendix C.

Issue 11: Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment

Report sections	
Description of issue and why the EAG has identified it as important	Included trials primarily restricted inclusion to patients with clear cell RCC, creating questions about the applicability of analyses to other RCC histologies. In addition, adjuvant pem is now available in routine practice, but was not available as part of routine practice when any of the included trials were conducted. Clinical advice to the EAG is that adjuvant pembrolizumab may reduce the subsequent effectiveness of IO treatments and improve prognosis for other types of treatment as patients will be scanned more regularly, leading to earlier detection and treatment of progression.
What alternative approach has the EAG suggested?	The EAG could not address these issues in this appraisal due to sparsity of evidence. However, a number of trials are emerging in different RCC histologies which will provide additional evidence in this area.
What is the expected effect on the cost-effectiveness estimates?	As adjuvant pem increases in use, it is likely that effect estimates from IO treatments will vary in practice from those observed in key trials. These may eventually attenuate the cost-effectiveness of IO-based treatments, particularly in 1st line.

Abbreviations: EAG, External Assessment Group; IO, immune-oncology; pem, pembrolizumab; RCC, renal cell carcinoma

Company comment:

The company comments on the subtypes of RCC, including the presence of sarcomatoid differentiation as an indicator of an especially aggressive form of RCC. The company also notes that CheckMate 9ER included 11.95% of patients whose cancer included sarcomatoid features, enhancing its generalisability.

The company comments further on adjuvant pembrolizumab as an issue in this appraisal; as the company also noted in response to clinical effectiveness Key Issue 6, adjuvant pembrolizumab is expected to impact sequencing for a range of therapies, including pembrolizumab + lenvatinib at 1st line.

Other stakeholder comments:

MSD note the limited number of responses available for the impact of prior adjuvant therapies from the structured expert elicitation and that this did not meet the recommended number of at least five in the MRC protocol.

EAG response:

The EAG notes the company's comments relating to CheckMate 9ER and agrees that adjuvant pembrolizumab is likely to impact a range of issues beyond cost-effectiveness, including optimal sequencing and the expected share of different treatments at 1st line. On the basis of clinical expert advice, the EAG consider that this issue applies to all first line IO-based combinations, not just first-line pembrolizumab plus lenvatinib.

The EAG agree that there is uncertainty in the estimates available for the impact from structured expert elicitation; however, the EAG would also note that the direction of impact of the use of adjuvant therapies is dependent on mechanism of action of the systemic treatment following adjuvant therapy and is clear based on basic biologic principles. A second use of the same treatment type is, on average, expected to result in reduced effectiveness, with the level of reduction dependent on the strength of response to the initial treatment and time since its use.

5. EAG REVIEW OF KEY ISSUES: ECONOMIC EVIDENCE

Issue 1: Inconsistency between prior appraisals

Report sections	
Description of issue and why the EAG has identified it as important	Previous NICE appraisals for RCC have used a range of modelling methods, leading to challenges in comparing across prior appraisals. This exacerbates decision risk for any one appraisal and has led to some possible inconsistencies in prior decision-making. For example, in TA858, the EAG concluded that pem+lenv was not cost-effective as compared to cabo in the population of patients with intermediate or poor risk; however, a similar conclusion would have been reached for the combination of nivo+ipi if it had been appraised at that time. As a result, pem+lenv combination therapy is only recommended for patients eligible for nivo+ipi combination therapy.
What alternative approach has the EAG suggested?	The EAG has proposed a common modelling framework for RCC based on a STM, with additional functionality to explore partitioned survival analysis-based results. This unified modelling framework also permits the exploration of treatment sequences and subsequent treatments given the NICE treatment pathway now includes multiple options and 1st, 2nd and 3rd lines.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on cost-effectiveness estimates is not with respect to their direction of travel but with respect to decision risk and corresponding uncertainties arising from inconsistencies in modelling methods.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; ipi, ipilimumab; lenv, lenvatinib; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; pem, pembrolizumab; RCC, renal cell carcinoma; STM, state transition model

Company comment:

The company raise two concerns relating to inconsistencies of this appraisal with prior appraisals:

- unexpected discrepancies in results between model structures; and
- increased uncertainty associated with modelling subsequent lines of treatment which they contend serves as a source of bias in the results.

The company considers that given the challenges in relation to lack of access to TTD for the majority of therapies that TTD should be assumed equal to PFS.

The company also considers that the hybrid state transition model with two lines of treatment may provide a better balance as it may address the inherent assumptions and limitations of a PartSA without being subject to the data limitations of 3rd and 4th line treatment options.

Finally, the company also raise concerns related to model run time, the lack of presentation of all scenarios at the time of production of the EAG report and inability to reproduce EAG results.

Other stakeholder comments

Kidney Cancer UK raise concerns that using a different modelling technique (specifically, a state transition model) risks introducing further decision risk, rather than overcoming it.

EAG response

The EAG disagrees that there are a high number of inconsistencies in this appraisal and reiterates that the goal of a pathways model is to flag, and where possible, resolve the many inconsistencies even between the prior appraisals (noted in this Issue). The discrepancies between results according to model structure are addressed in Economic Evidence Issue 7.

Whilst the EAG agree that there are data challenges relating to population of the hybrid state transition model structure, we would note that this is equally (and in fact more) true of a partitioned survival model, where subsequent treatment impacts are assumed to be independent of outcomes (a major assumption), and OS is extrapolated based upon observed data alone independently of expectations around subsequent treatment and observed PFS. We would disagree that the data challenges experienced in this model uniquely introduce bias. The uncertainty stemming from data challenges has been reflected within the analysis.

The data challenge the company raise in relation to the need to use the NMA to inform relative effectiveness for TTD applies equally to partitioned survival models where TTD is a key endpoint informing drug costs. Scenario analysis has been presented assuming TTD is equal to PFS. Available trial data would indicate that this assumption is somewhat [redacted].

The limited sample size at 3rd (n=101 for cabozantinib for PFS) and 4th line (n=29 for PPS) within the RWE is also raised as a concern. The EAG acknowledge this limitation; particularly for 4th line. The EAG would, however, note that the data identified from trials generally related to 2nd line and above and not just 2nd line. The 2nd line plus analyses in the EAG report therefore include a number of participants at 3rd line and beyond. However, the EAG notes as well that in the model base case only a small proportion of the time is spent in 3rd and 4th line of therapy which aligns with the low numbers receiving these treatments observed in the available real-world evidence sources (for example, for pazopanib in all-risk patients the time spent in 3rd and

4th line on and off treatment states is 16.9% and 2.1% respectively). As noted by the company in their own response, the majority of LYs are accrued in the first two lines of treatment. This means that assumptions made at 3rd and 4th line have a relatively limited impact on modelled outcomes (see the results of Scenario analyses 2 and 3). We would also note that these sample sizes are larger than have been used in a number of previous oncology STAs.

The EAG notes as well that the need to use strong assumptions to inform health state utility values is equally true of partitioned survival models, where a strong assumption is made that the observed data from 1st line pre- and post-progression reflects utilities for patients receiving later lines of treatment not observed in the trials.

At face, partitioned survival models require fewer assumptions. However, this is because a range of key and often unjustifiable assumptions, including those above, are built in and unacknowledged. This was raised as a key concern within NICE technical support document (TSD) 19.[2] Exploring uncertainty appropriately does not increase decision risk; it instead seeks to quantify it and describe its impacts. The alternative is to ignore its true extent.

Finally, the EAG acknowledge the issues with run-time with the hybrid state transition model. All scenarios are now presented within the updated results. In order to run the probabilistic sensitivity analyses (PSA) an alternative version of the model was produced which calculates the exponential function equivalent to the area under the curve to inform transitions for 2nd and later lines removing the need to use tunnel states. This reduces the model run time considerably (to three minutes on a standard laptop) and is explained in greater detail in the original EAG report Appendix R.

In regard to redaction of the UK RWE we would note that the company are able to replicate analyses using only trial data presented in Scenarios 6 and 7 with the data available to them.

Issue 2: Economic implications of trial generalisability to RWE

Report sections	
Description of issue and why the EAG has identified it as important	As a result of access to a robust RWE dataset, the EAG has been able to compare estimates for OS and PFS between trials and data from a UK cohort. Linked to Key Issue 6 in the clinical effectiveness analysis, it is generally the case across most treatments that RWE reflects lower survival than the corresponding trial evidence, though RDIs are also lower in RWE than the corresponding trials. This raises important questions about the generalisability of the trial evidence base as a whole as a suitable basis for understanding expected impacts in the UK population. For example, pem+lenv is cost-effective against cabo using the STM when trial data is

Report sections	
	used for effectiveness, patient characteristics, and subsequent treatment distribution together. An additional benefit arising from the use of RWE is it is considerably more mature than the corresponding trials, reducing extrapolation uncertainty.
What alternative approach has the EAG suggested?	The EAG has used RWE to parameterize curves for reference treatments in its base case, while maintaining relative treatment effects from corresponding NMAs at each line.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on the cost-effectiveness estimates is that LYs and QALYs will be decreased for most treatments compared to analyses using trial baselines. It may also be the case that a different pattern of cost-effectiveness results, possibly suggesting different decisions, would be in evidence using RWE instead of trial evidence.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; lenv, lenvatinib; LYs, life years; NMA, network meta-analysis; OS, overall survival; pem, pembrolizumab; PFS, progression free survival; RDI, relative dose intensity; RWE, real-world evidence; STM, state transition model; UK, United Kingdom

Company comment:

The company raise a number of concerns relating to the real-world evidence used, including a) apparent conflict with structured expert elicitation; b) external validity of the RWE and how this was assessed; and c) what the company regards as relatively sparse information relating to the characteristics of the dataset used.

The company also raises an objection to the EAG's assertion as to the comparative estimates of survival between RWE and trials, and the use of RWE as a comparatively more mature source to reduce extrapolation uncertainty. The company notes that use of trial data is unavoidable; that it is not the role of this appraisal to question the use of trial data for cost-effectiveness modelling; and that the uncertainty raised by the EAG is not, in fact, an uncertainty.

Other stakeholder comments:

Kidney Cancer UK note that the difficulties in generalisability of clinical trial data to real world evidence have been known for many years and that additional modelling may not be able to overcome these difficulties.

EAG response:

The EAG asserts that its systematic search, review and expert consultation have collectively identified the best available real-world evidence data source for this appraisal. It draws on UK-specific patients across a range of sites and contexts and over a recent but substantial time period. Specifically, the dataset includes patients from all regions of the UK, and of England specifically; includes a mix of secondary and tertiary centres; and includes patients across

urban and rural geographies. External validity assessment was carefully documented in the relevant sections of the EAG report. It is not unexpected that there would be imperfect agreement with expert elicitation given that elicitation was drawn primarily from experts in key academic centres, a point the EAG acknowledged; moreover, the structured expert elicitation is one data point used elsewhere in the EAG's analysis. The EAG also notes that the company does not believe it has had adequate information on generalisability. The EAG presented patient characteristics, visual depictions of treatment pathways, and summary information on survival curves. It is unlikely that additional information would have been forthcoming in any other presentation of trial data.

While the EAG agrees that it is not the role of this appraisal to question the role of randomised trials as a data source, it would be disingenuous to ignore that RWE has previously played an important role in NICE appraisals. It is a standard, if not central, issue in many NICE appraisals that RWE presents systematically different survival patterns than evidence from trials. The EAG regards it is for the Committee to determine what the appropriate baseline data are for natural history parameters. The EAG proposes that these most appropriate data are from RWE, and that RWE has an important part to play in understanding the likely distribution of patient characteristics in clinical practice. The RWE source preferred by the EAG benefits from comparatively superior generalisability to UK practice; exceptional completeness, especially at first and second line; and, by corollary, maturity of PFS outcomes at first and second line in terms of number of events accrued.

Issue 3: Maturing data relating to IO/TKI combinations have magnified uncertainties relating to their long-term effectiveness

Report sections	
Description of issue and why the EAG has identified it as important	Clinical effectiveness Key Issue 10 highlighted the evolution over time in survival outcomes, particularly for IO/TKI combinations, as well as some evidence of 'slippage' on OS and PFS outcomes. Indeed, there is [redacted] for cabo+nivo combination therapy. In the context of the cost-effective analysis, this exacerbates decision risk due to differential follow-up between IO/TKI combinations and generates additional extrapolation uncertainty. The longest-term available data for an IO/TKI combination relate to pem+axi combination therapy, which is not recommended in England. Slippage in estimated HRs for OS is reflected in a KM curve that converges with suni at later timepoints. A similar pattern is apparent for pem+lenv combination therapy with a data cut at 49.8 months median follow-up, but not for nivo+ipi combination therapy. Clinical input suggested that IO/TKI combinations would be expected to reflect similar long-term relative effectiveness as TKI monotherapy. As a result, the long-term effect of

Report sections	
	IO/TKI combinations remains unclear. Converging survival curves may be due to low numbers at risk, initial response driven by TKIs, loss of benefit when TKIs are stopped, or antagonistic impacts of TKI-related toxicity precluding optimal IO effectiveness.
What alternative approach has the EAG suggested?	The EAG undertook extensive scenario analyses to understand the impact of different long-term effectiveness scenarios.
What is the expected effect on the cost-effectiveness estimates?	As highlighted in clinical effectiveness Key Issue 10, it is likely that cost-effectiveness estimates for novel treatments drawing on comparatively less mature trials may be unduly optimistic. From an economic perspective, additional extrapolation uncertainty may increase decision risk.

Abbreviations: axi, axitinib; cabo, cabozantinib; EAG, External Assessment Group; HR, hazard ratios; IO, immune-oncology; ipi, ipilimumab; KM, Kaplan-Meier; lenv, lenvatinib; nivo, nivolumab; OS, overall survival; pem, pembrolizumab; PFS, progression free survival; suni, sunitinib; TKI, tyrosine kinase inhibitor

Company comment:

The company argues that cabozantinib + nivolumab may be disadvantaged due to appraisal later in the time frame as compared to other technologies, and asserts that the “EAG is suggesting that a product’s cost-effectiveness depends on the follow-up length of the pivotal trial source for effectiveness”. The company asserts further that appraisal and decision-making should acknowledge differences in length of the follow-up between studies.

They highlight than in addition to the issues raised by the EAG relating to nivolumab plus ipilimumab potentially being disadvantaged when using the hybrid state transition model structure due to higher than expected PPS benefit. They also highlight that the hazard ratio h has increased over time for pembrolizumab plus lenvatinib within CLEAR from 0.41 to 0.59 at the latest datacut and may not yet be stable meaning that a later datacut for CLEAR could prove even less advantageous to pembrolizumab plus lenvatinib relative to nivolumab plus ipilimumab and cabozantinib plus nivolumab where the company considers that HRs have been more stable over time.

Other stakeholder comments:

BMS note that the impact of the type of prior treatment on outcomes has not been fully explored within the scenarios presented and is likely to bias towards TKI monotherapy and IO+TKI

combinations. They consider this of particular relevance given the observed slippage in PFS and OS hazard ratios which they do not consider to have been adjusted for.

EAG response:

The impact of slippage in the hazard ratios over time and the timing of appraisal

The EAG agrees with the company that duration of follow-up is an important uncertainty for the committee to consider but disagrees with the company's reading of the key issue as described. There is a difference between an estimate of cost-effectiveness, which is always an approximation of the "true" cost-effectiveness of a drug. The true cost-effectiveness of a drug is not a function of trial follow-up time but rather of the drug's effectiveness with fully mature follow-up data in the real-world setting. This is important because it represents the challenges of *estimating* cost-effectiveness using trial data. What is presented in this appraisal is the current best estimate of cost-effectiveness based upon the available data at the time of this appraisal, along with an evaluation of the level of uncertainty within those estimates.

The EAG was unable to source the company's stated hazard ratio of 0.59 for the latest datacut from CLEAR (49.8 months). Motzer 2023[3] presents a hazard ratio of 0.47 in the all-risk population and 0.43 in the MSKCC intermediate/poor risk population. It would appear to the EAG that the change in PFS HRs within CheckMate 9ER and CLEAR is very similar over time (all-risk population: 0.51 to 0.59 over 4 datacuts in CheckMate 9ER and 0.41 to 0.47 over 4 datacuts in CLEAR; Figure 32 EAG report).

Finally, the EAG note that within the EAG base case, treatment effect waning is assumed to apply from 5 years onwards (~ 1 year after the current median follow-up for both CLEAR and CheckMate 9ER) limiting the impact of this issue on the model results.

The impact of prior treatment on outcomes

The EAG acknowledge the point raised by BMS in relation to the impact of the type of prior treatment on outcomes. This has been raised previously in the EAG report as a limitation of the current analysis. The trials available for 2nd line and later treatment often required treatment with a prior TKI (METEOR, NCT01136733, RECORD-1, TIVO-3) and, where they did not, had a high proportion of patients who had received prior TKI treatment (e.g. CheckMate 025). None of the trials including 2nd and further line patients were run in an era where IO combinations were available. This lack of evidence relating to optimal later line treatments following IO

combinations is flagged in EAG Key Issue 1. The lack of evidence relating to the impact of the type of previous treatment to inform the model was flagged in Section 4.3.1.8.

We would disagree that this biases in a meaningful way towards IO + TKI combinations as well as TKI monotherapy. Based upon the responses to expert elicitation presented in Section 4.2.5 of the EAG report:

"For patients receiving cabozantinib 2nd line, there was a lower proportion of patients expected to be alive and progression free at 3 years after receiving prior TKI monotherapy therapy (mean 14%; 95% CI 8% - 23%) than after nivolumab plus ipilimumab therapy (mean 29%; 95% CI 18% - 40%), or IO/TKI combination treatment (mean 31%; 95% CI 22% - 41%). One of the clinicians completing the survey noted that they would expect cabozantinib to perform less well after TKI monotherapy. Two clinicians noted they would expect cabozantinib to behave similarly following IO/IO and IO/TKI combinations. Dr Larkin noted that the activity of cabozantinib would be expected to be lower after receiving treatment with a prior TKI (particularly sunitinib, pazopanib or tivozanib) due to similarities in the mechanism of action and that this would be expected to be particularly evident following TKI monotherapy."

Based on fitting a basic exponential curve to the 3 data points available from expert elicitation and on comparing the impact of the three types of prior treatment, there is little difference between prior nivo+ipi and IO / TKI combinations (HR 1.001). There is, however, a greater difference between prior nivo+ipi and prior TKI monotherapy (HR 1.588). An exploratory scenario analysis has been presented including this impact(Scenario 76). In this analysis it was assumed that:

- The effectiveness of cabozantinib or axitinib immediately after TKI monotherapy would be impacted (these are the only TKI monotherapies allowed). Based on the UK RWE this makes up [redacted] of subsequent therapy after pazopanib, [redacted] after sunitinib, [redacted] after tivozanib and [redacted] after cabozantinib
- The effectiveness of these treatments would be reduced (this was assumed for simplicity, in reality it would be expected that the effectiveness of these treatments would be increased after IO combinations as the trials for these treatments included previous TKI monotherapy)

This scenario had a relatively limited impact due to the relatively low proportion of patients expected to receive TKI monotherapy directly after TKI monotherapy at first line.

The EAG would also note that the observed slippage in hazard ratios is accounted for via the assumptions made in relation to treatment effect waning as well as the use of a time-varying NMA in the base case.

Issue 4: Impact of RDI and toxicity on economic case

Report sections	
Description of issue and why the EAG has identified it as important	Toxicity was quantified using standard methods, but the extent and impact of toxicity remains highly uncertain. HRQoL information from company estimates did not pass face validity when scrutinised by clinical experts, including as relates hand and foot syndrome, diarrhoea, and fatigue; in addition, the EAG implemented a number of adjustments to capture the relative impacts of these three key AEs. Due to selection bias (i.e. the worst off patients being the least able to report impacts), the impact of key AEs is likely to be underestimated. The EAG could not obtain any relevant RWE to inform AE rates or impact. In addition, RDIs appear lower in clinical practice (i.e. based on the RWE) as compared to trials, though these data are not of high quality. The RDI for pem+lenv may be less reliable than for other treatments given it was estimated based on the median number of infusions.
What alternative approach has the EAG suggested?	The EAG explored scenarios relating to doubling AE impacts and examining RDIs from RWE instead of from relevant trials, as well as setting RDI to 100%. All RDI scenarios should be considered to understand the impact of differential quality of estimation and generalisability on cost-effectiveness estimates.
What is the expected effect on the cost-effectiveness estimates?	Increasing AE impacts reduces estimated QALYs from included treatments, whereas lower RDIs reduce treatment costs. Increased impact would be expected to reduce the cost-effectiveness of combination therapies relative to monotherapies. We would welcome additional input from the company during technical engagement on whether the differences in RDI between the different IO/TKIs calculated are realistic and if not alternative suggested inputs. The EAG will also seek additional clinical input on this point during technical engagement.

Abbreviations: AE, adverse events; EAG, External Assessment Group; HRQoL, health-related quality of life; IO, immune-oncology; lenv, lenvatinib; pem, pembrolizumab; QALYs, quality adjusted life years; RDI, relative dosing intensity; RWE, real world evidence; TKI, tyrosine kinase inhibitor

Company comment:

The company has supplied additional information for the RDIs for various treatments with the key points made being that:

- The new information supplied for PD-1 inhibitors relates to dose delays and interruptions and is defined, as in TA858, as the mean number of administrations received divided by the mean number of administrations expected during the time the patient was considered to be

on treatment. This appears to assume all patients remain on treatment for the maximum fixed duration period.

- An updated RDI of [redacted]% is provided for nivolumab as part of cabozantinib plus nivolumab using this method and an updated RDI of [redacted]% is provided for cabozantinib
- An updated RDI of 82.3% is provided for cabozantinib monotherapy which is stated to come from the EPAR
- Updated RDIs are provided for other treatments in the Appendix supplied by the company
- Trial follow-up may impact on the RDI and RDI was not always available for the same data cut as effectiveness data. Data is provided showing that the mean RDI for nivolumab increases in the later data cut 49.8% (median 18.1 months of follow-up) versus [redacted]% (median 44 months of follow-up) and remains similar for cabozantinib 73.9% (median 18.1 months of follow-up) versus [redacted]% (median 44 months of follow-up)

The company provided clarification on the source of this data in their clarification responses on 22nd September. The responses made it clear that there is an issue with the methods used in double-counting discontinuation as observed in the TTD KM for the calculation of the RDIs associated with IO treatments as they use the maximum intended duration of treatment within the denominators provided.

The company state that anecdotal feedback from clinicians they consulted suggests that lower dose intensities are achieved with pembrolizumab and nivolumab when used in combination with lenvatinib and cabozantinib resulting in delays in treatment and that the RDIs reported in CLEAR and CheckMate 9ER are in line with real world experience. The lower dose intensity achieved with the IOs is believed to be attributable to lenvatinib and cabozantinib due to being more potent multi-targeted TKIs compared to other TKIs such as axitinib. This is also reflected in the lower dose intensities also seen with lenvatinib and cabozantinib when used in combination with PD-1 and PD-L1 inhibitors.

The company also state that high RDIs are achieved (>90%) for PD-1 and PD-L1 inhibitors when used as monotherapy including in the adjuvant setting and for avelumab when used in combination with axitinib (86.8%) in line with clinical feedback to the EAG that axitinib and tivozanib may be better tolerated than other TKIs.

Other stakeholder responses:

Kidney Cancer UK note that kidney cancer patients (like all cancer patients) are likely to endure relatively serious side effects and request an explanation of how, and to what extent, this point is being incorporated into the overall assessment and scenario exploration.

EAG response:

The EAG observed that the company has updated the method of calculating RDIs based on the mean number of administrations received and expected. They stated this was conducted as per TA858. Subsequently, as part of round one technical engagement responses the EAG included four additional scenarios (apply all alternative RDI, state transition and PartSA and apply alternative RDI for IO combinations, state transition and PartSA) using the values provided by the company. Where both longer- and shorter-term follow-up data were provided, only longer term follow up was used for the respective treatments (namely, cabozantinib + nivolumab and sunitinib).

Results were presented as scenario analysis rather than the new RDIs being incorporated into the base case as the EAG was unable to verify the RDIs calculated for nivolumab and cabozantinib as part of nivolumab + cabozantinib combination, pembrolizumab as part of pembrolizumab + lenvatinib combination, ipilimumab as part of nivolumab + ipilimumab combination and sunitinib, as the mean number of administrations received and expected values used to calculate these RDIs were not clearly referenced in the company response. Further, it was also unclear to the EAG whether the revised method was aligned with the TTD data used i.e., whether the revised method of calculating RDI considered that early discontinuation has already been accounted for within the TTD Kaplan-Meier (KM).

In addition, regarding the lower dose intensities achieved with IOs, clinical opinion to the EAG sought after production of the EAG report prior to receipt of the new data indicated that: in CLEAR as patients had to receive 20 mg lenvatinib it is expected that the lower than expected median doses of pembrolizumab were caused by the toxicity due to the high dose of lenvatinib being attributed instead to IO toxicity and patients therefore having to miss dosing of pembrolizumab. In CheckMate 9ER, the TKI component (cabozantinib) is at 40 mg which is lower than the monotherapy dose (60 mg) and therefore more tolerable. The clinical feedback provided by the company was therefore not entirely in line with the clinical opinion provided to the EAG for CheckMate 9ER.

Following the first set of technical engagement the company responded to EAG requests for clarification on 22nd September. Based upon this there would appear to have been double counting in discontinuations between the RDI and TTD presented by the company for nivolumab and pembrolizumab as the difference between RDIs according to follow-up length indicates it is likely that the maximum possible treatment duration was used in the calculation. Within TA858 it is clear that the mean duration of treatment (rather than maximum duration of treatment) is used, which correctly avoids the issue of double counting of discontinuation.

The EAG therefore updated our base case as per the Table 7 below incorporating new company data where this was more relevant and references were provided and recalculating the RDIs for nivolumab as part of the cabozantinib plus nivolumab combination and pembrolizumab as part of the pembrolizumab plus lenvatinib combination to use the same methodology as TA858 for the duration of treatment and the new data provided by the company for the number of administrations received. Our methodology to the incorporation of lenvatinib has also been updated to better account for the different pill sizes and titration regime used in the UK; further details on this are provided in Section 6.3.8 For cabozantinib as part of cabozantinib plus nivolumab combination, the company's initial clarification response (CheckMate 9ER; A10a) calculated RDI based on the sum of the duration of the doses that are greater than 0mg/sum of duration of all doses (including dose of 0mg). However, the response as part of technical engagement (Table 1; Stakeholder response) included cabozantinib RDI calculation based on mean daily dose/maximum dose until disease progression or unacceptable toxicity. The EAG considered the method used as part of technical engagement response to be more appropriate and included in the EAG updated base case, as it aligned more closely with the method used in TA858. However, we would note that this method is likely to underestimate the total RDI somewhat as some patients may discontinue for reasons other than disease progression or unacceptable toxicity. The EAG presents a scenario analysis where all RDIs are set to 100% given the inconsistency in the methods used within the available RDIs.

The EAG also reiterate the difficulties in fully accounting for the impact of the toxicities experienced by patients with the available data. The impact has been explored to the extent possible within sensitivity and scenario analysis, but we consider it likely that the impact of toxicities is underestimated in the base case model.

Table 7: Relative dose intensities of treatments considered – updates to EAG base case following company clarification on the new RDI data provided

Treatment	Line	RDI, %	Current EAG base case (Trial data)		RDI, %	Current EAG scenario (Ipsen provided data)		EAG updated base case, RDI, %
			Source	Data cut-off (if available)		Source	Data cut-off (if available)	
Ave+axi	1L adv	Ave: 91.5 Axi: 89.4	Motzer et al 2019	June 20,2018	Ave: 86.8 Axi: 84.2	EPAR, Table 5, page 68	Jan, 2019	Ave: 86.8 Axi: 84.2
Cabo	1L adv	93.3	CABOSUN Clinical study report (as reported in TA542)	13 January 2017 for OS and 15 September 2016 for PFS	82.3	CABOSUN EPAR, Table 24, page 48	13 Jan 2017 (data cut off for survival; safety data set)	82.3
	2L	93.3	Assumed same as 1L	-	75.3	METEOR EPAR, Table 40, page 91	-	75.3
	3L	93.3	Assumed same as 1L	-	75.3			75.3
Lenv+evero	Prior VEGF (2L)	Lenv: 70.4 Evero: 89.3	CLEAR trial: Motzer et al 2021	-	Lenv: 73.5	To reflect trial 2L population in HOPE 205 study (EPAR, Table 38, page 107) Everolimus RDI not reported in EPAR	--	Lenv: 73.5¥ Evero: 89.3
	3L	Lenv: 70.4 Evero: 89.3	Same as 2L	-	Lenv: 73.5	Same as 2L	-	Lenv: 73.5¥ Evero: 89.3
Pem+lenv	1L adv	Lenv: 69.6 Pem: 62.9	CLEAR trial: Motzer et al 2021	28 Aug 2020	Lenv: 70.5 Pem: 59.1 (company provided) Pem: 98.8% ^ (EAG recalculated)	Lenv: EPAR, Table 35, page 101 Pem based on mean number of infusions received at 26.6 months median follow-up from EPAR, Table 36, page 101	28 Aug 2020	Lenv: 70.5¥ Pem: 98.8

Treatment	Line	RDI, %	Current EAG base case (Trial data)		RDI, %	Current EAG scenario (Ipsen provided data)		EAG updated base case, RDI, %
			Source	Data cut-off (if available)		Source	Data cut-off (if available)	
Cabo+nivo	1L adv	Nivo: [redacted] Cabo: [redacted]	CheckMate 9ER (clarification response; A10a)	-	Nivo: [redacted] (company provided) Nivo: [redacted] (EAG recalculated) * Cabo: [redacted]	CheckMate 9ER Nivo based on mean number of doses received (44-month follow-up data-cut) – aligns method with mean number of doses of pembrolizumab calculation. Cabo: aligns with same method of calculation as lenvatinib.	44 month follow up data cut – uses mean number of doses	Nivo: [redacted] Cabo: [redacted]
Suni	1L	81	CheckMate 9ER (clarification response; A10a)	-	81	CheckMate 9ER	44 month follow up data cut – uses mean number of doses	81
	2L+	81	Assumed same as 1L	-	83.9	RDI from METEOR – 2L/3L trial of Cabo vs. Suni EPAR, Table 40 ,page 91	ORR and PFS - 22nd May 2015, OS - 31st December 2015	83.9
Nivo+ipi	1L adv	Nivo induction : 79 Nivo maintenance : [redacted] Ipi : 79	CheckMate 214; Motzer et al 2018 For nivo, same RDI as cabo+nivo to be assumed for nivo mono	-	Nivo : 87.4 Ipi (CADTH) : 84.8 Ipi (EPAR) : 90	Nivo/Ipi: Based on CADTH report (source for which is not available) Ipi: Based on mean number	Nivo: Not available Ipi: 26-Jun-2017	Nivo induction : 90 Nivo maintenance : [redacted] Ipi : 90 The source of the data within

Treatment	Line	RDI, %	Current EAG base case (Trial data)		RDI, %	Current EAG scenario (Ipsen provided data)		EAG updated base case, RDI, %
			Source	Data cut-off (if available)		Source	Data cut-off (if available)	
			maintenance as data not available			of infusions administered EPAR, Table 20, page 52		the CADTH report is unclear and therefore EPAR data has been preferred for ipi and previous assumptions relating to nivo have been maintained

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; NICE, National Institute for Health and Care Excellence; NR, not reported; RDI, relative dose intensity; TA, technology appraisal; TKI, tyrosine kinas inhibitor

* calculated as: [redacted] ([redacted])

^ calculated as: 20.7/20.87 = 99.18% (20.87 calculated as, (14.45 (mean duration for pem indication column EPAR) * ((365.25/7)/12))/3)

¥ RDI data for lenvatinib has been used to calculate the proportion of patients receiving the 14mg dose (as opposed to 10mg or 18/20mg): see Section 6.3.8

Issue 5: Problems with the HRQoL data supplied by the company

Report sections	
Description of issue and why the EAG has identified it as important	HRQoL data supplied by the company did not have face validity with respect to the general population. In addition, HRQoL estimates were higher across health states than for most other appraisals. The EAG also noted a range of methodological problems with the HRQoL estimates, including the justification for model selection approach; a lack of cross-validation or external validation; and a lack of transparency relating to calculation steps between model estimation and mean utilities.
What alternative approach has the EAG suggested?	The EAG base case uses an alternative source considered to have greater face validity. Company estimates were tested in scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	The EAG's base case generates lower QALYs, leading to higher ICERs. However, the impact is relatively limited.

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Company comment:

The company note the following:

- The high utility values derived from the analysis of CheckMate 9ER are supported by other previously published studies assessing the cost-effectiveness of treatments with similar mechanisms of action.
- There is precedence in the literature for maintaining a high post-progression utility value, which aligns with the results of the CheckMate 9ER analysis.
- Ipsen suggest that the EAG perform a scenario analysis that calculates the proportional reduction from the trial and applies it to the general population utility, in addition to its planned scenario analysis using the CheckMate 9ER derived utilities in the model.
- Ipsen has sought further clarification on what they consider to be uncertainties introduced into the analysis via the EAG's approach to estimating utility from 2nd line onwards.

EAG response:

The EAG acknowledge the company's points regarding the validity of the CheckMate9ER utility values and the studies used to support the validity of the trial data. However, the EAG assessment report has extensively discussed the limitations surrounding CheckMate9ER and noted limitations surrounding both Ambavane et al.[4] and Bensimon et al[5] as supporting studies, see p321 of the EAG Assessment Report. The EAG maintain that the values from CheckMate9ER lack face validity and are therefore unsuitable for use in the base case analysis.

Similarly, regarding the post-progression utility value, the EAG has noted potential limitations surrounding Haddad et al.[6], McCrea et al.[7] and TA630[8] on p.321 of the EAG Assessment Report, which limits the generalisability of these published values to those reported in CheckMate9ER.

Furthermore, regarding the company's request for an additional scenario analysis whereby utilities are estimated using the proportional reduction from the CheckMate9ER study and applied to the general population utility, the EAG has added commentary to Section 6.3.11.1 of this document; this had already been provided.

The EAG note that Ipsen has sought further clarification what they consider to be uncertainties introduced into the analysis via the EAG's approach to estimating utility from 2nd line onwards. There was some uncertainty surrounding the progression-free utility in TA498 for 2nd line treatment as this was higher than the progressive disease (PD) utility reported in TA645 for 1st line treatment. The EAG therefore assumed that progression-free utility at 2nd line is equal to the utility of PD patients in 1st line, to prevent logical inconsistencies. Overall, due to the lack of robust HRQoL evidence for subsequent lines of treatment, the EAG used a multiplicative approach as outlined in the NICE Decision Support Unit (DSU) TSD 12 guidance to estimate the utility value for the 2nd line PD health state, and for the progression-free and PD health states of subsequent lines. We would note that there are also uncertainties with the companies preferred method: namely the strong assumption that the observed data from 1st line pre- and post-progression reflects utilities for patients receiving later lines of treatment not observed in the trials.

Issue 6: Outstanding uncertainties in application of severity modifiers

Report sections	
Description of issue and why the EAG has identified it as important	Application of the severity modifier remains unclear for multi-comparator decisions, such as in the current appraisal. The EAG has found that the relevance of the severity modifier depends on whether the comparator is current best practice or pairwise differences are calculated against every other treatment. In addition, the availability of different comparators will impact the estimated QALY shortfall in different risk groups. Comparison to current best practice suggests a proportional shortfall of 0.85 in the all-risk group but not in any of the risk-specific groups, which is counterintuitive. This finding is primarily because of the availability of high-effectiveness comparators in intermediate/poor risk patients, whereas in favourable risk patients, older treatments generate better prognoses; moreover, in all-risk populations, only TKI monotherapies are available via routine commissioning.

Report sections	
What alternative approach has the EAG suggested?	The EAG discusses application of the severity modifier as compared to current best practice as opposed to pairwise but has not applied the severity modifier. Until more detailed guidance is produced, the method of application of the severity modifier is a key uncertainty.
What is the expected effect on the cost-effectiveness estimates?	Application of a severity modifier will impact the cost-effectiveness threshold in different risk populations and to different degrees.

Abbreviations: EAG, External Assessment Group; QALYs, quality adjusted life years; TKI, tyrosine kinase inhibitor

Company comment:

The company requested the EAG address several queries:

- how and if severity modifiers were applied, and whether severity modifiers for a pairwise analysis have been performed;
- explain why consideration of market shares did not support a fully incremental approach; and
- undertake a pairwise severity modifier analysis accounting for the RWE-based market shares of 1L therapies.

The company also requested a “more comprehensive assessment from the EAG and a more prescriptive recommendation” as to the applicability of severity modifiers.

Other stakeholder comments:

Kidney Cancer UK and MSD also note the importance of resolving these uncertainties as of relevance beyond the current appraisal.

EAG response:

Within the updated analyses presented in this response the severity modifier is considered for pairwise analysis as well as the fully incremental approach. We present the severity modifier that would apply to each comparator individually for the base case. We would note, however, that pairwise analyses are generally best avoided as excluding relevant comparators from an incremental analysis can lead to serious errors in interpretation (e.g. leading to comparisons of interventions that are not on the efficient frontier).

The difference between consideration of market shares and a fully incremental approach is that the latter compares a new entrant to existing best practice in cost-effectiveness terms (that is, the next best non-dominated option), whereas a market share approach compares to current

practice. Based upon the company response to clarification question A23 the most recent data for the all-risk population indicate that the most frequently used treatments in the all-risk population in Q1 2023 are:

- Other IO / TKI combinations (pembrolizumab + lenvatinib, avelumab + axitinib and pembrolizumab + axitinib): [redacted]
- Nivolumab + ipilimumab: [redacted]
- Cabozantinib monotherapy: [redacted]
- Other TKIs: [redacted].

This indicates that current practice is increasingly made up of other novel therapies; comparison to which would not result in the application of a severity modifier as demonstrated in Table 8.

The EAG has applied the severity modifier, in line with prior precedent, on a deterministic basis. In order to understand the impact of the severity modifier in a probabilistic context, the EAG took the existing PSA results and examined what proportion would qualify for a 1.2 modifier for key comparators and populations (Table 8). In all populations and comparisons, except when comparing to TKI monotherapy in the intermediate / poor risk population, the anticipated impact would be very limited.

Table 8: Exploration of the impact of probabilistic application of the severity modifier

Population	Comparator	% of PSA runs qualifying for modifier
All-risk	Pazo	7.4%
Favourable risk	Pazo	0.04%
Intermediate / poor risk	Pem+lenv	0.02%
Intermediate / poor risk	Cabo	0%
Intermediate / poor risk	Pazo	47.8%

Abbreviations: cabo, cabozantinib; lenv, lenvatinib; pazo, pazopanib; pem, pembrolizumab; PSA, Probabilistic sensitivity analysis

The EAG consider that the provision of a more prescriptive recommendation as to the applicability of a severity modifier is not in its authority. The EAG believes that clarification of the intended application of NICE's severity modifier is for NICE to provide.

Issue 7: Impact of model structure on results

Report sections	
Description of issue and why the EAG has identified it as important	The EAG incorporated flexibility to undertake modelling in a state transition framework (EAG base case) or a PartSA framework (scenario analysis). Predicted LYs and QALYs were generally higher when using a PartSA. In particular, differences in the all-risk group were between 0.5 and 0.7 LYs, with differences more pronounced for TKI monotherapies than for cabo+nivo; but differences were even greater (0.9-2.0 LYs) in the favourable group, again with more substantial impacts for TKI monotherapies. In the intermediate/poor risk group, differences ranged from -0.03 to 1.3 LYs; in this risk group, estimates were similar between modelling approaches with the exception of nivo+ipi due to the use of FP NMA results. The FP NMA predicted a larger plateau for OS than for PFS; this is consistent with clinical advice received that there may be issues with the assessment of PFS for this particular combination and observation of higher than might be expected PPS in the nivo+ipi arm of the CheckMate 214 trial.
What alternative approach has the EAG suggested?	The EAG maintains that while both strategies are appropriate, it is for the committee to prefer one approach to the other. The EAG will explore drivers and plausibility of the two results during technical engagement.
What is the expected effect on the cost-effectiveness estimates?	While differences did not impact the overall result for cabo+nivo in the favourable or intermediate/poor risk groups, the EAG notes that this is a point for committee discussion.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; FP, fractional polynomial; lenv, lenvatinib; LY, life years; nivo, nivolumab; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PartSA, partitioned survival analysis; pem, pembrolizumab; PPS, post-progression survival; QALYs, quality adjusted life years; STM, state transition model; TKI, tyrosine kinase inhibitor

Company comment:

The company note that within the draft results supplied previously the hybrid state transition model (STM) and PartSA model structure appear to give markedly different results. They also ask the EAG to clarify whether clinical outcomes estimated by each model structure, and under different scenarios, have been validated by clinical experts and/or against the clinical expert elicitation exercise.

Other stakeholder comments:

Kidney Cancer UK note that they agree with the course of action proposed by the EAG.

EAG response:

The clinical validation conducted has been presented in the EAG report. Validation of every endpoint and every scenario was not considered feasible given the large number of scenarios (76) and potential treatment sequences (744 across all populations). Face validity checks were

conducted by the EAG as part of the quality control process during production of the updated results on the basis of the extensive clinical input already received.

In comparing the LYs gained across the two model structures while keeping all other settings the same (Table 9), it can be seen that within the EAG updated analysis the STM predicts similar LYs within PFS both on and off treatment. This is as would be expected as both analyses use the same PFS and TTD data. The only minor difference is in the favourable risk population where the UK RWE showed that treatment continued, on average, beyond progression for a short duration. This is handled differently in the two structures (assigned to PPS on treatment in the PartSA and to PFS in the STM, in order to avoid the need to split PPS states by whether the patient was still receiving the prior line of treatment or not).

Table 9: Comparison of LYs gained by model structure; results presented versus nearest non-dominated comparator

Structure	Technologies	PFS on treatment	PFS off treatment	PPS	Total
Risk population: All-risk					
State transition	Cabo+nivo	1.95	0.11	1.65	3.71
	Pazo	1.14	0.11	1.59	2.84
PartSA	Cabo+nivo	1.95	0.10	1.31	3.35
	Pazo	1.14	0.11	1.65	2.90
Risk population: Favourable risk					
State transition	Cabo+nivo	2.58	0.27	1.67	4.52
	Pazo	1.83	0.27	1.63	3.73
PartSA	Cabo+nivo	2.57	0.13	1.71	4.41
	Pazo	1.79	0.14	2.97	4.90
Risk population: Intermediate / poor risk					
State transition	Cabo+nivo	1.64	0.08	1.64	3.36
	Pem+lenv	2.29	0.09	1.24	3.62
	Cabo	1.79	0.09	1.58	3.46
PartSA	Cabo+nivo	1.64	0.08	1.24	2.95
	Pem+lenv	2.29	0.09	0.66	3.04
	Cabo	1.79	0.09	0.93	2.81

Abbreviations: cabo, cabozantinib; lenv, lenvatinib; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; PPS, post progression survival

There are differences in the PPS LYs as would be expected. This is because the PartSA model bases PPS on independent extrapolation of OS data, whereas the STM bases PPS on PFS for each subsequent line of treatment for each sequence, followed by PPS for the final line. In all three risk populations, increased total LYs are predicted using the STM for novel therapies with the expected LYs for TKI monotherapies other than cabozantinib being similar across models in the all-risk and intermediate / poor risk population, and lower in the favourable risk population.

Within the all-risk population these differences are very small in the pazopanib arm due to the completeness of the available OS data from the UK RWE (difference of 0.06 LYs). Differences are larger in the cabozantinib + nivolumab arm where data are less mature with a difference of 0.36 LYs (11%); in this model, the STM provides an increased expectation of long-term survival due to the allowance for additional lines of active treatment. The most frequently used active treatment after cabozantinib + nivolumab is expected to be lenvatinib + everolimus compared to pazopanib where patients are expected to receive sequences starting predominantly with nivolumab or cabozantinib. Lenvatinib + everolimus is predicted to have the most favourable PFS of the available 2nd line treatments in the PH NMA (HR 0.79 vs cabozantinib monotherapy and 0.48 vs nivolumab), which leads to expectation of increased PPS in addition to the longer time spent in PFS. Figure 4 demonstrates that the state transition model provides a good fit to the reference Kaplan Meier curve.

Figure 4: Overall survival model fit to Kaplan Meier data (sunitinib arm, all-risk population)

Within the favourable risk population the differences are even more pronounced for two reasons: the OS data are considerably less mature due to the better prognosis of these patients and the OS HR for cabozantinib + nivolumab within CheckMate 9ER is greater than 1, which leads to an expectation of reduced LYs in the PartSA model. This is compared to an expectation of increased LYs in the STM, where expected LYs are driven by the expectation of which subsequent therapies will be received and the performance of those subsequent therapies alone.

Figure 5 demonstrates that in the favourable risk population, the state transition model in general underpredicts overall survival when compared to the reference Kaplan Meier curve. This indicates that may be some impact of prior risk status on outcomes which could not be addressed with the data available.

There is considerable uncertainty within the clinical community as to what the expectations for long-term benefit for IO/TKI combinations are in the favourable risk population (previously raised in Clinical Key Issue 7). The results provided by the two model structures reflect this uncertainty.

Figure 5: Overall survival model fit to Kaplan Meier data (sunitinib arm, favourable risk population)

Within the intermediate / poor risk population, predicted LYs are highest in both models for the lenvatinib + pembrolizumab arm. This is driven by PFS gains. In both models, PPS LYs are expected to be lower than other key comparators; within the STM the active treatment expected to be used most often 2nd line is cabozantinib. The key difference between the two models is in the total LYs predicted for cabozantinib relative to cabozantinib + nivolumab, which reverses direction as in the STM the gains in PFS predicted from the NMA (i.e. as driven by results from CABOSUN) are not outweighed by the decreased PPS. In contrast, using OS data from CABOSUN directly provides more conservative estimates. Uncertainty in the comparison to cabozantinib is discussed in more detail in Economic Key Issue 9. As with the all-risk population the state transition model provides a good prediction of the overall survival Kaplan Meier data for the reference curve (Figure 6).

Figure 6: Overall survival model fit to Kaplan Meier data (sunitinib arm, intermediate / poor risk population)

Comparison of discounted QALY outcomes generally mirror the comparison of LYs with PPS QALYs being somewhat lower relative to LYs in the STM due to the lower utilities used at 3rd line plus as would be expected given the difference in model inputs (Table 10). This does not have a major impact on results and the ordering of the treatments in terms of effectiveness remains the same as in the comparison of LYs.

Table 10: Comparison of QALYs gained by model structure; results presented versus nearest non-dominated comparator

Structure	Technologies	PFS	1L AEs	PPS	Total
Risk population: All-risk					
State transition	Cabo+nivo	1.41	-0.03	0.83	2.22
	Pazo	0.88	-0.01	0.81	1.69
PartSA	Cabo+nivo	1.41	-0.03	0.77	2.15
	Pazo	0.88	-0.01	0.96	1.83
Risk population: Favourable risk					
State transition	Cabo+nivo	1.88	-0.03	0.81	2.67
	Pazo	1.39	-0.01	0.84	2.23
PartSA	Cabo+nivo	1.78	-0.03	0.94	2.70
	Pazo	1.31	-0.01	1.61	2.91

Structure	Technologies	PFS	1L AEs	PPS	Total
Risk population: Intermediate / poor risk					
State transition	Cabo+nivo	1.2	-0.03	0.83	2.00
	Pem+lenv	1.61	-0.03	0.63	2.23
	Cabo	1.3	-0.02	0.78	2.07
PartSA	Cabo+nivo	1.2	-0.03	0.74	1.91
	Pem+lenv	1.61	-0.03	0.36	1.96
	Cabo	1.3	-0.02	0.55	1.82

Abbreviations: 1l, 1st line; AEs, adverse events; cabo, cabozantinib; lenv, lenvatinib; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; PPS< post-progression survival; QALYs, quality adjusted life years

Table 11: Comparison of costs at list price by model structure; results presented versus nearest non-dominated comparator

		1L costs			Subsequent treatment			MRU			
Structure	**Technologies**	**Drug cost**	**Admin cost**	**AE cost**	**Drug cost**	**Admin cost**	**AE cost**	**1L**	**Subsequent treatment***	**EOL cost**	**Total cost**
Risk population: All-risk											
State transition	Pazo	£6,481	£324	£512	£44,753	£893	£688	£2,628	£14,422	£7,949	£78,649
	Cabo+nivo	£158,898	£3,242	£1,127	£34,672	£271	£920	£4,088	£12,897	£7,732	£223,847
PartSA	Pazo	£6,481	£324	£512	£41,312	£3,401	£620	£2,615	£7,603	£7,923	£70,790
	Cabo+nivo	£158,898	£3,242	£1,127	£29,592	£610	£542	£4,074	£6,874	£7,797	£212,756
Risk population: Favourable risk											
State transition	Pazo	£9,859	£395	£512	£45,497	£908	£699	£4,058	£14,662	£7,730	£84,321
	Cabo+nivo	£185,764	£3,445	£1,127	£34,157	£267	£907	£5,354	£12,707	£7,549	£251,276
PartSA	Pazo	£9,859	£395	£512	£40,442	£3,329	£607	£3,807	£9,457	£7,455	£75,862
	Cabo+nivo	£185,764	£3,445	£1,127	£29,037	£599	£532	£5,101	£7,316	£7,565	£240,485
Risk population: Intermediate / poor risk											
State transition	Cabo	£86,584	£387	£732	£43,582	£1,033	£671	£3,753	£13,775	£7,791	£158,308
	Pem+lenv	£173,402	£2,940	£1,062	£27,338	£229	£732	£4,622	£11,578	£7,745	£229,649
	Nivo+ipi	£80,711	£3,210	£335	£30,191	£243	£674	£2,277	£12,078	£8,056	£137,774
	Cabo+nivo	£140,562	£2,990	£1,127	£34,654	£271	£920	£3,487	£12,889	£7,822	£204,721
PartSA	Cabo	£86,584	£387	£732	£38,999	£4,542	£584	£3,753	£6,228	£7,945	£149,753
	Pem+lenv	£173,402	£2,940	£1,062	£25,646	£504	£837	£4,622	£5,665	£7,888	£222,567
	Nivo+ipi	£80,711	£3,210	£335	£26,278	£542	£781	£2,277	£8,055	£7,910	£130,097
	Cabo+nivo	£140,562	£2,990	£1,127	£29,909	£617	£548	£3,486	£6,833	£7,898	£193,969

Abbreviations: 1L, 1st line; admin, administration; AE, adverse event; cabo, cabozantinib; EoL, end of life; lenv, lenvatinib; MRU, medical resource use; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab

* includes on progression costs, these are only applied to the first progression in the PartSA

Comparison of discounted costs using the updated analysis shows similarity in the costs predicted for both model structures (Table 11). As would be expected 1st line drug, administration and AE costs are the same given the same TTD curves are used. At 2nd line plus the drug costs prediction within the state transition model are somewhat higher than within the PartSA, this differentially impacts on treatments; with those treatments which are least effective at 1st line generally seeing the greater increase in costs associated with later lines of treatment.

Table 12 presents a comparison of the ICERs at list price by comparator for the two model structures. Within the intermediate / poor risk population the results are relatively consistent (large ICERs are driven by small differences in QALYs) aside from the comparison to nivolumab + ipilimumab where reliance on PFS rather than OS to drive outcomes may present a conservative comparison as discussed elsewhere. In the favourable risk population results differ substantially as would be expected given that a numerical benefit in PFS within CheckMate 9ER, whereas the OS HR is >1.

The EAG would now consider the difference in results between model structures to have been adequately explained and would consider that both model structures provide value to the Committee in decision making dependent upon how the fundamental issue driving the differences (effectiveness in the favourable risk population) is interpreted.

Table 12: Comparison of list price ICERs by model structure

Structure	Technologies	Pairwise ICER	Incremental ICER
Risk population: All-risk			
STM	Suni	£263,297	-
	Pazo	£275,106	£35,580
	Tivo	£223,701	(dominated)
	Cabo+nivo	-	£275,106
PartSA	Suni	£445,511	-
	Pazo	£443,437	(dominated)
	Tivo	£379,118	(ext dominated)
	Cabo+nivo	-	£445,511
Risk population: Favourable risk			
STM	Suni	£358,676	-
	Pazo	£379,222	£32,471
	Tivo	£287,383	(dominated)
	Cabo+nivo	-	£379,222
PartSA	Suni	Cabo+nivo dominated	£0

Structure	Technologies	Pairwise ICER	Incremental ICER
	Pazo	Cabo+nivo dominated	(dominated)
	Tivo	Cabo+nivo dominated	£5,057,694
	Cabo+nivo	-	(dominated)
Risk population: Intermediate / poor risk			
STM	Suni	£237,872	-
	Pazo	£248,380	£36,780
	Tivo	£205,798	(dominated)
	Nivo+ipi	£123,562	(dominated)
	Cabo	Cabo+nivo dominated	£140,523
	Cabo+nivo		(dominated)
	Pem+lenv	SW quadrant £110,498	£450,638
PartSA	Suni	£282,147	-
	Pazo	£280,852	(dominated)
	Tivo	£242,097	(ext dominated)
	Nivo+ipi	£1,260,021	£156,172
	Cabo	£500,084	(dominated)
	Cabo+nivo	-	(ext dominated)
	Pem+lenv	SW quadrant £546,130	£897,283

Abbreviations: cabo, cabozantinib; ext, extendedly; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab, lenv, lenvatinib; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; STM, state transition model; suni, sunitinib; tivo, tivozanib

Issue 8: Subgroups in the context of changing comparators

Report sections	
Description of issue and why the EAG has identified it as important	Previous NICE recommendations in RCC have been optimised on the basis of risk status, and indeed only TKI monotherapies are available in routine commissioning for patients in the favourable risk group. As noted in clinical effectiveness Key Issues 7 and 9, there is evidence of effect modification by risk group in both CheckMate 9ER and the broader evidence base; however, as regards cabo+nivo, the company's perspective is that this treatment should be principally considered in an all-risk group. The NICE manual notes that there should be clear justification and plausibility for patient subgroup definition; the EAG has received clinical advice that subgroups based on risk are indeed salient for clinical decision-making.
What alternative approach has the EAG suggested?	The EAG has explored the impact of risk groups on cost-effectiveness results.
What is the expected effect on the cost-effectiveness estimates?	The EAG notes that risk group-specific cost-effectiveness results rely on different combinations of comparators than all-risk cost-effectiveness results, and thus may lead to different conclusions about the cost-effectiveness of cabo+nivo by risk group. The all-risk results whilst providing more certainty in the comparison to TKI monotherapies are

Report sections	
	less relevant for decision making than the favourable risk results as according to best practice guidance TKI monotherapies should not be used in patients who are able to receive combination therapies in the intermediate / poor risk group.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; nivo, nivolumab; TKI, tyrosine kinase inhibitor

Company comment:

The company notes that the EAG have acknowledged that the cost-effectiveness analyses conducted for the all-risk population possesses the least uncertainty compared to the intermediate/poor and favourable risk subgroups. The company reiterates its position that cabozantinib + nivolumab should be appraised in the all-risk population.

EAG response:

This issue is addressed within the response to Decision Problem Key Issue 4.

Issue 9: Dominance of cabozantinib in the intermediate/poor risk population

Report sections	
Description of issue and why the EAG has identified it as important	In cost-effectiveness results for the intermediate/poor risk population, cabo dominates cabo+nivo (and other novel combinations). However, the EAG notes that the underpinning trial for cabo, CABOSUN, included a high dose as part of a monotherapy; and clinical advice to the EAG noted that CABOSUN showed an unusually large effect, a discrepancy noted in previous appraisals (e.g. TA858).
What alternative approach has the EAG suggested?	The EAG notes that this is an area for Committee scrutiny.
What is the expected effect on the cost-effectiveness estimates?	The EAG notes that the clinical validity of this specific finding is a point for Committee discussion.

Abbreviations: cabo, cabozantinib; EAG, External Assessment Group; nivo, nivolumab; TA, technology appraisal

Company comment:

The company offered a number of comments on the CABOSUN trial, including comparisons between CABOSUN and other trials, and reiteration of the EAG's assessment of the trial's high risk of bias. The company also compared CheckMate 9ER to CABOSUN in terms of Eastern Cooperative Oncology Group (ECOG) performance status (PS) distribution.

Other stakeholder comments:

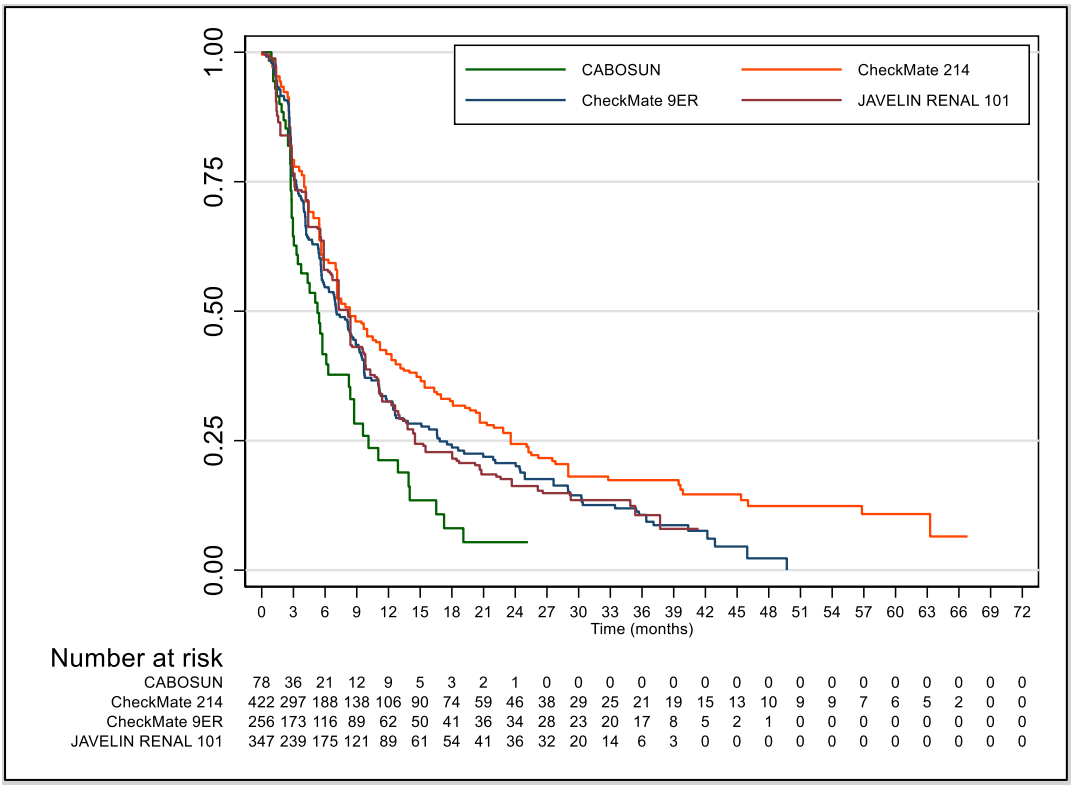
BMS request the Committee to consider exclusion of cabozantinib at 1st line as a scenario analysis given its relatively low usage (9%) and the difficulties with the data highlighted by

the EAG. They also highlight that TA858 predicted higher life years for pembrolizumab plus lenvatinib and nivolumab plus ipilimumab when compared to cabozantinib.

EAG response:

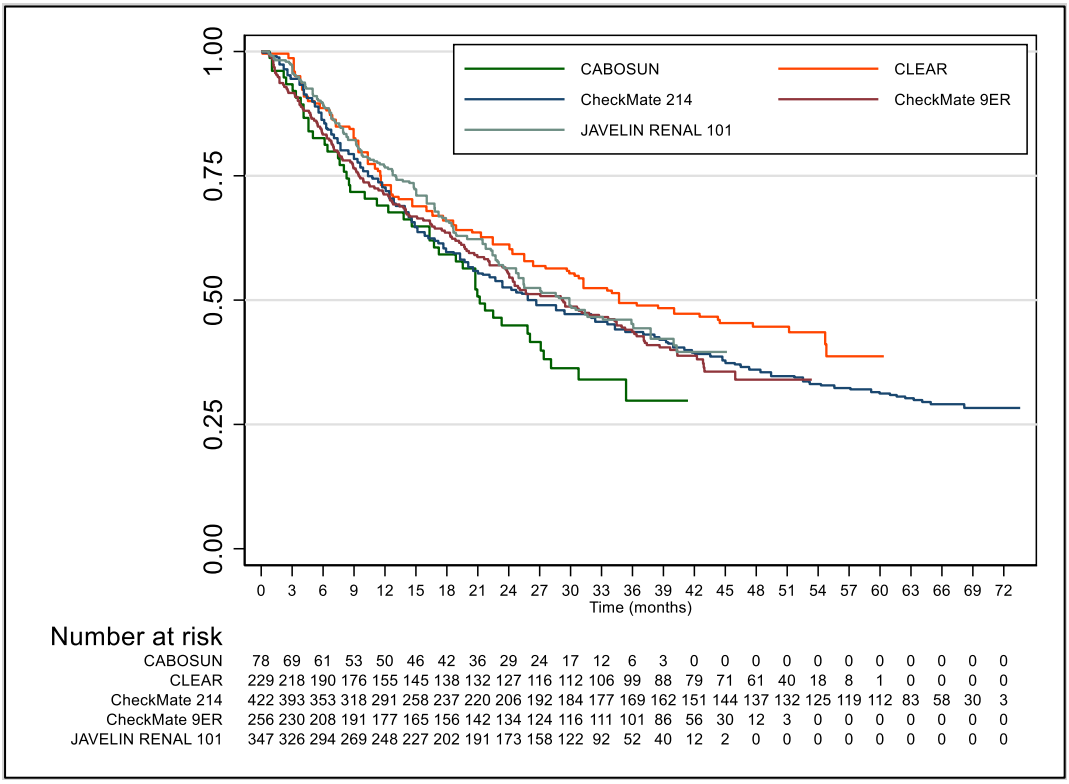
The EAG acknowledges the points raised by the company in terms of CABOSUN risk of bias, and agrees that ECOG PS distribution skews more positively for CheckMate 9ER than for CABOSUN. While the EAG agrees with the company that this is likely to lead to worse survival outcomes for CABOSUN, it is less clear that this would also translate into a larger relative effect for CABOSUN. However, the EAG agrees that the comparatively higher proportion of bone metastases in CABOSUN as compared to other comparative trials may provide another important reason for differences in patterns, though clinical advice to the EAG on this point was mixed; and indeed PFS was also investigator-assessed in CABOSUN. However, none of these points fully resolves the ambiguity. To explore this further, the EAG has developed two plots analogous to Figures 17 and 18 in the EAG report but including only patients in intermediate and poor risk groups. Both Figure 7 and Figure 8 reveal that even amongst intermediate and poor risk patients, sunitinib patients in CABOSUN had worse outcomes. This suggests that there are additional risks in this population that may not be quantifiable.

Figure 7: PFS in intermediate/poor risk group patients receiving sunitinib



Abbreviations: PFS, progression free survival

Figure 8: OS in intermediate/poor risk group patients receiving sunitinib



Abbreviations: OS, overall survival

We note that in TA858, neither nivolumab plus ipilimumab or pembrolizumab plus lenvatinib were considered cost-effective when compared to cabozantinib monotherapy. This is the reason that the recommendation for pembrolizumab plus lenvatinib is only where “nivolumab with ipilimumab would otherwise be offered.” Nivolumab plus ipilimumab was not compared to cabozantinib monotherapy in the preceding appraisal (TA780).

The EAG already present pairwise analyses for comparison against pembrolizumab plus lenvatinib and, separately, nivolumab plus ipilimumab in the event the Committee would find these probative in a similar way to TA858.

6. OTHER ISSUES RAISED

6.1. Structured expert elicitation methodology

The Medical Research Council (MRC) protocol[9] does not require between expert interaction (see the application of the protocol in Chapter 10). Principle 9 discusses the need to recruit experts motivated to undertake the task optimally. It notes that "a SEE [structured expert elicitation] may want to explore any differences in expert performance that emerge." It does not go as far as to require presentation of information from other experts back to participants. The exercise conducted for this appraisal took place at a time concurrent to a number of NHS strikes, as noted in the EAG report this made recruitment difficult particularly as payment was not offered. Experts taking part by definition were highly motivated by altruistic reasons to take part. We would note that the variation in expected answers is captured using the method recommended in the reference protocol Principle 8 (mathematical aggregation; see Table 15 in the protocol). Results were also presented back to Dr Larkin for comment as part of the exercise to aid in interpretation.

The EAG notes the company's comments relating to population seen in clinical practice. The EAG was unable to present baseline characteristics from RWE data sources to clinicians as these data were not ready with enough time. The EAG was unable to ensure consistency between experts because this would presume that a specific, standard population could be formalised; ideally, this would have been derived from RWE. The EAG acknowledges this as a limitation of the analysis.

It is acknowledged that some questions being answered by fewer than five experts is a limitation within the analysis. As noted in the EAG report, questions were prioritised so that those of most relevance to the decision problem for cabozantinib + nivolumab were posed to the maximum number of experts. Consistency within expert responses can be assessed using the measures presented in the report (variance, 95% confidence interval [CI]). The variance within the fitted distributions for those questions answered by fewer than five experts does not substantially differ from those answered by more than five experts and in many cases is in fact lower.

6.2. Clinical effectiveness

6.2.1. Trial characteristics

The EAG confirms that "% prior surgery" does in fact refer to nephrectomy. This has now been updated. The EAG has also updated the proportion of patients in CheckMate 9ER with subsequent systemic treatment.

6.2.2. Study-level risk of bias

The EAG acknowledges the company's point that attrition in the CheckMate 9ER is predominantly attributable to treatment discontinuation as a result of disease progression, and therefore linked to the primary study endpoint. It considered the company's request to revise the overall risk of bias of CheckMate 9ER on this basis to be justified. As such, the EAG revised all included trials for the attrition domain to ensure discontinuation because of study endpoints was not considered in the judgment of attrition bias. This resulted in a number of changes to the sub-domain assessing whether imbalances were unexpected; 13 trials, including CheckMate 9ER, have amended judgments for this sub-domain (see judgments for Q3.1, Table 1 of Appendix D in the EAG's original report).

The EAG notes the company's point regarding the approach to missing data in CheckMate 9ER, vis-a-vis the approach taken in CLEAR and CheckMate 214. The EAG considers there to be more comprehensive information around the handling of partial dates (using single imputation methods) in the statistical analysis plans of CheckMate 9ER (https://classic.clinicaltrials.gov/ProvidedDocs/77/NCT03141177/SAP_003.pdf) and CheckMate-214 (https://classic.clinicaltrials.gov/ProvidedDocs/49/NCT02231749/SAP_000.pdf) when compared to the statistical analysis plan of CLEAR (https://classic.clinicaltrials.gov/ProvidedDocs/61/NCT02811861/SAP_001.pdf). The EAG further maintains that single imputation approaches are not ideal for handling missing data. However, given the reassessment of attrition in CheckMate 9ER, the EAG considers the limitations of these approaches to present an unclear, instead of high, risk of bias as these limitations would only pertain to the handling of missing data from moderate, non-differential attrition unrelated to study endpoints.

Amendments to the consideration of what constituted "unexpected" imbalances, and a consequent reconsideration of the impact of non-ideal approaches to handling missing data, resulted in changes to the risk of attrition bias for four trials, including CheckMate 9ER, from "High" to "Unclear". Furthermore, since the attrition bias domain is a key domain in assessing overall risk of bias, the study-level risk of bias was also amended for four trials, including CheckMate 9ER, from "High" to "Unclear" (see Table 12 of the EAG report and Table 1 of Appendix D [original EAG report]).

6.2.3. Discontinuation rates

The EAG preferred estimates relating to discontinuation arising from treatment-emergent AEs where these were available. Thus, the EAG did not use estimates presented in Table 7, which pertain to treatment-related AEs, but rather from Table 17 of the submission of 3 April.

The EAG also welcomes the company's clarification as to the definition used in trials of drug combinations. For consistency, the EAG has updated the estimates used in CLEAR based on the Motzer (2021) paper. Revised estimates from the NMA are provided in the report. This did not change the EAG's conclusions.

6.2.4. Risk group

The EAG has noted this point.

6.2.5. Baseline characteristics of RWE trials

The EAG notes the corrections made to the table.

Comparisons to the McGrane et al. 2022 paper[10] are misleading. The EAG's estimates are cross-sectional (i.e. how many patients have received or are receiving each line of treatment at database lock) while McGrane et al. presented longitudinal estimates. The EAG notes that the McGrane paper presents an earlier datacut of the same database used within the EAG's analysis. The EAG does not have access to earlier datacuts.

Finally, clinical advice to the EAG suggests it is unsurprising that the nephrectomy rates are different between the RWE and the trials, given that in trial populations, patients and their clinicians may choose to pursue a more aggressive "upfront" treatment strategy to maximise probability of attaining complete response.

6.2.6. Indirect treatment comparisons

The EAG notes that it stated the overall NMA was an all-risk comparison. As stated in the original report, there was rarely an explicit distinction between within-trial distributions of risk comparing those that only included intermediate and poor risk patients and those that excluded poor risk. The EAG undertook sensitivity analyses excluding trials with no patients at poor risk and subgroup analyses focusing on patients at intermediate or poor risk. Moreover, the comparison represented by the CABOSUN trial is a "spoke" in the network, thus there is minimal, if any, impact on results in the all-risk network. Inclusion of CABOSUN does not magnify uncertainty.

The EAG acknowledges the points further raised by Ipsen in its response relating to the challenges with transparency stability that inhere to FP NMA as a method, and the differences in results between the EAG and Ipsen's FP NMAs. The EAG reiterates that this was the basis for presenting a 'standard' proportional hazards NMA as well. The EAG does not regard that the use of first-order polynomials is a panacea; as explained in response to clarification questions, first-order polynomials for PFS all-risk models generated comprehensively worse fit indices than second-order polynomial models. Finally, the EAG reiterates that the 'inconsistencies' in application of models within the intermediate/poor risk group at first line are strictly constrained by data availability.

The EAG also notes comments by BMS with respect to the validity of survival projections in the EAG's FP NMA. However, the EAG reiterates that by definition, survival curves for treatments parameterized against a different reference curve than the comparator in the originating trial will generate different survival estimates.

6.2.7. Critique of outputs considered

The EAG has addressed this in response to clinical effectiveness Key Issue 3.

6.3. Cost-effectiveness model development

6.3.1. Critique of real-world evidence

The EAG notes that it would be unreasonable to expect a generalisable source of RWE to include data on pembrolizumab + lenvatinib, as the relevant NICE guidance was published in January 2023. Similarly, it is unreasonable to expect that cabozantinib + nivolumab would be represented in a source of evidence generalisable to the UK. It is inaccurate to suggest that the exclusion of these treatments is probative for generalisability, especially as the key use of RWE is to parameterise baseline risk. The EAG responds to further points relating to generalisability in cost-effectiveness Key Issue 2.

MSD queried the geographic spread of included centres in the RWE source preferred by the EAG. The EAG reiterates its reassurance that the geographic spread includes all regions of the UK in a way that is broadly representative of UK clinical practice.

BMS raise a number of queries relating to the suitability of both the RWE and the parametric fits used to extrapolate and parameterize the RWE reference curves. The EAG has already justified its preference for RWE elsewhere, drawing on a number of criteria including expected generalizability for clinical practice, and observing that the RWE are comparatively mature. While BMS note that the Covid-19 pandemic may have impacted treatment outcomes for patients, it is not clear that this would have had a systematic impact on the

reference curves used. In its arguments relating to the suitability of parametric fits for RWE, BMS asserts that flexible parametric models are likely to generate a better fit to the data due to the relatively similarity in fit indices of a range of standard parametric fits to the trial data. The EAG note that an alternative explanation is equally plausible; that when curves are mature, the choice of distribution is associated with comparatively less uncertainty. BMS also argue that the RWE would not be able to capture the impact of OS and PFS slippage. The EAG believes that this arises from a misapprehension as to the basis for slippage, which is in fact due to relative treatment effects for newer treatments, and not due to the outcome patterns for sunitinib. In the event, the use of an FP NMA and treatment effect waning would account for the role of slippage in a way that would be impossible by alternative parametric fits.

In addition, the EAG do not agree with BMS's implied assertion, namely that extrapolation findings in the context of a clinical trial would generalize to an RWE context. The EAG considered a range of fits and did not regard that flexible parametric fits were justified given the data analysed. The EAG also undertook a range of validation exercises for model results described elsewhere in this addendum.

6.3.2. Indirect comparisons

The EAG reiterates that like any curve selection process, a range of information points were used to arrive at a decision. All curve selection requires subjectivity and the EAG did not regard that additional curve fits would meaningfully reduce any uncertainty arising.

The EAG used a combination of criteria, as explained in depth in the EAG's report, and as substantially informed by Wiksten et al (2020).[11] As a headline estimate of statistical appropriateness, differences in Akaike information criterion (AIC) of less than five were used. This is a standard guideline, and in the event the EAG agrees that AIC cannot be the only criterion for selection. In addition to this, the EAG visually inspected a range of curves in terms of observed fit to data, and the area under the survival curve.

The EAG is pleased to clarify that the time horizon used for calculation of restricted mean survival time was 40 years, the goal of which was to address any curve fits where estimates of PFS exceeded estimates of OS (and thus set aside any OS curve fits where OS estimates were less than PFS estimates).

The EAG has already presented networks by risk group in Appendix E of its original report.

Figure 21 already indicates that the reference treatment is sunitinib.

The EAG has already provided an account of why some of the survival curves are implausible, with particular regard to pembrolizumab + lenvatinib.

6.3.3. Expert elicitation

As noted previously the EAG acknowledges the inability to recruit sufficient experts to allow for at least five responses to all questions and inability to ensure consistency between experts through the presentation of a specific, standard population as a limitation of the analysis.

In addition, the EAG acknowledges some incommensurability between the populations implied in expert elicitation and the trial populations but disagrees from an epidemiological perspective that this is a form of “bias” in the analysis. It is likely this incommensurability was attenuated somewhat as well given clinicians primarily came from major centres in RCC, where better outcomes would be expected. Finally, it is not at all clear that this incommensurability is inappropriate given, for example, the use of expert input to understand long-term extrapolation from trial-based curves as a routine part of health technology assessment (HTA) decision-making.

The EAG reiterates that the expert elicitation is one data point used in curve selection and was primarily used in selecting PFS curves. The EAG also reiterates that the impact is limited given the high level of maturity within the observed UK RWE.

6.3.4. Treatments included

While the EAG acknowledges that conditional analysis of outcomes would have been of value, the sample size for any one sequence would have posed serious estimatability issues. Thus, the EAG did not undertake this.

6.3.5. Treatment effectiveness and extrapolation

The EAG has already provided a full account of the challenges and limitations of the FP methods, including as regards challenges including the CLEAR trial, and has already discussed the comparative strengths and benefits of PH NMAs vs FP NMAs. The EAG also reiterates that there is always an element of subjectivity in curve selection. The strength of the EAG’s method is the number and range of checks and datapoints used to undertake this process. In short, the EAG agrees with the points raised by the company in relation to the challenges that accrue to FP NMAs as a general modelling strategy but observes that none of these points are new.

The EAG also reiterates that the choice to use a PH NMA for 2nd line treatments was due as much to sparseness of the evidence network as it was to the results generated from that analysis.

In addition, the EAG observes that another reason for which PH NMAs were preferred for pembrolizumab + lenvatinib in the intermediate and poor risk population (where this treatment strategy is relevant) is because the EAG did not have access to relevant pseudo-individual patient data (IPD) PFS data for this risk group.

The EAG has provided plots in Appendix F of the implied hazard ratio over time for both OS and PFS resulting from the final economic model calculations once all adjustments have been applied.

In conclusion, the EAG notes that it is for the Committee to decide which NMAs—FP or PH—should inform the base case. However, neither strategy is without its challenges, and the EAG has undertaken to be transparent as to their relative merits. In addition, it is inaccurate to state that the FP NMAs themselves are a point of inconsistency; both strategies have been used in prior appraisals. The EAG has presented both for clarity.

6.3.6. Pooling of BSC outcomes

The DSU raised a query as to whether pooling BSC outcomes across risk groups was appropriate. Figure 9 presents post-progression survival for patients not receiving another active line of treatment across all lines stratified by risk status at first-line. The log-rank test associated with this was p=0.15. Given this the EAG considered it appropriate to pool outcomes.

Figure 9: BSC PPS by risk status at 1st line

Abbreviations: BSC, best supportive care; fav, favourable risk; int/poor, intermediate / poor risk; PPS, post progression survival

6.3.7. Adverse events

The company notes inconsistencies in the application of adverse events with recent appraisals (which used a naïve comparison of Grade 3+ adverse events occurring in more than 5% of patients in each arm, as opposed to inclusion of additional Grade 1 and 2 events noted as important by clinical experts, and informing relative effectiveness with NMA data). The EAG would consider that the current approach is a step forward, although as noted in Economic Key Issue 4 we may still not be able to fully capture the impact of toxicities with the data available. Scenario analysis has already been provided exploring the impact of naïve comparison (Scenario 58). The difference in QALYs is minimal when compared to the base case (increase of 0.03 QALYs for cabozantinib plus nivolumab, and between 0 and 0.01 QALYs for TKI monotherapies in the all-risk population).

6.3.8. Resource use and costs

The company note that they have received feedback from clinical experts at an advisory board that the theoretical advantage of administering lenvatinib with pembrolizumab every 6 weeks may not be realised due to the high dose of lenvatinib used resulting in significant

adverse events requiring the patient to be seen in clinic every 3 weeks. It was not clear which clinicians were consulted by the company or how many were consulted.

The EAG consulted two clinicians (Dr Larkin and Dr Challapalli) and NHSE regarding the issue of lenvatinib dosing and how this dosing interacts with administration of pembrolizumab. Both clinicians consulted considered that patients would be unlikely to receive every-3-weeks dosing of pembrolizumab as part of the protocol to address required dosing adjustments for lenvatinib. Both acknowledged the issues with toxicity associated with lenvatinib when given in combination treatment using the starting dose of 20mg from the SPC (this is the maximum possible dose and often not tolerated). Both noted that due to this many clinicians instead titrate patients up to as close to 20mg as possible often starting at 10mg and titrating up in 4mg steps every 2 weeks (pills come in 4mg and 10mg sizes). NHSE added that clinical practice is varied in that some clinicians titrate up to 20mg and others work downwards. Regardless of whether off-label titration is done or the SPC dose is used, dose adjustments are performed as part of an oncologist face to face appointment or, more frequently, via a short phone call rather than at an additional scheduled appointment for pembrolizumab administration. The optimal dose of lenvatinib is usually achieved within the first 2-3 months. Both clinicians consulted considered that doses of either 10mg, 14mg or 20mg are given in the long-term which aligns with the CLEAR trial protocol. NHSE considered that some clinicians also use the 18mg dose. The resource use in the model already accounts for an oncologist consultation every 4 weeks, for some patients an additional consultation at 2 and 6 weeks may be required (maximum additional cost of £328).

Because lenvatinib is priced the same for a 4mg tablet as a 10mg tablet, UK titration practices may result in increased costs which have not been captured in the model. In order to more accurately capture the dosing of lenvatinib the following approach has been used in the updated EAG base case:

- All patients are assumed to receive 10mg for the first 2 weeks
- 75% of patients are assumed to receive 14 mg for the next 2 weeks (based upon TA858 assumption that 25% of patients cannot tolerate more than 10mg which was confirmed as reasonable by Dr Larkin)
- 18% of patients are assumed to receive 18mg for 2 weeks and then 20mg for 2 weeks based upon the mean RDI of 70.5% reported in the trial and 10, 14 and 20mg being the relevant long-term doses. This was confirmed as reasonable by Dr Larkin
- Patients are assumed to receive 0.429 x 4mg and 1.196 x 10mg pills after the first 8 weeks based upon the company response to clarification questions Table 3 in TA858

Scenario analysis is also presented using NHSE input on the long-term doses used in practice: 25% at 10mg, 40% at 14mg, 20% at 18mg and 15% at 20mg which are broadly consistent with the above and result in a slightly higher RDI of 73.5% (not accounting for any missed doses).

It should be noted that the EAG updated base case attempts to capture as accurately as possible the cost of lenvatinib as used in the CLEAR trial rather than the cost as used in practice as the relative effectiveness data for pembrolizumab plus lenvatinib are taken from the trial rather than from UK practice. This is why the trial-based RDI has been used to calculate the proportion receiving each dose in the long-term. If, in fact, patients stabilise on lower doses in practice than in the trial, it may be that the effectiveness seen in CLEAR will not be replicated in UK practice.

In addition to the impact on cost, there are patient-related issues to be considered. Dr Challapalli noted that the issues with toxicity of lenvatinib are a significant concern for patients as they may worry that a lower dose might result in reduced effectiveness, or try to be “brave” and therefore not report toxicity as early as would be ideal to manage dosing. These issues are more pronounced than for other IO / TKI combinations. This is because lenvatinib, unlike the other TKIs, is used at the maximum possible starting dose.

Finally, the EAG considered how to handle the dosing of lenvatinib within lenvatinib plus everolimus. During this consideration it was noted that the maximum modelled dose had been 20mg rather than the 18mg in the SPC. This model was amended to use 18mg (one 10mg tablet and 2 x 4mg tablets). Again, it was assumed that 25% of patients would receive 10mg in the long-term in line with the dosing within lenvatinib plus pembrolizumab. Given the reported RDI of 70.4% this resulted in an estimate of 48% of patients receiving the 14mg dose and 27% receiving the 18mg dose long-term.

6.3.9. Uncertainty

The EAG disagrees that there are an unusually high number of inconsistencies in this appraisal and reiterates that the goal of a pathways model is to resolve the many inconsistencies including between the prior appraisals. In addition, the EAG notes that modelling results from both structures and both NMA strategies are presented. The EAG also disagrees that the “inconsistency” between long-term data cuts and RDI estimates is best resolved in the way described by the company, i.e. by using immature data cuts from clinical trials. Ultimately, the EAG stresses that using the longest follow-up available is critical to avoid discarding valuable information, and the EAG has previously commented that there is no obvious common follow-up for all trials. Points relating to the structured

expert elicitation are addressed above, but it bears repeating that this was one datapoint used in curve selection.

6.3.10. Model validation

The EAG agree with MSD that exploration of calibration techniques is of interest during Phase 2. However, the EAG would note that as per the response to Key Issue 7 the difference in outcomes between the two model structures is limited in the intermediate / poor risk and all-risk populations.

BMS highlight differences between the EAG model results and previous appraisals regardless of the structure used, for example 2 – 77% in LYs and QALYs for nivolumab plus ipilimumab compared to prior appraisals for the PartSA structure.

The EAG notes that this is not a function of inconsistency between our model and prior appraisals, it is a function of inconsistency between prior appraisals themselves as demonstrated in Table 13. The difference in life years predicted for the same treatment across appraisals is >100% in a number of cases. These appraisals all used the same model structure. The reason for inconsistency is largely that the data available to inform the models have changed over time. This has also been the case for this appraisal. In fact, it is a strength of this appraisal compared to prior appraisals that more mature data are available for a number of comparators. This is especially relevant given the role of slippage in estimates of OS and PFS outcomes for certain treatments.

Rather than casting doubt on the EAG's findings, this highlights the importance of NICE's pathways pilot in that the use of a common model reference framework creates the conditions for future appraisals to rationalise updated projections, account for what drives updated projections, and support Committees to make empirically supported decisions as to whether the inconsistencies are justified.

Table 13: Differences in LYs and QALYs across prior appraisals*

Treatment	Population	TA	LYs	QALYs
Suni	Int/poor	780	5.35	[redacted]
		542	[redacted]	[redacted]
	All	512	3.31	[redacted]
		858	4.73	[redacted]
		785	[redacted]	[redacted]
Nivo+ipi	Int/poor	858	4.71	[redacted]
		780	6.89	[redacted]

Cabo+nivo	Int/poor	785	[redacted]	[redacted]
Pazo	Int/poor	780	5.35	[redacted]
		542	[redacted]	[redacted]
	All	512	3.48	[redacted]
		785	[redacted]	[redacted]
Tivo	All	512	3	[redacted]
		785	[redacted]	[redacted]
		858	4.73	[redacted]
Cabo	Int/poor	858	4.08	[redacted]
		542	[redacted]	[redacted]
Pem+lenv	Int/poor	858	4.80	[redacted]

*Information taken from model files supplied to the EAG, these are at different stages in each appraisal as noted previously in Appendix L in the original EAG report. Information has been redacted in line with redacting in each appraisal

6.3.11. Additional scenarios

The company requested a number of additional scenarios across both rounds of consultation.

6.3.11.1. Response to requests from consultation round 1

The majority of the scenarios requested in round one were provided with the updated results supplied in the original EAG report in Appendix Q. The exceptions and rationale for exclusion are noted below:

- 5. Use RWE to model reference treatment outcomes (i.e., sunitinib) calibrated based on clinical expert opinion using both hybrid STM and PartSA
  - This scenario has not been provided as we do not believe it is appropriate given the discrepancy in absolute survival estimates from the expert elicitation which was conducted primarily with experts from academic centres and the UK RWE which contains a more generalisable dataset of patients from all regions of the UK, and of England specifically; a mix of secondary and tertiary centres; and patients across urban and rural geographies.
- 8. Conduct a pairwise severity modifier analysis accounting for the RWE-based market shares of 1L therapies using both hybrid STM and PartSA
  - The rationale for not undertaking this scenario is provided within Economic Key Issue 6; in short, it is not in the EAG's province to communicate precedent for this.
- 11. Apply TTD for 1st line reference treatment (i.e., sunitinib) based on Checkmate9ER both hybrid STM and PartSA
  - This scenario has not been provided as using TTD data from CheckMate 9ER alongside RWE data for PFS and time to progression (TTP) would not be appropriate. This would involve selective inclusion of data from different sources for different endpoints without a clear rationale. Scenarios 6 and 7 provide trial-based

analyses for the hybrid STM and PartSA which include the use of TTD data for sunitinib from CheckMate 9ER.

In response to the company request for a scenario analysis applying the proportional reduction in utilities derived from CheckMate9ER study to the general population as an additional approach to using the trial data using both hybrid STM and PartSA, the EAG would like to clarify that the existing scenario provided using CheckMate 9ER utilities for all lines did this for the hybrid STM. An additional scenario has been added looking at this for the Part SA and a scenario examining the impact of removing age adjustment whilst still using CheckMate 9ER utilities for the hybrid STM.

The company also asked the EAG to run the hybrid Markov model using two lines of treatment, applying costs and utilities for two lines using the same methodology as in the PartSA model. Later clarification received by the EAG 2nd October (3 days prior to delivery of this response) revealed that this request was to include 3rd and 4th line treatment as one-off costs in the state transition model. As this would require restricting the model at short notice this request could not be fulfilled, however, the EAG would expect the impact to be limited. Data from the UK RWE is used to inform subsequent treatment durations currently in the state transition model as in the PartSA; the key differences are in the timing of costs (applied correctly per cycle and therefore discounted correctly in the state transition model and applied as a simplified one off cost in the PartSA model) and accuracy of the durations on treatment (applied per treatment type received in the state transition model and applied as a simplified weighted average in the PartSA model). As the company themselves note 3rd and 4th line treatments make up only a small proportion of the total cost and QALY impact in the model base case and therefore the impact of amending the calculations to the, less accurate, simplified version used in the PartSA would also be expected to be limited.

Finally, the EAG would also like to clarify that in Scenarios 22 and 23, a gradual convergence of the hazards starting at Year 5 is assumed, resulting in equal hazards at year 20.

6.3.11.2. Response to requests from consultation round 2

Additional scenarios requested during the second company consultation response are listed below first for the state transition model and then for the PartSA:

- Hybrid STM with 2L of treatments and AEs rate informed by individual trials
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and PH NMA to inform 1L relative effectiveness
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and TTD=PFS

- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and FP NMA to inform pem+lenv relative effectiveness
- Hybrid STM with 2L of treatments and AEs rate informed by individual trials and all company alternative RDIs
- Hybrid STM with 2L of treatments and AEs rate informed by individual trials and all company RDIs (IOs only)
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and PH NMA to inform 1L relative effectiveness and all company alternative RDIs
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and PH NMA to inform 1L relative effectiveness and all company RDIs (IOs only)
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and TTD=PFS all company alternative RDIs
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and TTD=PFS and all company RDIs (IOs only)
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and FP NMA to inform pem+lenv relative effectiveness and all company alternative RDIs
- Hybrid STM with 2L of treatments, AEs rate informed by individual trials, and FP NMA to inform pem+lenv relative effectiveness and all company RDIs (IOs only)
- PartSA model structure, and AEs rate informed by individual trials
- PartSA model structure, AEs rate informed by individual trials, and TTD=PFS
- PartSA model structure, and AEs rate informed by individual trials and all company alternative RDIs
- PartSA model structure, and AEs rate informed by individual trials and all company RDIs (IOs only)
- PartSA model structure, AEs rate informed by individual trials, and TTD=PFS and all company alternative RDIs
- PartSA model structure, AEs rate informed by individual trials, and TTD=PFS and all company RDIs (IOs only)

The company defined their preferred base case to be the state transition model with assumptions as follows:

- Preferred source to inform 1L treatment efficacy: proportional hazards NMA for all treatments
- Limit to two lines of treatment
- Time on treatment informed directly from the PFS
- Rate of AEs informed directly from individual trials
- RDIs informed by the company's alternative RDIs

They also requested the production of a similar set of analyses using the PartSA model:

- Preferred source to inform 1L treatment efficacy: proportional hazards NMA for all treatments
- Limit to two lines of treatment
- Time on treatment informed directly from the PFS
- Rate of AEs informed directly from individual trials
- RDIs informed by the company's alternative RDIs

Given the volume of these requests in the context of the EAG already having provided a large number of scenario analyses instead of providing 18 additional scenarios the EAG has instead provided the company base case where each of the assumptions are applied in increments starting from the revised EAG base case. It should be noted that in respect to the request to use the company RDIs; as noted in the response to Economic Key Issue 4 the new RDIs provided for nivolumab and pembrolizumab are incorrect as they use the maximum duration of treatment (rather than mean) within the denominator. This would only be correct if no discontinuation was included in the model (either via TTD or PFS). The EAG therefore present the preferred company base case using our own corrected RDI information using the new data for the numerators provided by Ipsen and new data source for the duration of treatment within CLEAR provided by Ipsen as well as the incorrect data provided by Ipsen in order to present the Committee with an accurate preferred company base case.

BMS also requested a number of additional scenarios:

- It is unclear exactly what is requested in Key Issue 6, however, we take this to be a request for exploration of the use of trial data to information sunitinib extrapolations. This was already provided in Scenario analyses 6 and 7
- Scenarios assuming equal effectiveness for pembrolizumab plus lenvatinib and another IO / TKI. This was already provided (Scenario analyses 43 and 44).
- Scenario analyses exploring the attenuation of cabozantinib and other TKIs across treatment lines when the previous treatment included a treatment of the same mechanism of action; this scenario analysis has been provided as discussed in Economic Key Issue 3
- Scenario analyses excluding cabozantinib as a first-line treatment: the Committee already has access to pairwise ICERs for all scenarios
- Scenario analyses balancing model selection and FP NMA results with clinical expert opinion and clinical trial data: extensive scenario analyses around curve selection and reference curve data source have already been provided

6.3.11.3. Scenario analyses conducted on the EAG base case

The final list of scenarios run on updated EAG base was determined based upon the scenarios which had a high level of impact within the initial analyses (original EAG report Appendix Q), requests from Ipsen and BMS and is:

- Scenario 1: model structure (PartSA vs state transition)
- Scenario 3: state transition 2 lines
- Scenario 6: primary source of data (trial vs RWE)
- Scenario 7: primary source of data (trial vs RWE, PartSA)
- Scenario 11: PH NMA for all lines
- Scenario 13: FP NMA for pem+lenv
- Scenario 21: PH NMA for all lines, PartSA
- Scenario 18: TTD assumed equal to PFS
- Scenario 20: TTD relative effectiveness for nivo+ipi informed by simple HR between PFS and TTD from CheckMate 214
- Scenario 24: Gradual TE waning between 5 and 20 years for IO / TKIs
- Scenario 26: No TE waning
- Scenario 29: Weibull curve for PFS for 1L sunitinib
- Scenario 41: RDIs set to 100%
- Scenario 50: CheckMate 9ER utilities applied to all lines
- Scenario 58: AE data from individual trials rather than NMA
- New Scenario 73: Using TTNT data as a proxy for PFS for nivo+ipi
- New Scenario 74: Using TTNT data as a proxy for PFS for nivo+ipi and the PH NMA at 1st line
- New Scenario 75: Using estimates from NHSE for the proportion of patients using each long-term dose of lenvatinib within pembrolizumab plus lenvatinib
- New Scenario 76: exploratory testing around the impact of prior TKI monotherapy on TKI monotherapy in 2nd line
- New Scenarios 77-86; steps to produce the company base case and preferred PartSA analysis with and without incorrectly calculated company RDIs

6.3.12. Benefits not captured in the QALY calculation

BMS consider that the long-term PFS benefits of nivolumab plus ipilimumab may not be adequately captured as the RWE does not capture the plateau observed in CheckMate 214. The EAG regards that the FP NMA reflects this plateau to the extent that it is supported by trial evidence, but also that the presence of a plateau is defined in part by the relative effectiveness to the chosen sunitinib curve (which is unlikely to be identical to the sunitinib curve in CheckMate 214). However, the EAG also notes that this reflects a deeper issue in

the use of survival outcomes in appraisals, specifically the poor surrogacy for PFS and OS for this treatment. Indeed, BMS also consider that the models may not adequately capture benefits from nivolumab plus ipilimumab observed post progression including a significant observed benefit in the time from randomisation to first and second subsequent treatments or death. The EAG take this up in a separate scenario analysis using time to next treatment data for nivolumab plus ipilimumab.

6.4. Individual patient feedback

The EAG received two additional stakeholder responses from patients, each nominated by, and associated with, a different patient organisation (Kidney Cancer UK and Action Kidney Cancer, who each provided their own response).

The EAG notes the comments from Kidney Cancer UK about the need to clarify the basis for indirect treatment comparisons in appraisals and a request for clearer standards for forward evidence generation. The EAG notes that the first point is a recurring theme in appraisals. While methods for indirect treatment comparisons have advanced considerably in the preceding decade, the EAG agrees that direct, head-to-head trial evidence will generally provide comparative effectiveness estimates of greater certainty. The EAG would suggest that the Committee consider this in formulating recommendations for evidence generation moving forwards.

Both stakeholders highlighted the complexity of the current treatment pathway and the difficulties that this presents to patients and clinicians. As treatments can be dependent on prior therapies that a person has received, clinicians are required to think ahead to plan the most appropriate order of treatments. Patients may be unable to make informed decisions about their treatment, due to the complex rules about treatment sequences and the lack of head-to-head comparisons for some treatment options. Timely appointments and the need for clear information and communication with patients about their options is needed but not always done, and delays in diagnosis and treatment may reduce treatment options. As treatment depends on risk status, it is essential that this is appropriately assessed. Greater evidence is needed to appropriately target effective treatments to the right populations, and thus reduce over- or under-treatment. Treatment options for stage 4 RCC were considered to be particularly confusing for patients. Finally, frequent hospital visits add to the burden of the condition through long journeys and the related expenditure.

Lengthening survival while also ensuring improvements in quality of life was considered to be the key aim of treatment. One patient noted that extended life without quality of life would not be an adequate outcome. One patient highlighted the importance of being able to

engage in normal life activities and both patients highlighted the importance of psychological outcomes.

Combination therapies could be considered a success if they improve quality of life and don't, for example, leading to a doubling of side effects. One patient noted that the side effects of treatments can lead to the development of other serious conditions, such as osteoporosis and diabetes, with consequential impacts on their quality of life. With regards to cabozantinib plus nivolumab, one patient highlighted the risk of dysgeusia with cabozantinib that can lead to significant weight loss. It was noted by one patient that those people with RCC who are frailer may not be suitable candidates for cabozantinib plus nivolumab.

Both stakeholders highlighted the importance of shared decision making in RCC, and that to facilitate this, patients should be informed and able to make treatment choices in full understanding of the relative risks and benefits and how these fit with their own personal circumstances and preferences.

Both stakeholders discussed the enormous mental health burden of RCC on the lives of patients and the lack of routine mental health and peer support at all stages of the condition. It was also noted that the burden of RCC extends into other areas of patients' lives, such as impacting on family life and work.

One patient noted the importance of considering the full patient pathway, as opposed to the appraisal of cabozantinib plus nivolumab itself. It was also considered important that the pathway appraisal be kept up to date to ensure it best represented the latest available treatments and evidence base.

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Appendix A: Quality Control and Model Amendments

Internal quality control checks were carried out using PenTAG's internal quality control checklist (series of white box and black box tests based loosely on the TechVER protocol[12]).

Table 14: Results of quality control checks

Check	Result	Amends made
White box tests		
Basic validity checks		
Are total LYs greater than total QALYS?	Pass	N/A
Are undiscounted results greater than discounted results?	Pass	N/A
Are totals in the detailed results the same as totals in the summary results? Does the sum of breakdowns equal the total?	Pass	N/A
Is there a totals column for costs, QALYs and LYs in the patient flow sheet? Do these totals match the sum of the individual cost items in the patient flow sheet?	Pass	N/A
Do all model arms have appropriate costs in each area? Check disaggregated costs to ensure results make sense.	• STM – pass • PartSA – issues identified (no subsequent treatment costs included for lenv+evero)	Excel model amended (changes were made in "Treatment sequence" sheet and "Resource use and costs" sheet as mentioned in Section 2.1.2)
Do the cohort numbers and the sum of all the health state transition probabilities add to 1 in all cycles? Check that the number of patients in each health state is never <0.	Pass	N/A
Does the first row of the trace (in STMs) refer to the correct input?	Pass	N/A
Do all patients die before the age of 100	Pass	N/A
For incremental analysis, have strictly dominated treatments been removed from the analysis and have ICERs been calculated against the next non-dominated treatment? Have extendedly dominated treatments been appropriately presented?	Pass	N/A
For models with subgroup analysis, are 1) input values comparing whole population	Checked following other model amends – pass	N/A

Check	Result	Amends made
and subgroups, and 2) absolute outcomes for costs and QALYs, directionally sensible, given clinical knowledge?		
Is there a model diagram and does it reflect the calculations being carried out in the model?	Not present in Excel front end Diagram in report matches calculations	Model diagram added to Excel front end
Are data sources listed in the model next to relevant inputs?	Data sources are clearly listed next to relevant inputs, with the following exceptions • In resource use and costs tab, no source given for Diarrhoea_IO induced AE, cell G155.	Data source added
Cost checks		
Are all costs taken from the most recent available publication?	Yes, PSSRU 2022 and NHS reference costs 2021-2022 have been used as appropriate.	N/A
Are all costs presented using the same price year?	Yes 2014/5 prices were used in the model for EoL costs. These were inflated to 2022 values, as appropriate. This is made clear in the model.	N/A
How have resource assumptions been validated?	Yes – validated during clinician interviews	N/A
Have any PAS or similar commercial discounts been included? Have PAS discounts been applied correctly (drug cost * (1- PAS))?	Pass	N/A
Has wastage been applied correctly?	Pass – method of moments used for nivo+ipi; packs assigned on cycle of receipt for oral drugs	N/A
Have the latest drug prices been used—i.e. as listed on the eMIT or the BNF/ MIMS?	Pass	N/A
Utilities checks		
Are the utilities in the model lower than for those of the same age in the general population?	Pass	N/A
Are utilities for AEs included? If not, has justification for their omission them provided? If AE utilities are **included**, are they applied for the full duration of the AE?	Pass	N/A
Clinical input checks		

Check	Result	Amends made
For survival analysis, ensure that: • curves do not cross • the proportion remaining alive (or on treatment etc.) match the proportion in the KM data • the curves have a good visual fit to the KM data	Pass	N/A
Is mortality applied correctly based on the description provided in the model? Does survival in the model match the survival curve used, if all influences on baseline mortality are removed?	Pass	N/A
Is the absolute and conditional probability of survival in all cases less than or equal to age-matched values from the general population?	Pass	N/A
For models that are supposed to apply a lifetime horizon, are ≥ 99% of patients dead in both arms at the end of the time horizon?	Pass	N/A
Does application of AEs correctly account for rates vs probabilities	Pass	N/A
For models that use HRs, is the proportional hazards assumption justified?	Considerations around this discussed in ITC section	N/A
Model settings check		
Are the switches/settings (e.g. the options for selecting comparator, patient population, type of costs etc.) placed appropriately and easy to find and understand? Check the right set of inputs and changes in these settings are reflected in the model results.	Pass	N/A
Is there a column of base case settings to which the user can refer, or a switch to revert all controls to base case settings?	No	Added
Do patient flow sheet / calculations look up correct and relevant comparator/intervention inputs?	Issue identified within state transition model with the calculations for effectiveness not applying the TTD curve correctly	Amends made to the f_pf_mk_ComputeTPs function
Check that there are no hidden tabs	Issues identified	Hidden sheets were unhidden

Check	Result	Amends made
For Excel models, do all VLOOKUP formulae have 'FALSE' at the end of the calculation (or 'TRUE' if required)? Also, check for 'MATCH' and whether this is ended with a ',0' or a ',1'	Pass	N/A
For Excel models, ensure there are no #REF! errors in any formulae	Pass	N/A
For Excel models: check the list of named ranges via Name Manager: • Ensure all cell names are appropriate and descriptive • If possible, remove any named ranges with #REF values (i.e. ones that have been deleted during development) • Ensure there are no duplicate names within the Name Manager • Check that all parameters are scoped within the workbook	Pass	N/A
Black box tests		
If all costs are set to zero, check that the total cost comes in at zero	• Minor issue identified which was caused by MRU_on_L5 for sequences of 4 active treatments in state transition model • PartSA - Pass	Amended how model was handling NULL inputs
For drug costs based on height, weight or body surface area, increase and decrease these values to ensure that costs increase and decrease as expected	Pass – applies to nivo+ipi only	N/A
Set discontinuation to 0 for all cycles: check that patients remain on treatment for their life course	Pass	N/A
Set discontinuation to 100% in the first cycle: check that no patients are on treatment at the end of the first cycle	Code not set up to handle 0 / 0, required to perform check To be amended in Phase 2	N/A
Set the dose intensity to 0%: check that drug costs are 0	Pass	N/A
Set all utilities to zero: check that total QALY gain is zero	Pass	N/A

Check	Result	Amends made
Set all utilities to one (and any detrimental effects including age adjustment to zero): check that the total undiscounted QALY gain is equal to LYs gained	Pass	N/A
Set the probability of all AEs to zero: check that there are more QALYs and less costs in each arm	Pass	N/A
Set mortality to zero: check that the undiscounted LYs is equal to the time horizon	40.03559 LYs (rounding due to weekly cycle)	N/A
Change the time horizon of the model (if variable): check that the outputs and results change accordingly	Issue with non-matching lengths of vectors being used in the R model caused the code to fall over	Code amended, retested, passed
Set the discount rates to zero: check that the undiscounted costs and QALYs equal the discounted costs and QALYs	Pass	N/A
Check that the model presents undiscounted and discounted outcomes Divide the undiscounted QALYs by the undiscounted LYs for the overall model and, where applicable, individual health states. Does the model output average utility make sense compared with the input utilities? E.g. is the output utility similar to, or the same as, the input utility for each health state, and does it lie between the best and worst utility values possible for the condition?	Pass	N/A
Change each parameter in turn: each time, check that the ICER changes	Issues identified: • Amending cycle length causes the model to error • Changing source of cabo+nivo and pem+lenv survival outcomes did not change the results • Using FP NMA at 2nd line plus caused the R code to fall over • Switches not linked up to the R output tables for AE impact scenarios	Scheduled flexible cycle length calculation amendment for Phase 2 Amended Excel model to fix formulae for cabo+nivo and pem+lenv survival outcomes Amended the R model to include code to allow the model to apply the FP NMA at 3rd line to cabo as a reference treatment Linked switches for AE impact scenarios to R tables

Abbreviations: AE, adverse event; BNF, British National Formulary; cabo, cabozantinib; eMIT, electronic Medicines Information Tool; EoL, end of life; evero, everolimus; FP, fractional polynomial; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IO, immune oncology; ipi, ipilimumab; ITC, indirect treatment comparison; KM, Kaplan Meier; LYs, life years; MIMS, Monthly Index of Medical Specialties; MRU, medical

resource use; N/A, not applicable; nivo, nivolumab; NMA, network meta-analysis; PartSA, partitioned survival analysis; PAS, patient access scheme; pazo, pazopanib; pem, pembrolizumab; PSSRU, personal social services resource unit; QALY, quality adjusted life year; STM, state transition model; suni, sunitinib; tivo, tivozanib; TTD, time to discontinuation

Appendix B: Scenario analysis using TTNT as a proxy for effectiveness for nivolumab plus ipilimumab

Based upon clarification questions received from Ipsen on 22nd September the EAG further explored the reasons behind the results being produced by the state transition model for nivolumab plus ipilimumab lacking directional consistency with TA858. One key factor identified was a poor level of surrogacy between PFS and OS for nivolumab plus ipilimumab, specifically. This had been previously raised by the EAG in Economic Key Issue 7. The EAG considered the data available to explore this issue and decided based upon this to produce an alternative scenario analysis considering TTNT as a potential alternative surrogate for OS for nivolumab plus ipilimumab. This endpoint has the benefit of not being prone to issues with "false progression" due to tumor flare which may potentially be experienced when considering RECIST-assessed progression. Using TTNT as a proxy for PFS is, however, also an imperfect way to estimate the effectiveness of nivolumab plus ipilimumab somewhat as patients who are too sick to receive a new active line of treatment (i.e. patients who go on to BSC) are only coded as having an event when they die within the Kaplan Meier. However, given the poor surrogacy between PFS and OS for nivolumab plus ipilimumab it provides an additional point of evidence for consideration. The truth is likely to lie between the two analyses.

For reference, the HR for TTNT in CheckMate 214 is [redacted] compared to 0.86 (0.73, 1.01) for PFS.

The below methods were used to produce the sensitivity analysis using TTNT rather than PFS for CheckMate 214 within the FP NMA.

The EAG fractional polynomial NMA was repeated for the untreated, intermediate/poor risk population with TTNT time-to-event data substituted for PFS in the CheckMate 214 trial. Pseudo-IPD data were obtained in the same way as data in the EAG report, by digitizing [reference, fig 3].[13]

The frequentist stage of the FP analysis gave four models within 5 points of the minimum AIC, which are summarized in Table 15: Details of model selection for TTNT sensitivity analysisTable 15. For each of these models, a Bayesian step provided DIC values for random and fixed effects models, and the minimum of the two was selected for each model, though differences were marginal.

The model with exponents (-2, 0.5) had minimum DIC among the four (Table 11). Given this, this model was selected for consistency with the model selected previously as the preferred

FP NMA for PFS in the base case and as this represented a best-case scenario for nivolumab plus ipilimumab.

Table 15: Details of model selection for TTNT sensitivity analysis

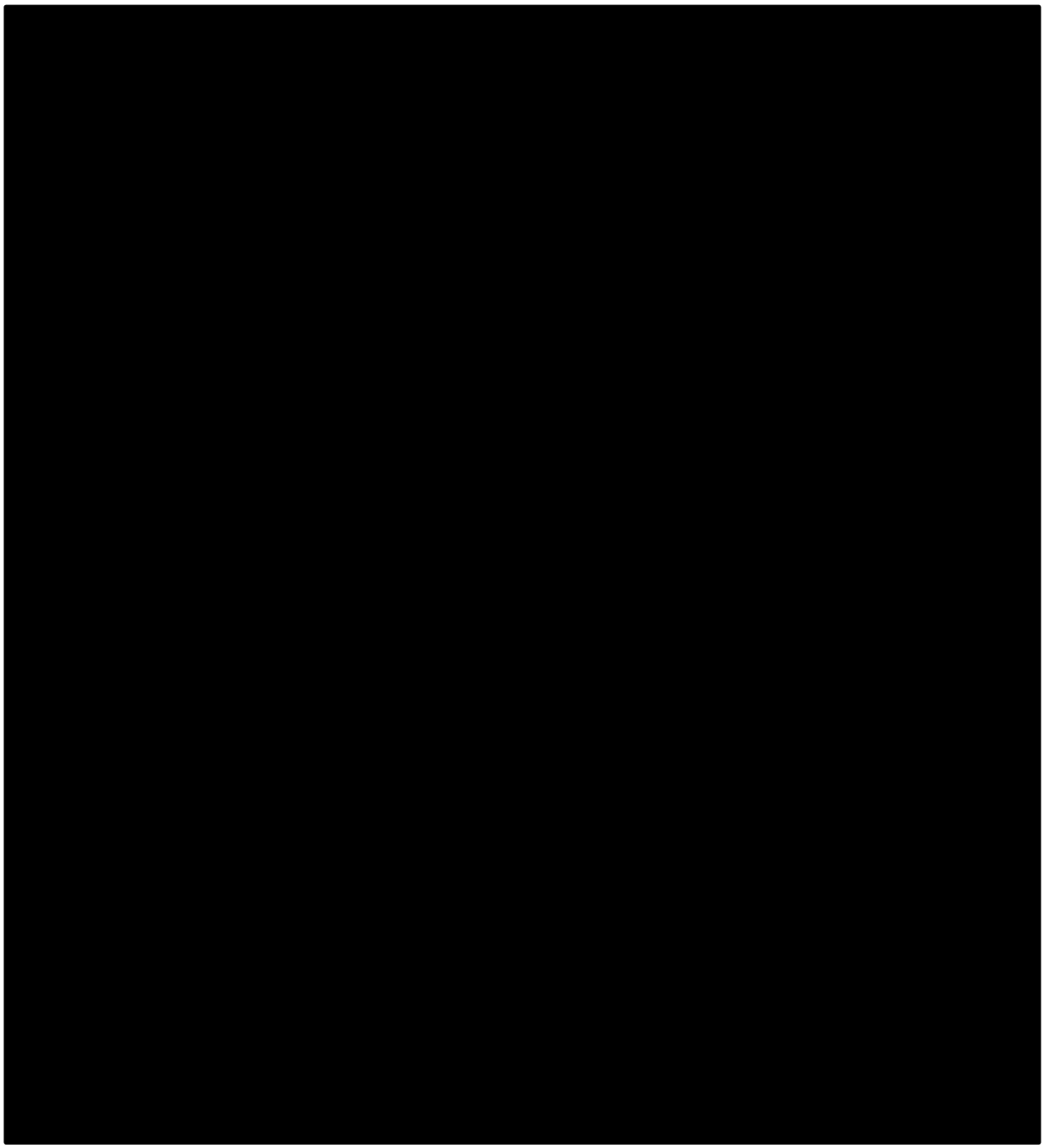
Exponent 1	Exponent 2	AIC	Type	DIC
-1	-0.5	845.61	FE	869.00
-2	0	845.58	RE	863.50
-1	0	842.21	FE	847.80
-2	**0.5**	**841.71**	**FE**	**845.10**

Abbreviations: AIC: Akaike Information Criterion, DIC: Deviance Information Criterion, FE: fixed effects model, RE: random effects model.

Notes: The exponents and fit statistics are shown for those four FP models within 5 points of minimum AIC. The selected model is shown in bold.

The hazard ratio and survival plots for the selected model are shown in Figure 10. The corresponding figure under the main analysis is EAG report figure 28. Under the sensitivity analysis, there is a less pronounced inflexion in the HR in the initial period for nivolumab plus ipilimumab. In the longer term under the sensitivity analysis, there is a continuing decline in HR for nivolumab plus ipilimumab, and an incline for nivolumab plus cabozantinib, whereas in the original analysis (EAG report) the long-term HR is or is approaching horizontal (time-independent). Expected long-term PFS is higher for nivolumab plus ipilimumab compared to nivolumab plus cabozantinib, in both the original analysis and all the candidate models (Table 15) in the sensitivity analysis including the selected model.

Figure 10: Hazard ratio and survival plots for PFS (untreated, intermediate/poor risk) in the selected model from the TTNT sensitivity analysis



Abbreviations: Ave, avelumab; Axi, axitinib; Cabo, cabozantinib; Ipi, ipilimumab; Nivo, nivolumab; PFS, progression free survival; Suni, sunitinib

Notes: TTNT data substituted within the CheckMate 214 trial; see text for details.

Appendix C: Additional FP NMA plots

The plots below have been restricted to show only the treatments considered of interest to the NICE decision problem for each risk subgroup.

Figure 11: 1st line PFS, all-risk, FP NMA predicted survivor functions

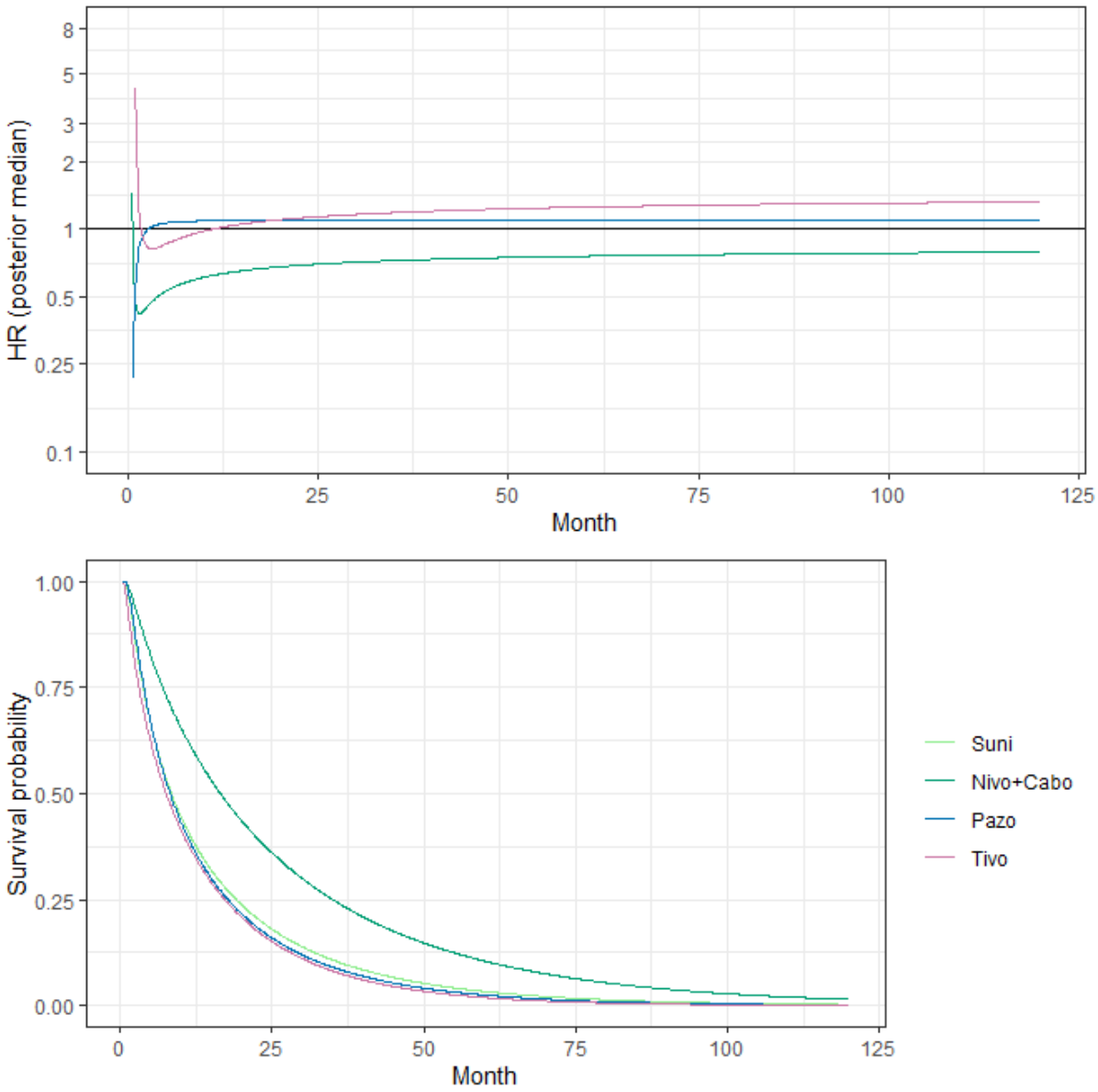


Figure 12: 1st line OS, all-risk, FP NMA predicted survivor functions

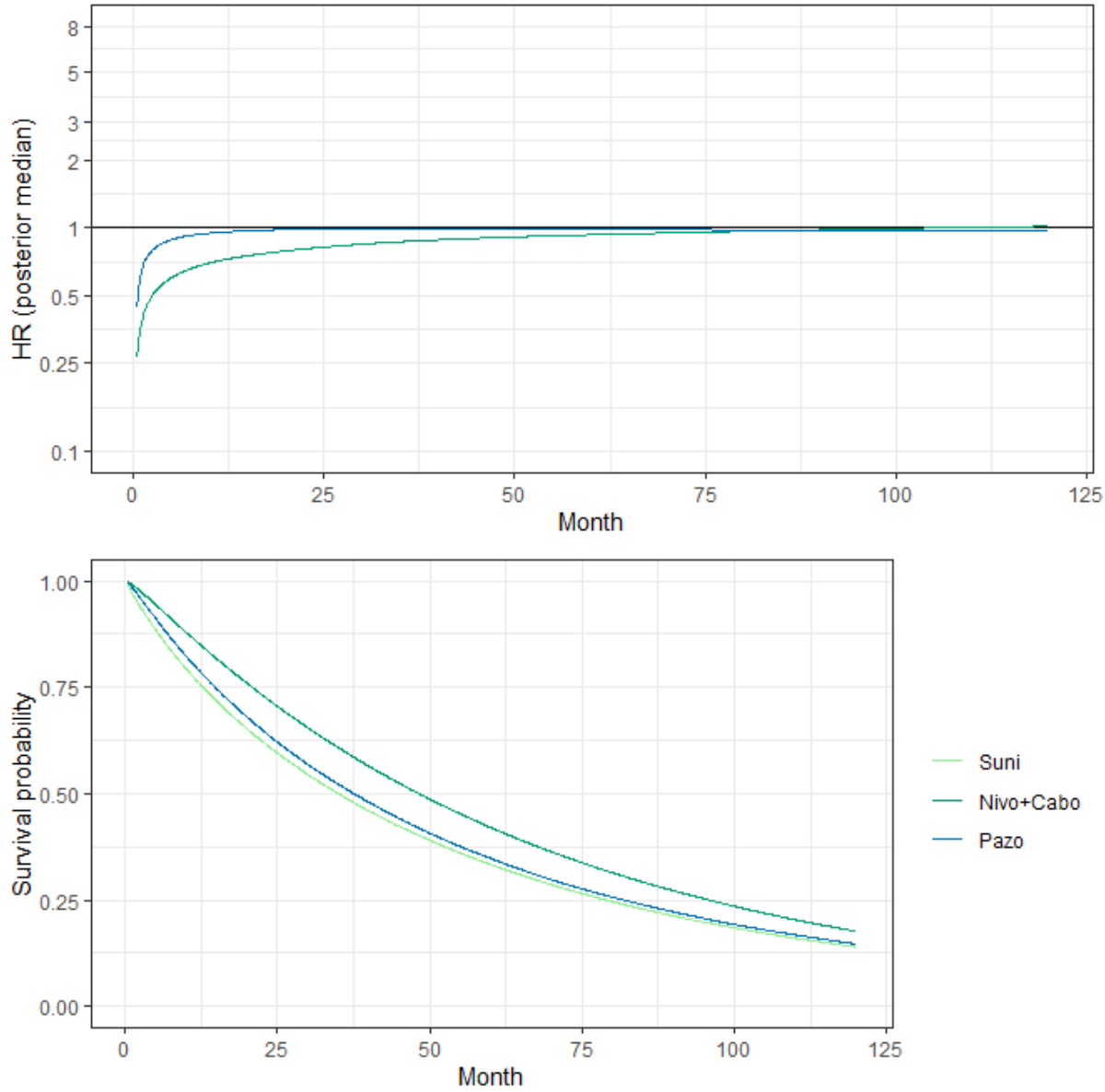


Figure 13: 1st line PFS, intermediate / poor risk, FP NMA predicted survivor functions

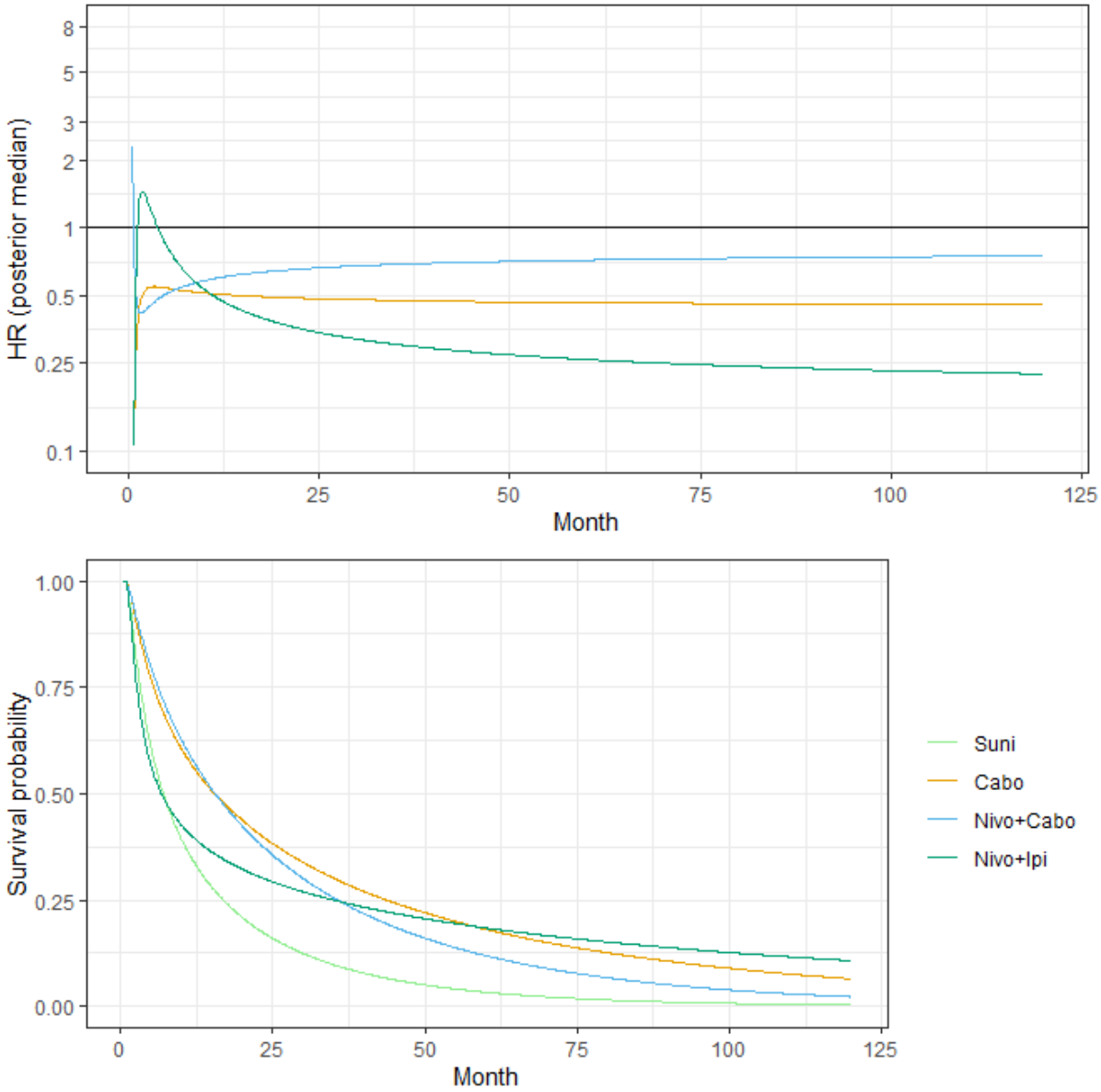
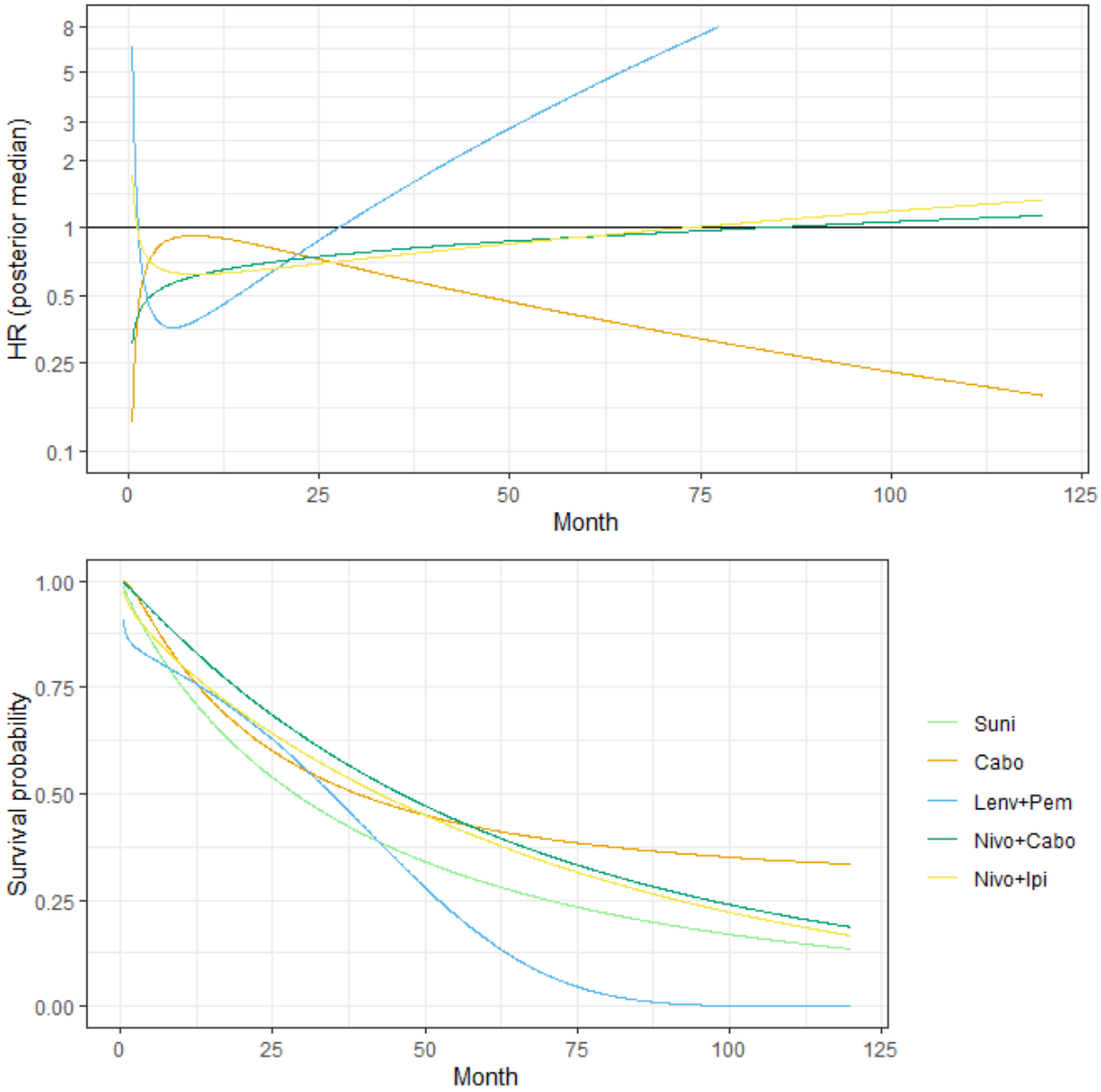


Figure 14: 1st line OS, intermediate / poor risk, FP NMA predicted survivor functions



Appendix D: Detailed breakdown of EAG base case state transition and PartSA results

Table 16: Summary of LY gain by health state (all-risk, cabo+nivo vs next best non-dominated comparator: pazopanib)

Health state	LY Cabo+nivo (X)	LY Pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.109	0.115	-0.006	0.006	0%
1L: on treatment	1.945	1.144	0.801	0.801	50%
2L: off treatment	0.288	0.158	0.130	0.130	8%
2L: on treatment	0.843	0.541	0.302	0.302	19%
3L: off treatment	0.026	0.109	-0.083	0.083	5%
3L: on treatment	0.142	0.365	-0.223	0.223	14%
4L: off treatment	0.001	0.009	-0.007	0.007	0%
4L: on treatment	0.007	0.054	-0.048	0.048	3%
BSC	0.353	0.341	0.011	0.011	1%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.715**	**2.837**	**0.878**	**1.611**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 17: Summary of LY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator: pazopanib)

Health state	LY Cabo+nivo (X)	LY Pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.274	0.266	0.008	0.008	1%
1L: on treatment	2.582	1.828	0.753	0.753	49%

Health state	LY Cabo+nivo (X)	LY Pazo (Y)	Increment	Absolute increment	% absolute increment
2L: off treatment	0.288	0.164	0.124	0.124	8%
2L: on treatment	0.844	0.562	0.282	0.282	18%
3L: off treatment	0.026	0.113	-0.087	0.087	6%
3L: on treatment	0.142	0.379	-0.237	0.237	15%
4L: off treatment	0.001	0.009	-0.008	0.008	1%
4L: on treatment	0.007	0.056	-0.050	0.050	3%
BSC	0.353	0.355	-0.001	0.001	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**4.517**	**3.733**	**0.784**	**1.549**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 18: Summary of LY gain by health state (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: lenvatinib plus pembrolizumab)

Health state	LY Cabo+nivo (X)	LY Pem+lenv (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.076	0.093	-0.016	0.016	1%
1L: on treatment	1.636	2.289	-0.653	0.653	54%
2L: off treatment	0.285	0.170	0.115	0.115	10%
2L: on treatment	0.834	0.530	0.304	0.304	25%
3L: off treatment	0.026	0.034	-0.008	0.008	1%
3L: on treatment	0.141	0.153	-0.013	0.013	1%
4L: off treatment	0.001	0.008	-0.006	0.006	1%

Health state	LY Cabo+nivo (X)	LY Pem+lenv (Y)	Increment	Absolute increment	% absolute increment
4L: on treatment	0.007	0.046	-0.039	0.039	3%
BSC	0.349	0.296	0.053	0.053	4%
Death	0.000	0.000	0.000	0.000	0%
Total	**3.356**	**3.618**	**-0.263**	**1.209**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 19: Summary of QALY gain by health state (all-risk, cabo+nivo vs next best non-dominated comparator: pazopanib)

Health state	QALY Cabo+nivo (X)	QALY Pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.074	0.079	-0.005	0.005	1%
1L: on treatment	1.315	0.790	0.525	0.525	59%
2L: off treatment	0.130	0.082	0.048	0.048	5%
2L: on treatment	0.455	0.322	0.134	0.134	15%
3L: off treatment	0.013	0.048	-0.035	0.035	4%
3L: on treatment	0.064	0.185	-0.121	0.121	14%
4L: off treatment	0.001	0.004	-0.003	0.003	0%
4L: on treatment	0.003	0.021	-0.018	0.018	2%
BSC	0.166	0.164	0.003	0.003	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.223**	**1.695**	**0.528**	**0.892**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 20: Summary of QALY gain by health state (favourable risk, cabo+nivo vs next best non-dominated comparator: pazopanib)

Health state	QALY Cabo+nivo (X)	QALY Pazo (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.177	0.175	0.002	0.002	0%
1L: on treatment	1.670	1.214	0.456	0.456	56%
2L: off treatment	0.128	0.083	0.045	0.045	6%
2L: on treatment	0.448	0.326	0.122	0.122	15%
3L: off treatment	0.013	0.049	-0.036	0.036	4%
3L: on treatment	0.063	0.187	-0.125	0.125	15%
4L: off treatment	0.001	0.004	-0.004	0.004	0%
4L: on treatment	0.003	0.021	-0.018	0.018	2%
BSC	0.164	0.166	-0.002	0.002	0%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.666**	**2.226**	**0.440**	**0.809**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 21: Summary of QALY gain by health state (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: lenvatinib plus pembrolizumab)

Health state	QALY Cabo+nivo (X)	QALY Pem+lenv (Y)	Increment	Absolute increment	% absolute increment
1L: off treatment	0.052	0.062	-0.009	0.009	1%
1L: on treatment	1.117	1.525	-0.409	0.409	61%
2L: off treatment	0.130	0.083	0.047	0.047	7%
2L: on treatment	0.456	0.303	0.153	0.153	23%
3L: off treatment	0.013	0.017	-0.003	0.003	0%
3L: on treatment	0.064	0.073	-0.009	0.009	1%
4L: off treatment	0.001	0.003	-0.003	0.003	0%
4L: on treatment	0.003	0.021	-0.017	0.017	3%
BSC	0.167	0.142	0.025	0.025	4%
Death	0.000	0.000	0.000	0.000	0%
Total	**2.003**	**2.229**	**-0.226**	**0.675**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care; LY, life years; vs, versus

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 22: Summary of costs by health state

	1L costs			Subsequent treatment			MRU			
Technologies	**Drug cost**	**Admin cost**	**AE cost**	**Drug cost**	**Admin cost**	**AE cost**	**1L**	**Subsequent treatment**	**EOL cost**	**Total cost**
Risk population: All-risk										
Suni	£6,836	£275	£604	£43,410	£906	£692	£2,628	£14,362	£7,962	£77,675
Pazo	£6,481	£324	£512	£44,753	£893	£688	£2,628	£14,422	£7,949	£78,649
Tivo	£27,787	£336	£408	£43,435	£971	£660	£2,628	£14,328	£7,966	£98,517
Cabo+nivo	£158,898	£3,242	£1,127	£34,672	£271	£920	£4,088	£12,897	£7,732	£223,847
Risk population: Favourable risk										
Suni	£10,336	£320	£604	£44,133	£921	£704	£4,058	£14,602	£7,743	£83,420
Pazo	£9,859	£395	£512	£45,497	£908	£699	£4,058	£14,662	£7,730	£84,321
Tivo	£42,269	£413	£408	£44,158	£987	£671	£4,058	£14,567	£7,747	£115,279
Cabo+nivo	£185,764	£3,445	£1,127	£34,157	£267	£907	£5,354	£12,707	£7,549	£251,276
Risk population: Intermediate / poor risk										
Suni	£5,443	£258	£604	£42,874	£895	£684	£2,080	£14,185	£8,048	£75,069
Pazo	£5,137	£296	£512	£44,200	£882	£679	£2,080	£14,244	£8,035	£76,064
Tivo	£22,024	£305	£408	£42,898	£959	£652	£2,080	£14,151	£8,052	£91,528
Nivo+ipi	£80,711	£3,210	£335	£30,191	£243	£674	£2,277	£12,078	£8,056	£137,774
Cabo	£86,584	£387	£732	£43,582	£1,033	£671	£3,753	£13,775	£7,791	£158,308
Cabo+nivo	£140,562	£2,990	£1,127	£34,654	£271	£920	£3,487	£12,889	£7,822	£204,721
Pem+lenv	£173,402	£2,940	£1,062	£27,338	£229	£732	£4,622	£11,578	£7,745	£229,649

Abbreviations: admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Table 23: Summary of predicted resource use by category of cost (all-risk, cabo+nivo vs next best non-dominated comparator: pazopanib)

Item	Cost Cabozantinib plus nivolumab (X)	Cost Pazopanib (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£158,898	£6,481	£152,417	£152,417	90%
Admin cost (1L)	£3,242	£324	£2,918	£2,918	2%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition cost (2L+)	£34,672	£44,753	£-10,081	£10,081	6%
Admin cost (2L+)	£271	£893	£-622	£622	0%
AE cost (2L+)	£920	£688	£233	£233	0%
MRU 1L	£4,088	£2,628	£1,460	£1,460	1%
MRU 2L+	£12,897	£14,422	£-1,525	£1,525	1%
EOL	£7,732	£7,949	£-217	£217	0%
Total	**£223,847**	**£78,649**	**£145,198**	**£170,088**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 24: Summary of predicted resource use by category of cost (favourable risk, cabo+nivo vs next best non-dominated comparator: pazopanib)

Item	Cost Cabozantinib plus nivolumab (X)	Cost Pazopanib (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£185,764	£9,859	£175,905	£175,905	90%
Admin cost (1L)	£3,445	£395	£3,050	£3,050	2%
AE cost (1L)	£1,127	£512	£615	£615	0%
Drug acquisition cost (2L+)	£34,157	£45,497	£-11,340	£11,340	6%

Item	Cost Cabozantinib plus nivolumab (X)	Cost Pazopanib (Y)	Increment	Absolute increment	% absolute increment
Admin cost (2L+)	£267	£908	£-641	£641	0%
AE cost (2L+)	£907	£699	£208	£208	0%
MRU 1L	£5,354	£4,058	£1,296	£1,296	1%
MRU 2L+	£12,707	£14,662	£-1,956	£1,956	1%
EOL	£7,549	£7,730	£-181	£181	0%
Total	**£251,276**	**£84,321**	**£166,955**	**£195,192**	**100%**

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Table 25: Summary of predicted resource use by category of cost (intermediate / poor risk, cabo+nivo vs next best non-dominated comparator: lenvatinib plus pembrolizumab)

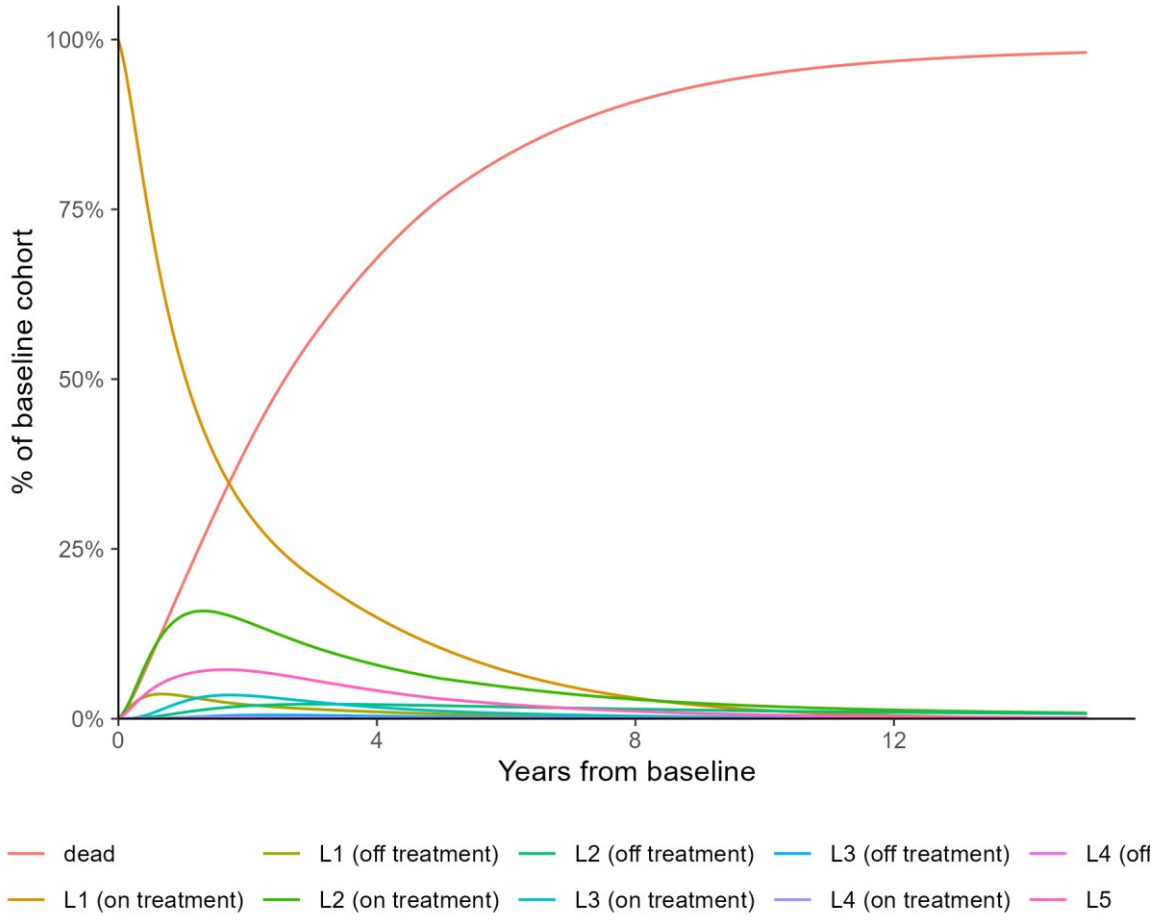
Item	Cost Cabozantinib plus nivolumab (X)	Cost Lenvatinib plus pembrolizumab (Y)	Increment	Absolute increment	% absolute increment
Drug acquisition cost (1L)	£140,562	£173,402	£-32,840	£32,840	76%
Admin cost (1L)	£2,990	£2,940	£49	£49	0%
AE cost (1L)	£1,127	£1,062	£65	£65	0%
Drug acquisition cost (2L+)	£34,654	£27,338	£7,316	£7,316	17%
Admin cost (2L+)	£271	£229	£42	£42	0%
AE cost (2L+)	£920	£732	£187	£187	0%
MRU 1L	£3,487	£4,622	£-1,135	£1,135	3%
MRU 2L+	£12,889	£11,578	£1,311	£1,311	3%
EOL	£7,822	£7,745	£76	£76	0%
Total	**£204,721**	**£229,649**	**£-24,928**	**£43,023**	**100%**

Item	Cost Cabozantinib plus nivolumab (X)	Cost Lenvatinib plus pembrolizumab (Y)	Increment	Absolute increment	% absolute increment

Abbreviations: 1L, 1st line; 2L, 2nd line; 2L+, 2nd line-plus; admin, administration; AE, adverse event; EOL, end of life; MRU, medical resource use

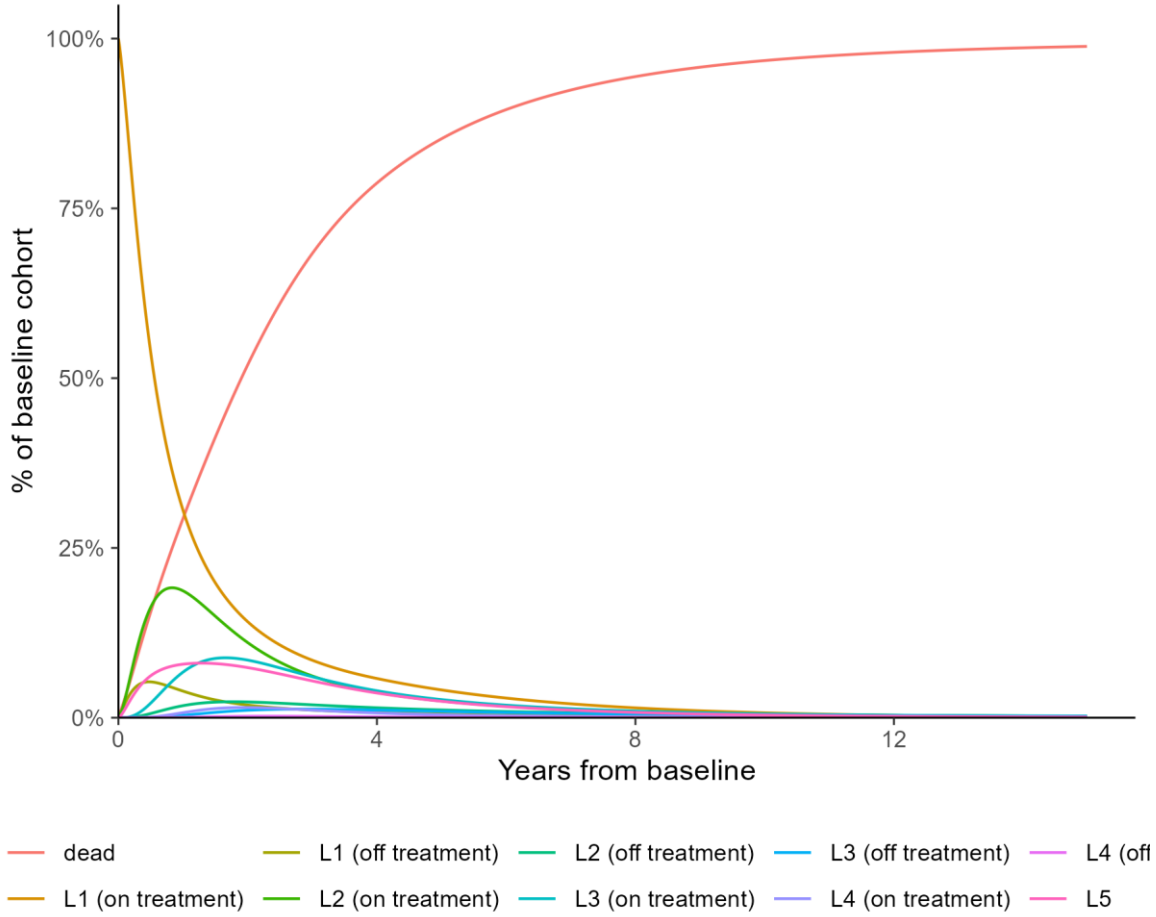
Discrepancies in sums due to rounding errors: totals shown are calculated on unrounded numbers

Figure 15: Markov trace: All-risk, cabozantinib plus nivolumab



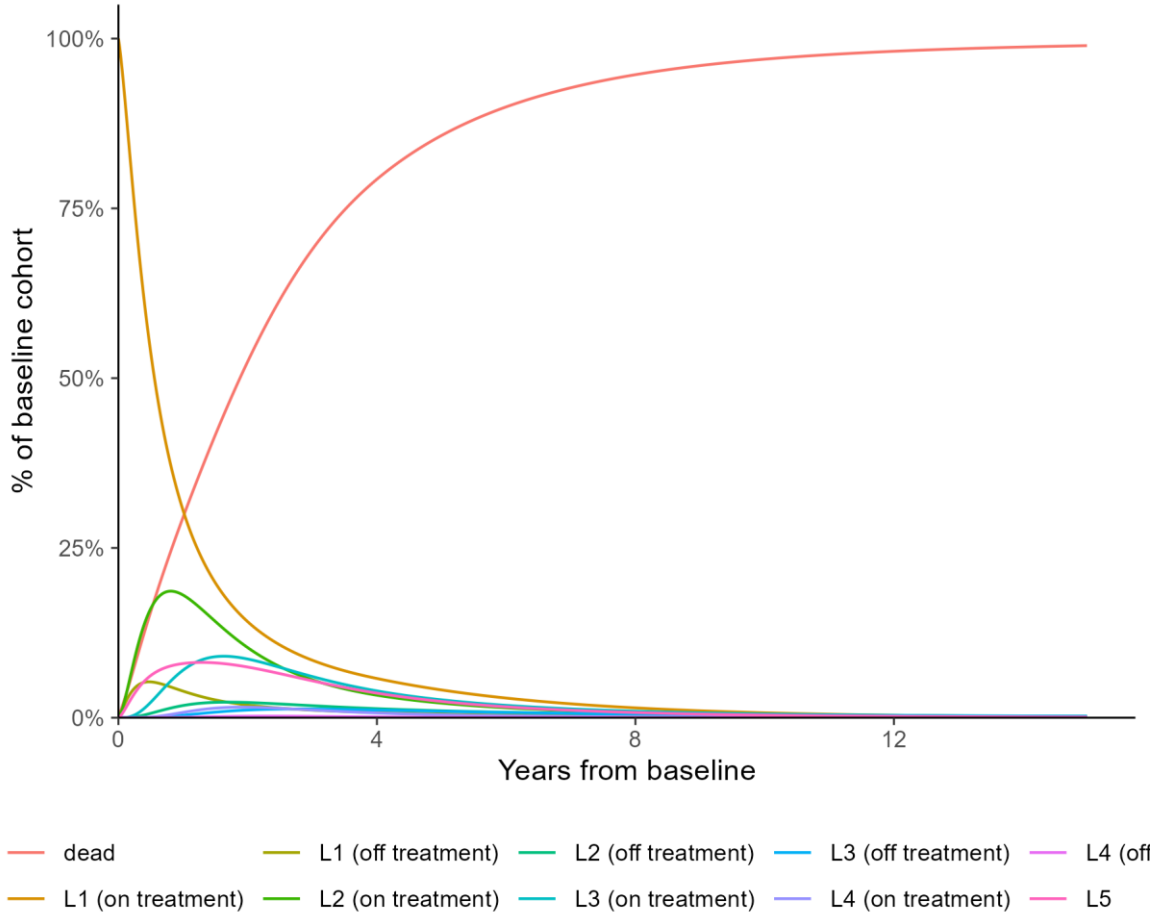
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 16: Markov trace: All-risk, pazopanib



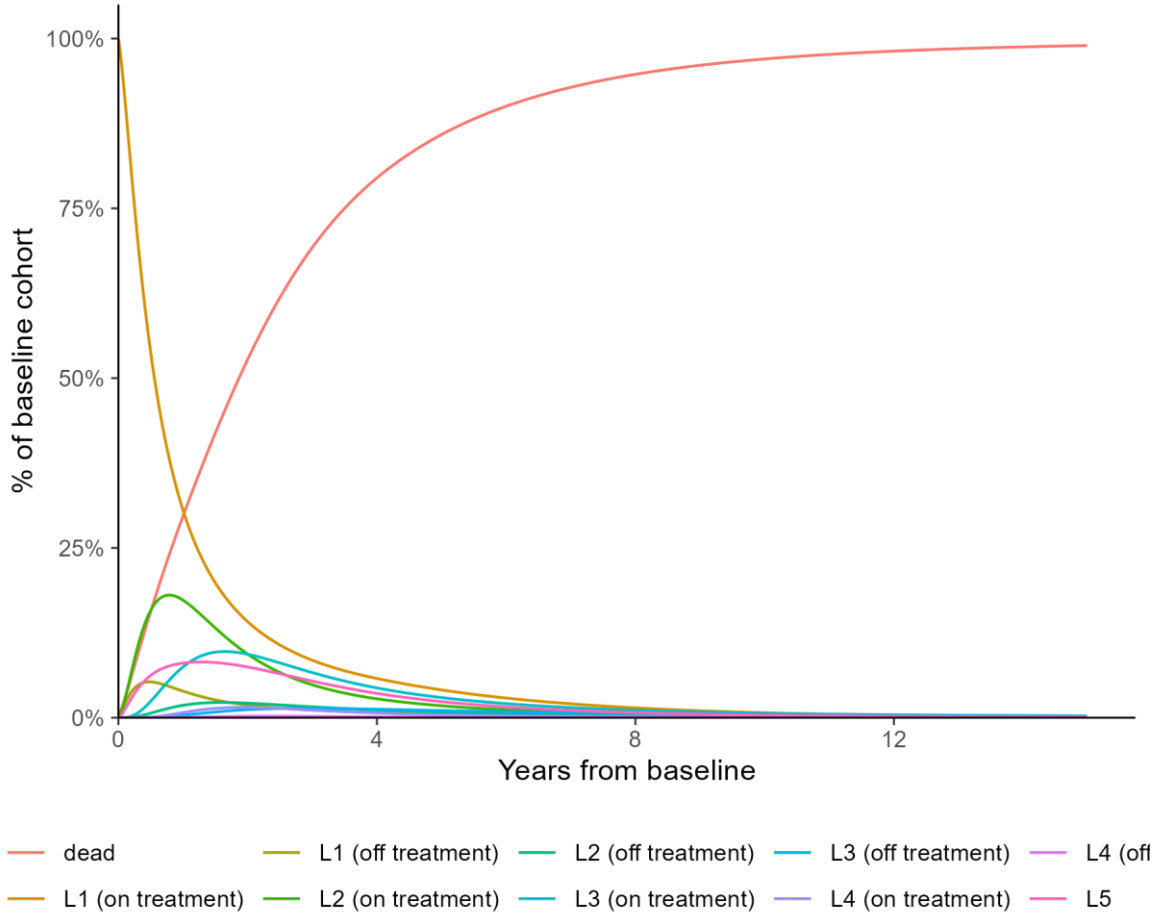
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 17: Markov trace: All-risk, sunitinib



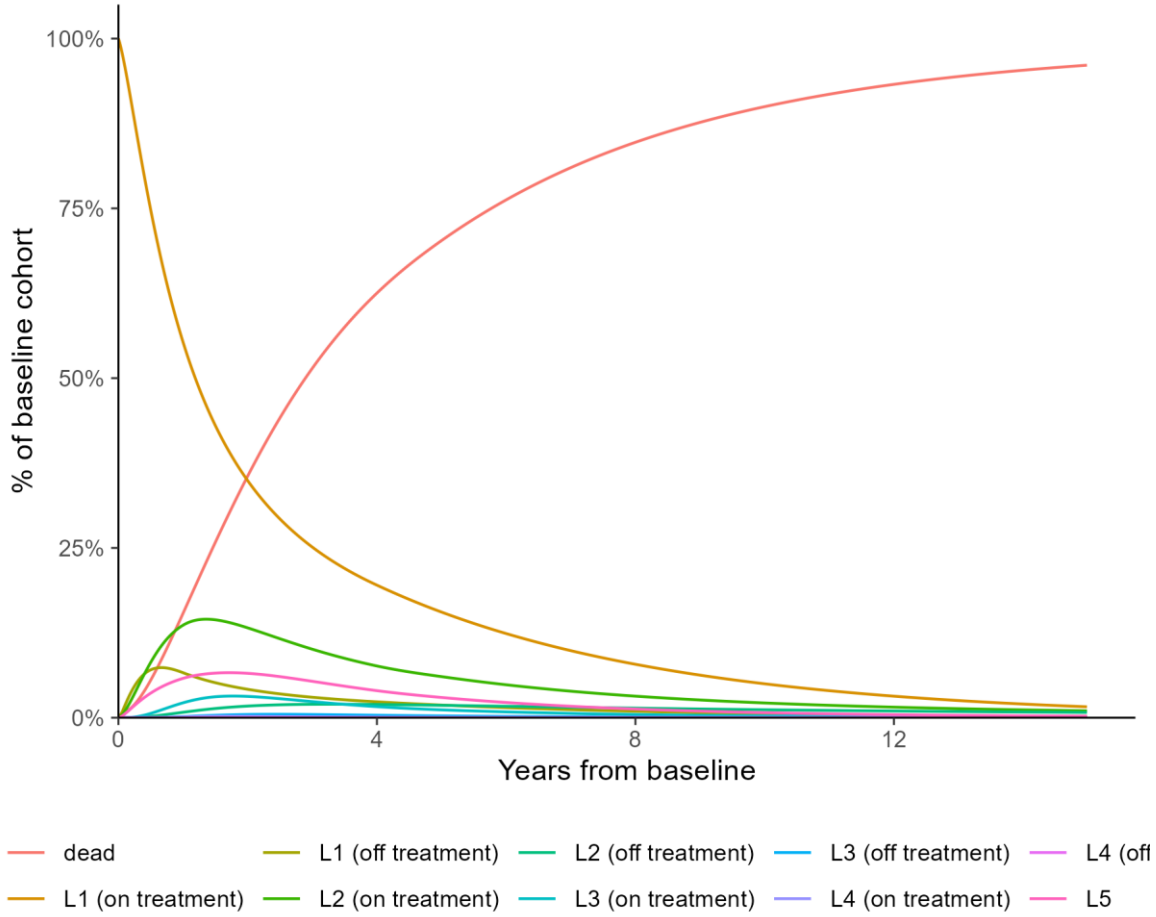
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 18: Markov trace: All-risk, tivozanib



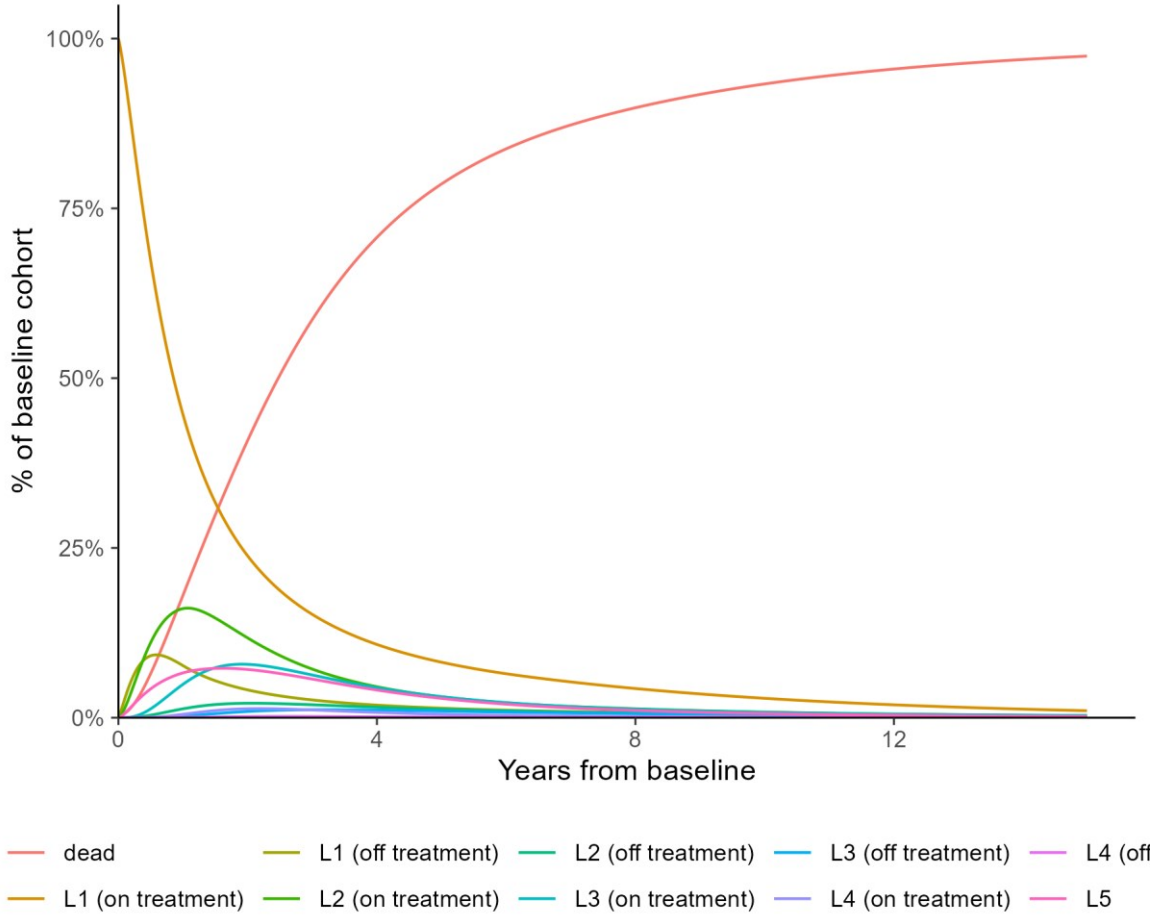
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 19: Markov trace: Favourable risk, cabozantinib plus nivolumab



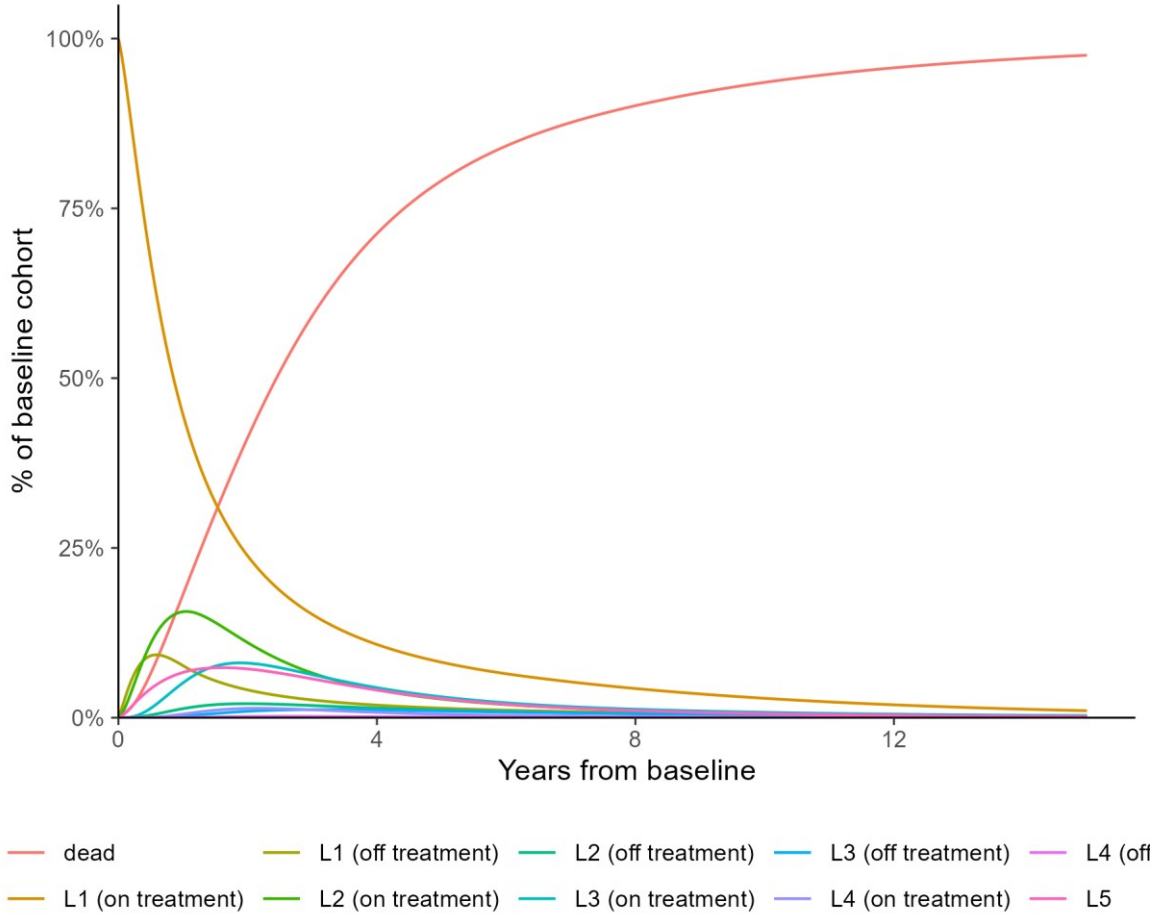
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 20: Markov trace: Favourable risk, pazopanib



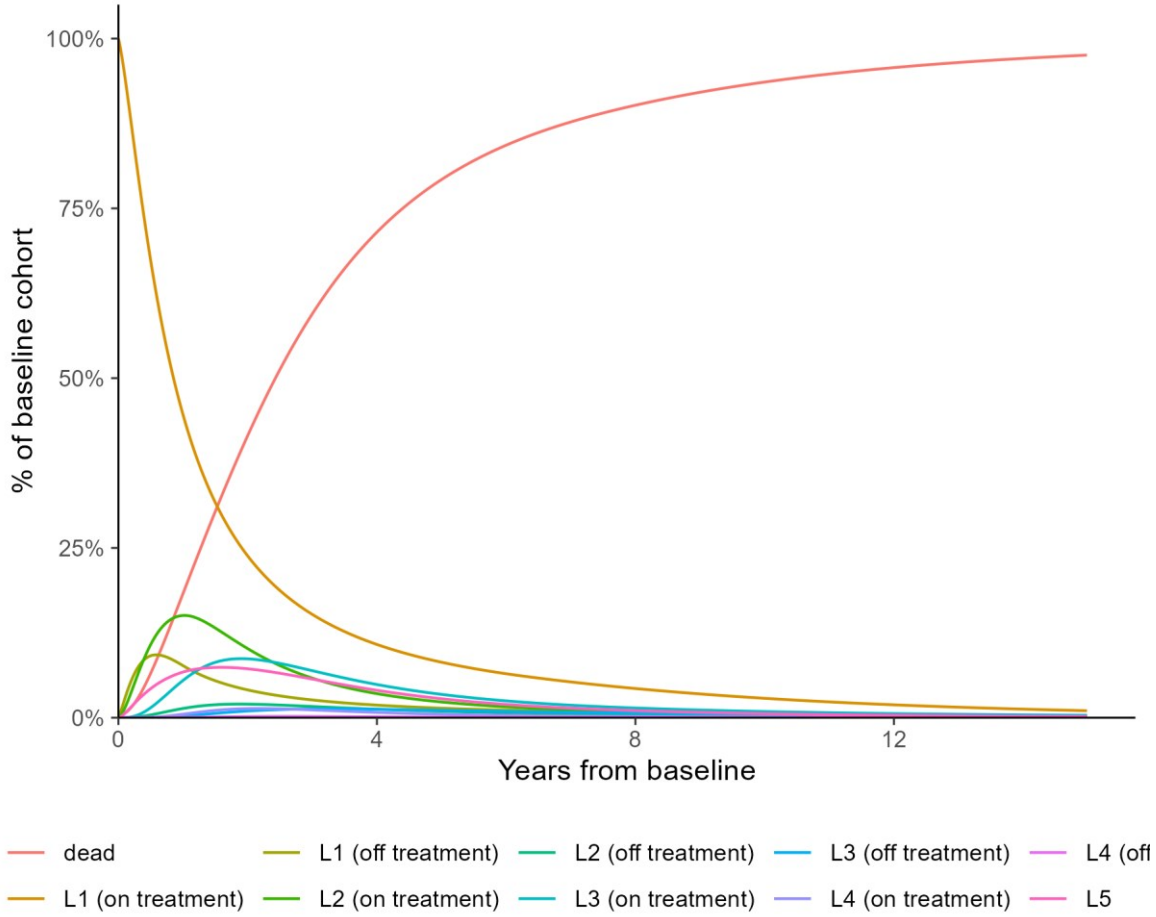
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 21: Markov trace: Favourable risk, sunitinib



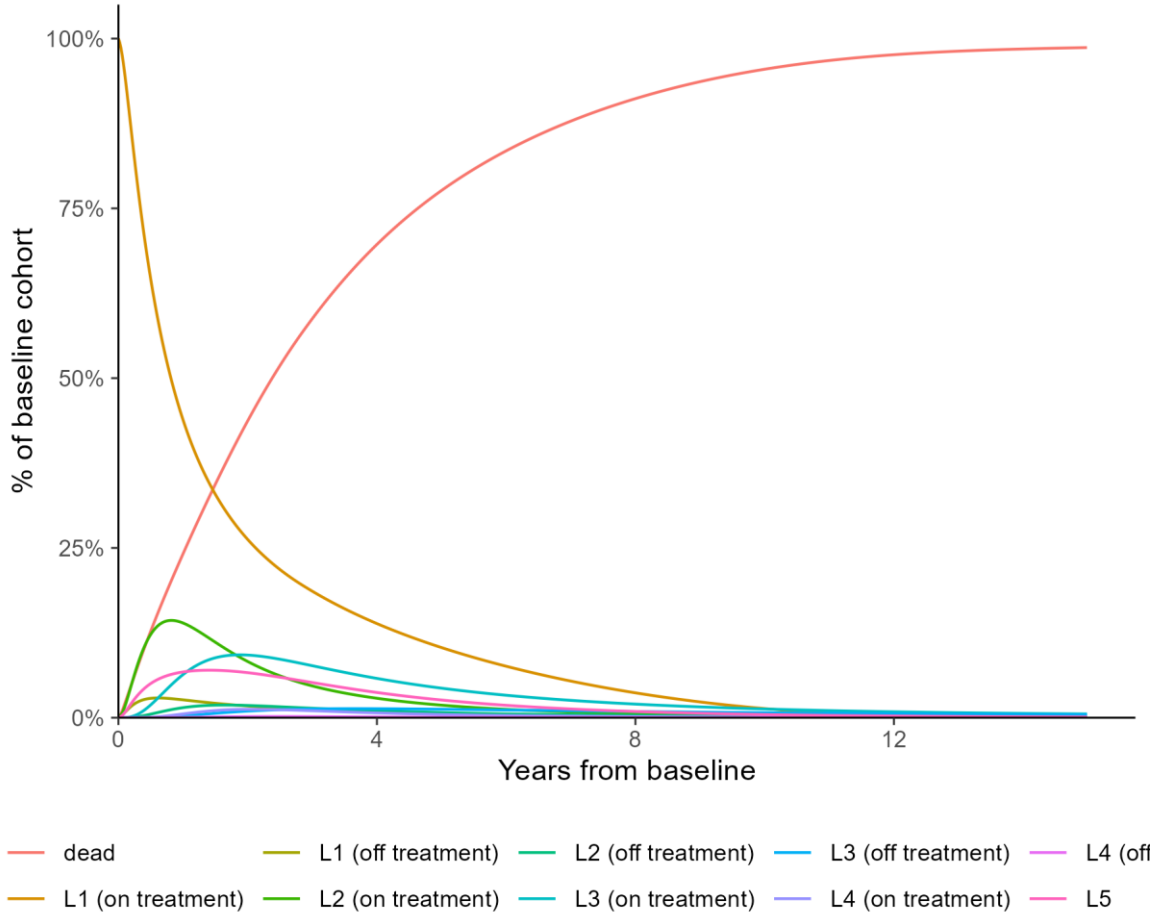
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 22: Markov trace: Favourable risk, tivozanib



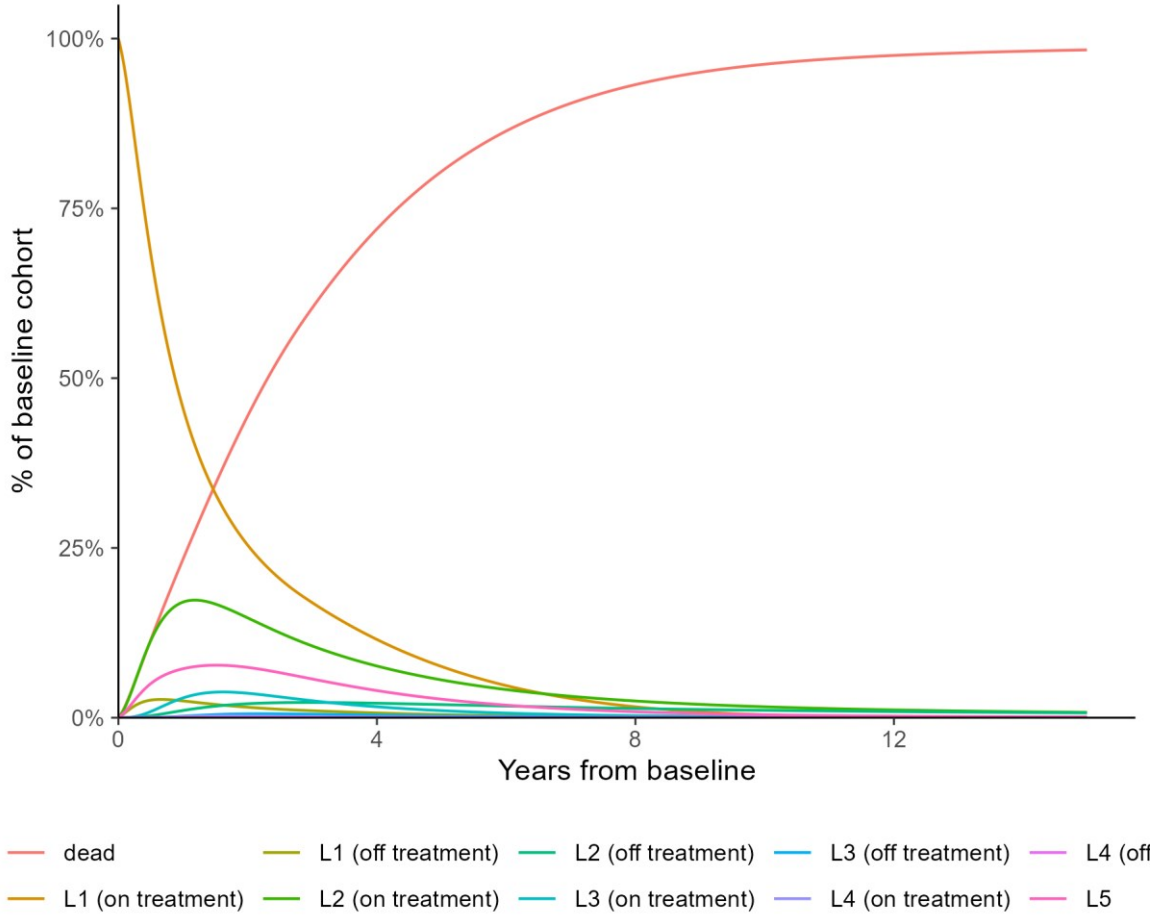
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 23: Markov trace: Intermediate / poor risk, cabozantinib



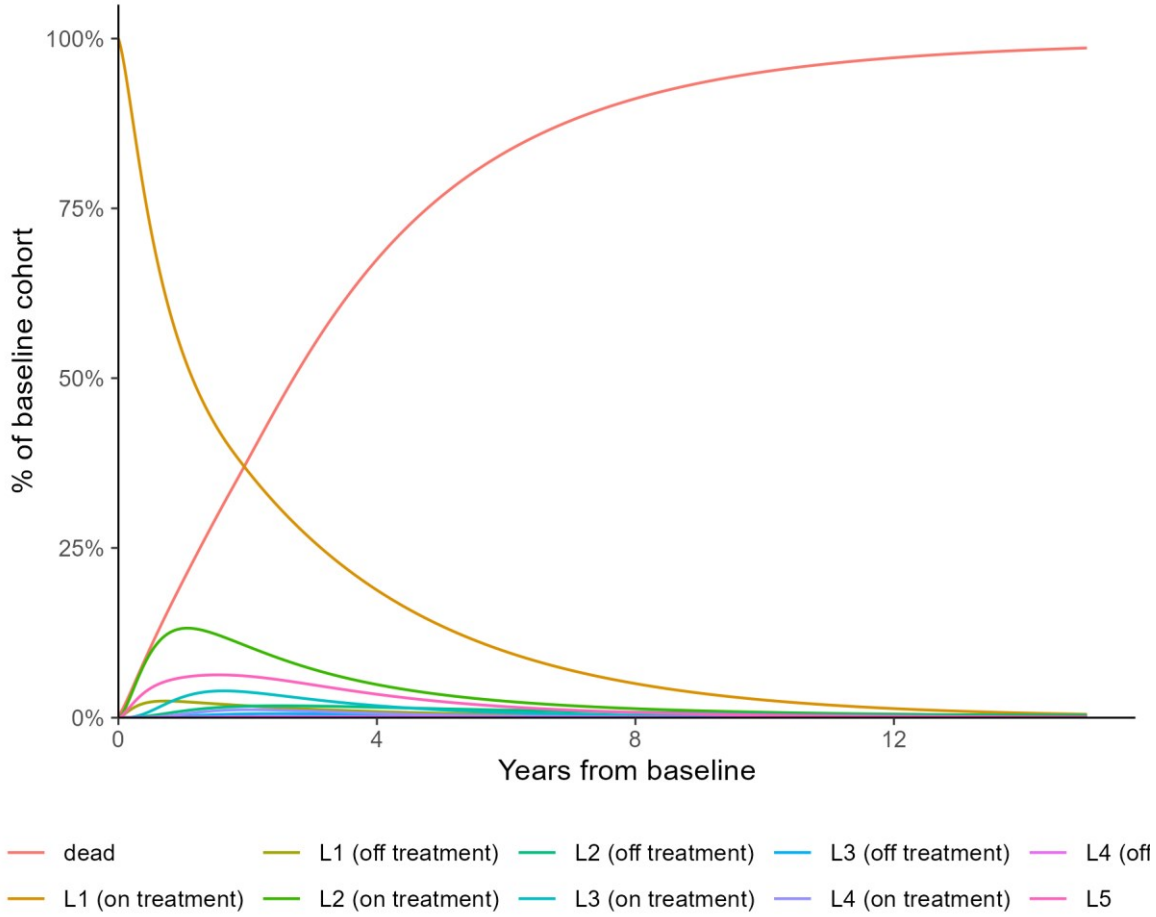
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 24: Markov trace: Intermediate / poor risk, cabozantinib plus nivolumab



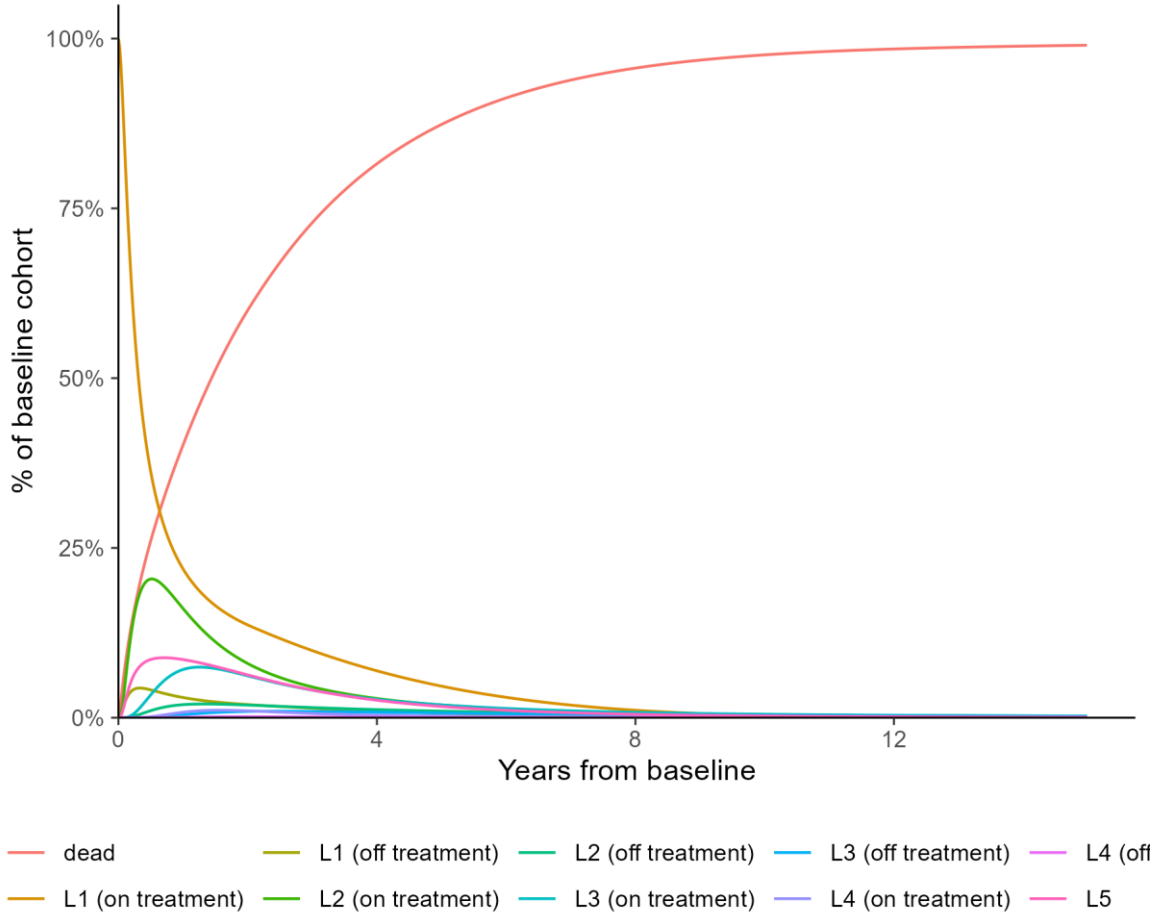
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 25: Markov trace: Intermediate / poor risk, lenvatinib plus pembrolizumab



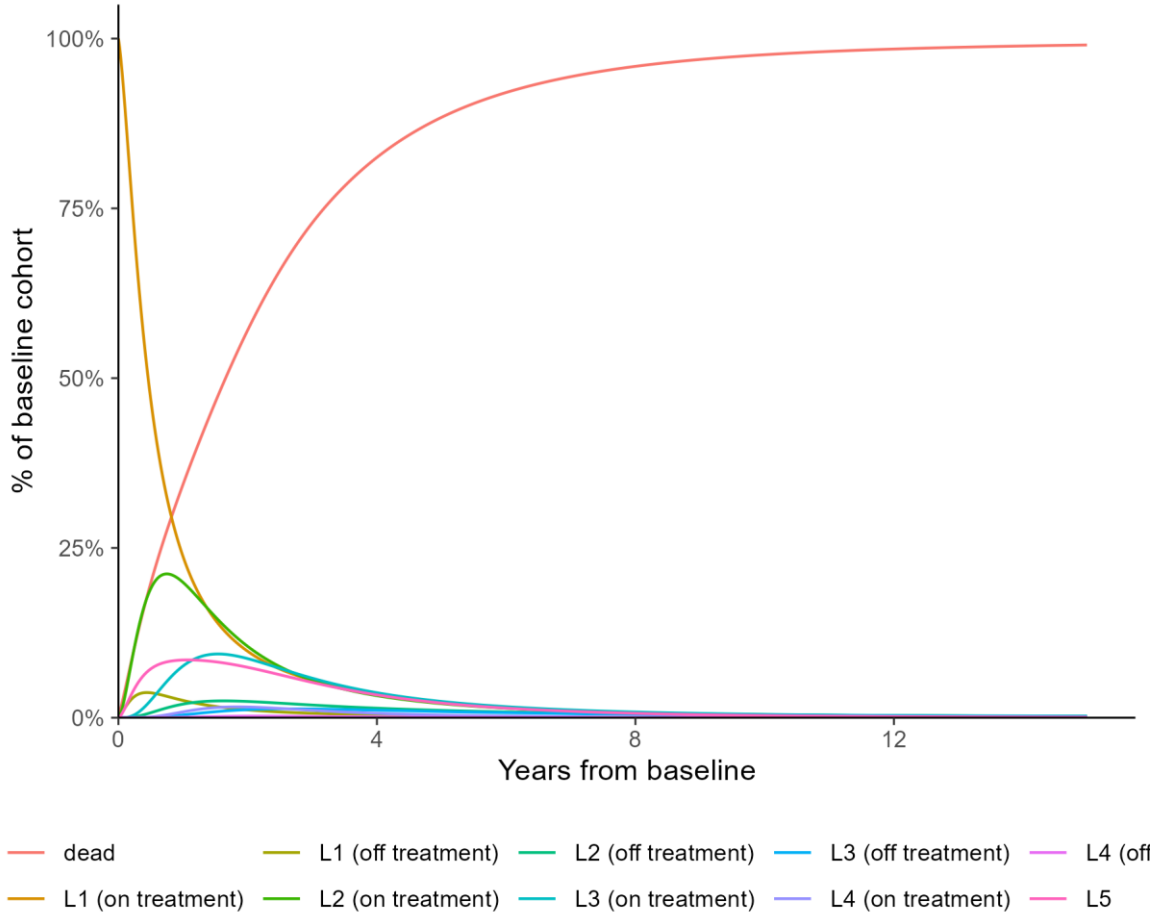
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 26: Markov trace: Intermediate / poor risk, nivolumab plus ipilimumab



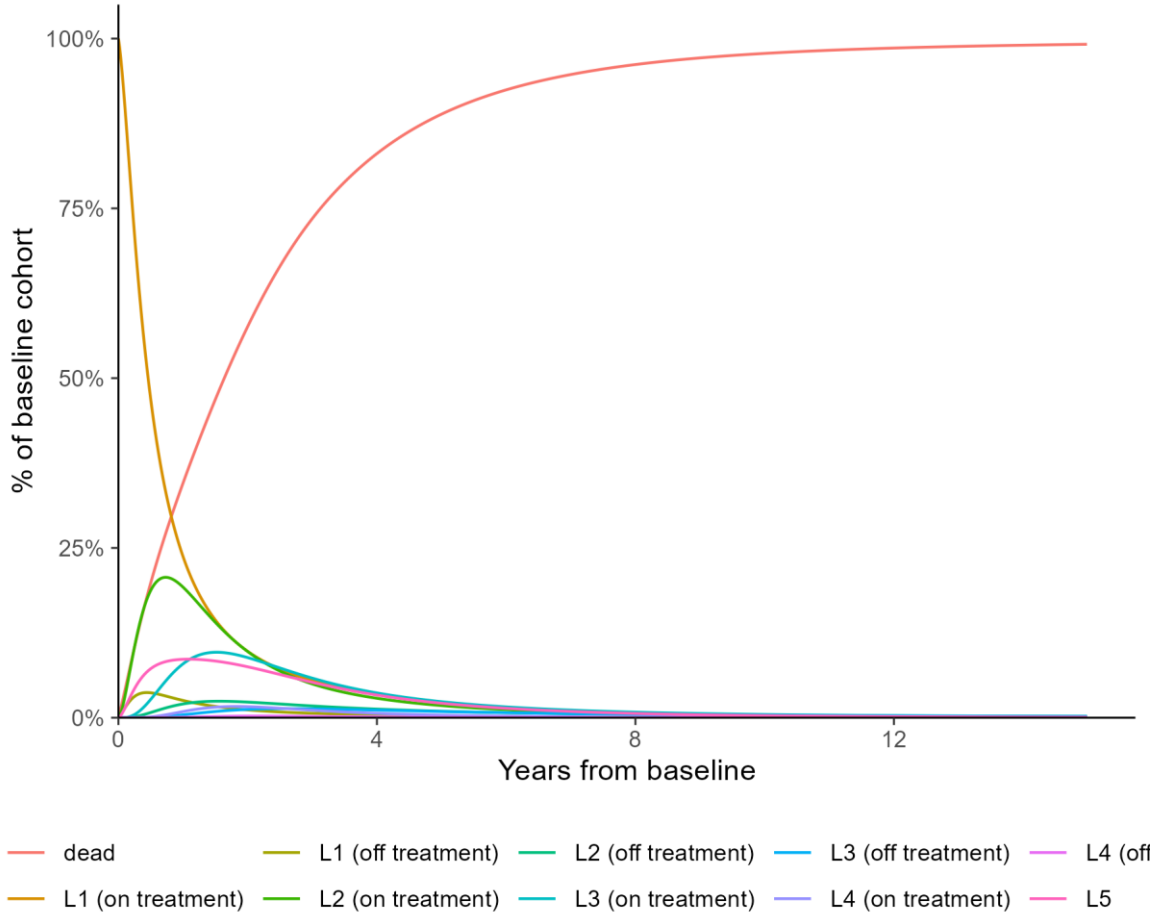
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 27: Markov trace: Intermediate / poor risk, pazopanib



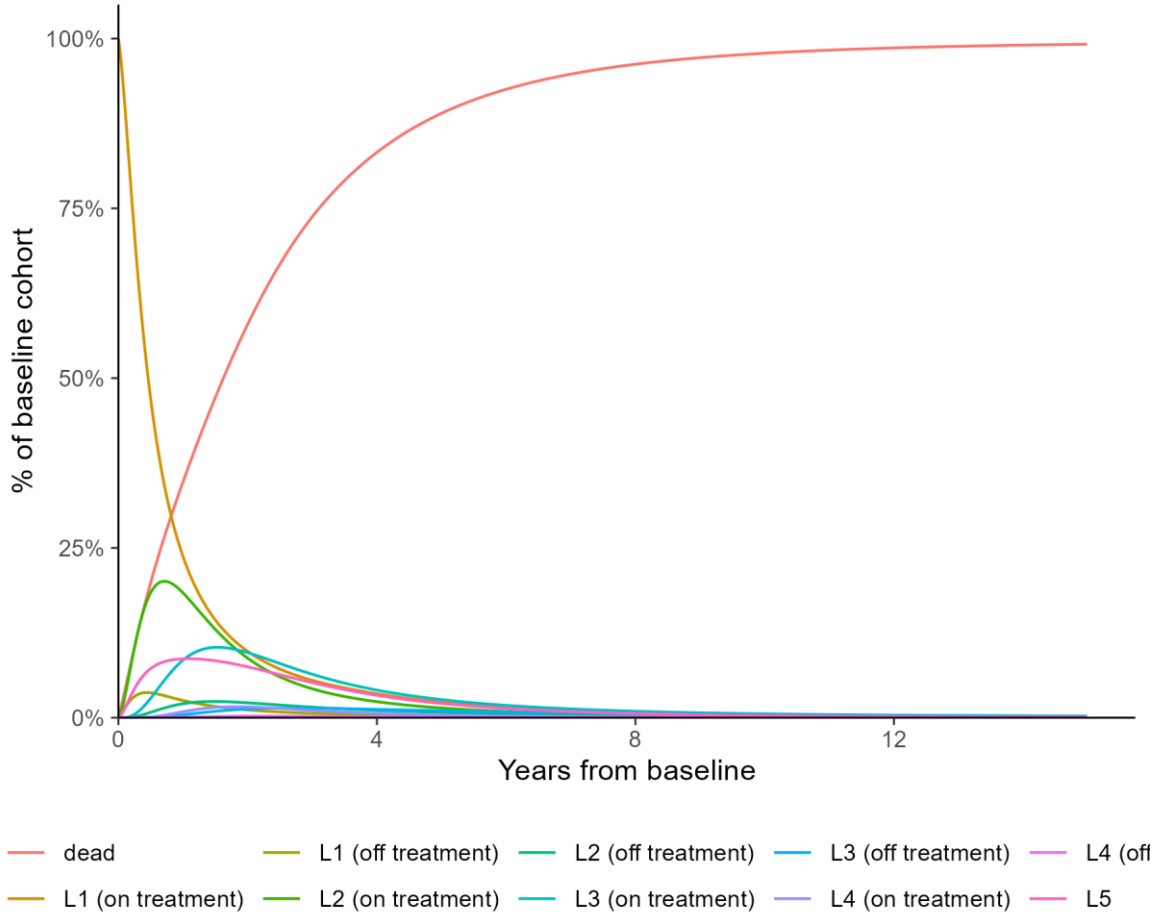
Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 28: Markov trace: Intermediate / poor risk, sunitinib



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Figure 29: Markov trace: Intermediate / poor risk, tivozanib



Abbreviations: L1, 1st line; L2, 2nd line; L3, 3rd line; L4, 4th line; L5, 5th line

Table 26: PartSA analysis life years

	PFS on treatment	PFS off treatment	PPS on treatment	PPS off treatment	Total
All-risk					
Cabo+nivo	1.95	0.10	0.00	1.31	3.35
Pazo	1.14	0.11	0.00	1.65	2.90
Tivo	1.14	0.11	0.00	1.65	2.90
Suni	1.14	0.11	0.00	1.65	2.90
Favourable risk					
Cabo+nivo	2.57	0.13	0.01	1.70	4.41
Pazo	1.79	0.14	0.04	2.93	4.90
Tivo	1.79	0.14	0.04	2.93	4.90
Suni	1.79	0.14	0.04	2.93	4.90
Intermediate/poor risk					
Cabo+nivo	1.64	0.08	0.00	1.24	2.95
Nivo+ipi	0.98	0.11	0.00	1.83	2.92
Pem+lenv	2.29	0.09	0.00	0.66	3.04
Pazo	0.89	0.07	0.00	1.32	2.28
Tivo	0.89	0.07	0.00	1.32	2.28
Suni	0.89	0.07	0.00	1.32	2.28
Cabo	1.79	0.09	0.00	0.93	2.81

Abbreviations: cabo, cabozantinib; ipi, ipilimumab; lenv, lenvatinib; LYG, life years gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; PPS, post progression survival; suni, sunitinib; tivo, tivozanib

Table 27: PartSA QALYs

	PFS	PPS	AE	AE PPS	Total
All-risk					
Cabo+nivo	1.41	0.78	-0.03	-0.01	2.15
Pazo	0.88	0.98	-0.01	-0.01	1.83
Tivo	0.88	0.98	-0.01	-0.01	1.84
Suni	0.88	0.98	-0.01	-0.01	1.84
Favourable risk					
Cabo+nivo	1.78	0.95	-0.03	-0.01	2.70
Pazo	1.31	1.62	-0.01	-0.01	2.91
Tivo	1.31	1.62	-0.01	-0.01	2.91
Suni	1.31	1.62	-0.01	-0.01	2.91
Intermediate/poor risk					
Cabo+nivo	1.20	0.75	-0.03	-0.01	1.91

	PFS	PPS	AE	AE PPS	Total
Nivo+ipi	0.76	1.12	-0.01	-0.02	1.86
Pem+lenv	1.61	0.39	-0.03	-0.02	1.96
Pazo	0.68	0.81	-0.01	-0.01	1.47
Tivo	0.68	0.81	-0.01	-0.01	1.47
Suni	0.68	0.81	-0.01	-0.01	1.47
Cabo	1.30	0.56	-0.02	-0.01	1.82

Abbreviations:AE, adverse event; cabo, cabozantinib; env, lenvatinib; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; PFS, progression free survival; PPS, post progression survival; QALYs, quality adjusted life years; suni, sunitinib; tivo, tivozanib

Table 28: PartSA costs

				Subsequent treatment			MRU				
	Drug cost	Admin cost	AE cost	Drug cost	Admin cost	AE cost	Pre-progression cost	Post-progression cost	EOL cost	On progression cost	Total
All-risk											
Cabo+nivo	£158,898	£3,242	£1,127	£29,592	£610	£542	£4,074	£2,346	£7,797	£4,528	£212,756
Pazo	£6,481	£324	£512	£41,312	£3,401	£620	£2,615	£2,955	£7,923	£4,648	£70,790
Tivo	£27,787	£336	£408	£43,045	£4,038	£553	£2,615	£2,955	£7,923	£4,648	£94,306
Suni	£6,836	£275	£604	£40,565	£3,474	£597	£2,615	£2,955	£7,923	£4,648	£70,491
Favourable risk											
Cabo+nivo	£185,764	£3,445	£1,127	£29,037	£599	£532	£5,101	£2,873	£7,565	£4,443	£240,485
Pazo	£9,859	£395	£512	£40,442	£3,329	£607	£3,807	£4,907	£7,455	£4,550	£75,862
Tivo	£42,269	£413	£408	£42,138	£3,953	£541	£3,807	£4,907	£7,455	£4,550	£110,441
Suni	£10,336	£320	£604	£39,711	£3,400	£585	£3,807	£4,907	£7,455	£4,550	£75,674
Intermediate/ poor risk											
Cabo+nivo	£140,562	£2,990	£1,127	£29,909	£617	£548	£3,486	£2,257	£7,898	£4,576	£193,969
Nivo+ipi	£80,711	£3,210	£335	£26,278	£542	£781	£2,277	£3,381	£7,910	£4,674	£130,097
Pem+lenv	£173,402	£2,940	£1,062	£25,646	£504	£837	£4,622	£1,183	£7,888	£4,482	£222,567
Pazo	£5,137	£296	£512	£41,702	£3,433	£626	£2,079	£2,432	£8,081	£4,692	£68,989
Tivo	£22,024	£305	£408	£43,452	£4,076	£558	£2,079	£2,432	£8,081	£4,692	£88,106
Suni	£5,443	£258	£604	£40,949	£3,506	£603	£2,079	£2,432	£8,081	£4,692	£68,646
Cabo	£86,584	£387	£732	£38,999	£4,542	£584	£3,753	£1,674	£7,945	£4,554	£149,753

Abbreviations: admin, administration; AE, adverse event; cabo, cabozantinib; EOL, end of life; lenv, lenvatinib; mru, medical resource use; nivo, nivolumab; PartSA, partitioned survival analysis; PAS, patient access scheme; pazo, pazopanib; pem, pembrolizumab; suni, sunitinib; tivo, tivozanib

Table 29: PartSA results (ordered in increasing cost)

	Total			Incremental				
Technologies	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER cabo + nivo vs comparator (£/QALY)	ICER incremental (£/QALY)
All-risk								
Suni	£70,491	2.90	1.84	-	-	-	£445511	-
Pazo	£70,790	2.90	1.83				£443437	(dominated)
Tivo	£94,306	2.90	1.84				£379118	(ext dominated)
Cabo+nivo	£212,756	3.35	2.15	£142,265	0.45	0.32		£445511
Favourable risk								
Suni	£75,674	4.90	2.91	£0	-	-	Cabo+nivo dominated	-
Pazo	£75,862	4.90	2.91				Cabo+nivo dominated	(dominated)
Tivo	£110,441	4.90	2.91	£34,767	-	0.01	Cabo+nivo dominated	£5057694
Cabo+nivo	£240,485	4.41	2.70					(dominated)
Intermediate/ poor risk								
Suni	£68,646	2.28	1.47	£0	-	-	£282147	-
Pazo	£68,989	2.28	1.47				£280852	(dominated)
Tivo	£88,106	2.28	1.47				£242097	(ext dominated)
Nivo+ipi	£130,097	2.92	1.86	£61,452	0.64	0.39	£1260021	£156172
Cabo	£149,753	2.81	1.82				£500084	(dominated)
Cabo+nivo	£193,969	2.95	1.91					(ext dominated)
Pem+lenv	£222,567	3.04	1.96	£92,469	0.13	0.10	SW quadrant £546130	£897283

Abbreviations: cabo, cabozantinib; ext, extended; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; lenv, lenvatinib; LYG, life year gained; nivo, nivolumab; PartSA, partitioned survival analysis; pazo, pazopanib; pem, pembrolizumab; QALY, quality adjusted life year; suni, sunitinib; SW, south west; tivo, tivozanib; vs, versus

Appendix E: Scenario Analysis Pairwise Tables

Table 30: Base case pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,847	2.22	3.71				
Pazo	£78,649	1.69	2.84	£145,198	0.53	0.88	£275106
Tivo	£98,517	1.66	2.76	£125,329	0.56	0.95	£223701
Suni	£77,675	1.67	2.78	£146,172	0.56	0.93	£263297
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.00	3.36				
Nivo+ipi	£137,774	1.46	2.44	£66,947	0.54	0.92	£123562
Pem+lenv	£229,649	2.23	3.62	£-24,928	-0.23	-0.26	SW quadrant £110498
Pazo	£76,064	1.49	2.50	£128,656	0.52	0.85	£248380
Tivo	£91,528	1.45	2.43	£113,193	0.55	0.92	£205798
Suni	£75,069	1.46	2.45	£129,652	0.55	0.91	£237872
Cabo	£158,308	2.07	3.46	£46,413	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 31: Scenario analysis 1 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£212,756	2.15	3.35				
Pazo	£70,790	1.83	2.90	£141,966	0.32	0.45	£443437
Tivo	£94,306	1.84	2.90	£118,450	0.31	0.45	£379118
Suni	£70,491	1.84	2.90	£142,265	0.32	0.45	£445511
Risk population: Favourable risk							
Cabo+nivo	£240,485	2.70	4.41				
Pazo	£75,862	2.91	4.90	£164,623	-0.21	-0.49	Cabo+nivo dominated
Tivo	£110,441	2.91	4.90	£130,044	-0.22	-0.49	Cabo+nivo dominated
Suni	£75,674	2.91	4.90	£164,811	-0.21	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£193,969	1.91	2.95				
Nivo+ipi	£130,097	1.86	2.92	£63,872	0.05	0.03	£1260021
Pem+lenv	£222,567	1.96	3.04	£-28,597	-0.05	-0.09	SW quadrant £546130
Pazo	£68,989	1.47	2.28	£124,980	0.45	0.67	£280852
Tivo	£88,106	1.47	2.28	£105,863	0.44	0.67	£242097
Suni	£68,646	1.47	2.28	£125,324	0.44	0.67	£282147

Table 32: Scenario analysis 3 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£216,115	2.15	3.54				
Pazo	£57,089	1.46	2.32	£159,026	0.69	1.22	£228912
Tivo	£75,971	1.40	2.19	£140,145	0.75	1.35	£185638
Suni	£56,037	1.43	2.26	£160,078	0.72	1.28	£220844
Risk population: Favourable risk							
Cabo+nivo	£243,658	2.60	4.35				
Pazo	£62,403	1.99	3.20	£181,255	0.61	1.15	£296395
Tivo	£92,358	1.93	3.06	£151,300	0.67	1.28	£224936
Suni	£61,423	1.96	3.14	£182,235	0.64	1.21	£283822
Risk population: Intermediate / poor risk							
Cabo+nivo	£196,994	1.93	3.19				
Nivo+ipi	£123,198	1.27	2.02	£73,796	0.66	1.17	£111186
Pem+lenv	£221,094	2.13	3.39	£-24,100	-0.20	-0.21	SW quadrant £122448
Pazo	£54,771	1.25	2.00	£142,223	0.68	1.19	£208480
Tivo	£69,260	1.19	1.87	£127,734	0.74	1.32	£172222
Suni	£53,698	1.22	1.94	£143,296	0.71	1.25	£201260
Cabo	£133,384	1.75	2.72	£63,610	0.19	0.47	£338484

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 33: Scenario analysis 6 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£219,107	2.08	3.35				
Pazo	£59,154	1.55	2.49	£159,953	0.52	0.86	£305164
Tivo	£88,689	1.63	2.64	£130,418	0.45	0.70	£292575
Suni	£65,908	1.65	2.68	£153,199	0.43	0.66	£355214
Risk population: Favourable risk							
Cabo+nivo	£250,712	2.48	3.99				
Pazo	£65,850	2.06	3.27	£184,862	0.41	0.72	£448806
Tivo	£107,490	2.15	3.44	£143,222	0.33	0.55	£433567
Suni	£73,005	2.16	3.48	£177,707	0.31	0.51	£564209
Risk population: Intermediate / poor risk							
Cabo+nivo	£207,061	1.99	3.21				
Nivo+ipi	£161,651	1.83	3.06	£45,410	0.16	0.16	£276798
Pem+lenv	£254,757	3.05	5.42	£-47,697	-1.06	-2.20	SW quadrant £44997
Pazo	£56,822	1.40	2.24	£150,239	0.59	0.97	£255000
Tivo	£82,789	1.48	2.39	£124,272	0.51	0.82	£242510
Suni	£63,397	1.49	2.44	£143,664	0.50	0.78	£288227
Cabo	£135,555	2.02	3.20	£71,506	-0.03	0.02	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 34: Scenario analysis 7 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£218,621	3.66	6.76				
Pazo	£70,009	3.37	6.55	£148,612	0.29	0.21	£519752
Tivo	£94,376	3.38	6.55	£124,245	0.28	0.21	£442270
Suni	£70,249	3.37	6.55	£148,372	0.29	0.21	£516251
Risk population: Favourable risk							
Cabo+nivo	£248,487	3.38	5.71				
Pazo	£73,617	3.61	6.24	£174,870	-0.23	-0.53	Cabo+nivo dominated
Tivo	£109,872	3.62	6.24	£138,615	-0.23	-0.53	Cabo+nivo dominated
Suni	£73,960	3.61	6.24	£174,528	-0.23	-0.53	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£206,277	3.27	5.65				
Nivo+ipi	£161,992	3.35	5.92	£44,285	-0.08	-0.27	Cabo+nivo dominated
Pem+lenv	£249,954	4.03	7.82	£-43,677	-0.76	-2.17	SW quadrant £57756
Pazo	£67,955	2.92	5.53	£138,322	0.35	0.12	£390800
Tivo	£88,864	2.92	5.53	£117,413	0.35	0.12	£336480
Suni	£68,165	2.91	5.53	£138,112	0.36	0.12	£388580
Cabo	£143,328	3.14	5.37	£62,949	0.13	0.28	£485812

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 35: Scenario analysis 11 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£229,417	2.35	3.95				
Pazo	£78,649	1.69	2.84	£150,768	0.66	1.12	£229908
Tivo	£98,517	1.66	2.76	£130,900	0.69	1.19	£190195
Suni	£77,675	1.67	2.78	£151,742	0.68	1.17	£222122
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£213,547	2.16	3.65				
Nivo+ipi	£171,494	1.82	3.06	£42,053	0.34	0.59	£124853
Pem+lenv	£229,649	2.23	3.62	£-16,101	-0.07	0.03	SW quadrant £237882
Pazo	£76,064	1.49	2.50	£137,483	0.68	1.15	£203410
Tivo	£91,528	1.45	2.43	£122,019	0.71	1.22	£172361
Suni	£75,069	1.46	2.45	£138,478	0.70	1.20	£196994
Cabo	£163,435	2.14	3.54	£50,112	0.02	0.10	£2359677

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 36: Scenario analysis 13 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,847	2.22	3.71				
Pazo	£78,649	1.69	2.84	£145,198	0.53	0.88	£275106
Tivo	£98,517	1.66	2.76	£125,329	0.56	0.95	£223701
Suni	£77,675	1.67	2.78	£146,172	0.56	0.93	£263297
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.00	3.36				
Nivo+ipi	£137,774	1.46	2.44	£66,947	0.54	0.92	£123562
Pem+lenv	£206,815	1.76	2.78	£-2,094	0.25	0.57	Cabo+nivo dominant
Pazo	£76,064	1.49	2.50	£128,656	0.52	0.85	£248380
Tivo	£91,528	1.45	2.43	£113,193	0.55	0.92	£205798
Suni	£75,069	1.46	2.45	£129,652	0.55	0.91	£237872
Cabo	£158,308	2.07	3.46	£46,413	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 37: Scenario analysis 20 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,847	2.22	3.71				
Pazo	£78,649	1.69	2.84	£145,198	0.53	0.88	£275106
Tivo	£98,517	1.66	2.76	£125,329	0.56	0.95	£223701
Suni	£77,675	1.67	2.78	£146,172	0.56	0.93	£263297
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.00	3.36				
Nivo+ipi	£184,236	1.84	2.96	£20,484	0.16	0.39	£125015
Pem+lenv	£229,649	2.23	3.62	£-24,928	-0.23	-0.26	SW quadrant £110498
Pazo	£76,064	1.49	2.50	£128,656	0.52	0.85	£248380
Tivo	£91,528	1.45	2.43	£113,193	0.55	0.92	£205798
Suni	£75,069	1.46	2.45	£129,652	0.55	0.91	£237872
Cabo	£158,308	2.07	3.46	£46,413	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 38: Scenario analysis 21 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£218,775	2.37	3.76				
Pazo	£70,790	1.83	2.90	£147,986	0.54	0.86	£276125
Tivo	£94,306	1.84	2.90	£124,469	0.53	0.86	£235638
Suni	£70,491	1.84	2.90	£148,284	0.54	0.86	£277106
Risk population: Favourable risk							
Cabo+nivo	£240,485	2.70	4.41				
Pazo	£75,862	2.91	4.90	£164,623	-0.21	-0.49	Cabo+nivo dominated
Tivo	£110,441	2.91	4.90	£130,044	-0.22	-0.49	Cabo+nivo dominated
Suni	£75,674	2.91	4.90	£164,811	-0.21	-0.49	Cabo+nivo dominated
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,016	2.17	3.47				
Nivo+ipi	£157,919	2.09	3.33	£46,097	0.08	0.13	£549457
Pem+lenv	£222,567	1.96	3.04	£-18,550	0.21	0.42	Cabo+nivo dominant
Pazo	£68,989	1.47	2.28	£135,027	0.71	1.19	£190975
Tivo	£88,106	1.47	2.28	£115,910	0.70	1.19	£165749
Suni	£68,646	1.47	2.28	£135,371	0.71	1.19	£191685
Cabo	£158,685	1.81	2.78	£45,331	0.36	0.69	£126345

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 39: Scenario analysis 24 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,339	2.21	3.69				
Pazo	£78,649	1.69	2.84	£144,690	0.52	0.86	£278645
Tivo	£98,517	1.66	2.76	£124,822	0.55	0.93	£226238
Suni	£77,675	1.67	2.78	£145,664	0.55	0.91	£266474
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.00	3.36				
Nivo+ipi	£137,774	1.46	2.44	£66,947	0.54	0.92	£123562
Pem+lenv	£229,649	2.23	3.62	£-24,928	-0.23	-0.26	SW quadrant £110498
Pazo	£76,064	1.49	2.50	£128,656	0.52	0.85	£248380
Tivo	£91,528	1.45	2.43	£113,193	0.55	0.92	£205798
Suni	£75,069	1.46	2.45	£129,652	0.55	0.91	£237872
Cabo	£158,308	2.07	3.46	£46,413	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 40: Scenario analysis 26 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,279	2.21	3.69				
Pazo	£78,649	1.69	2.84	£144,630	0.52	0.85	£279065
Tivo	£98,517	1.66	2.76	£124,762	0.55	0.93	£226538
Suni	£77,675	1.67	2.78	£145,604	0.55	0.91	£266851
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.00	3.36				
Nivo+ipi	£137,774	1.46	2.44	£66,947	0.54	0.92	£123562
Pem+lenv	£229,649	2.23	3.62	£-24,928	-0.23	-0.26	SW quadrant £110498
Pazo	£76,064	1.49	2.50	£128,656	0.52	0.85	£248380
Tivo	£91,528	1.45	2.43	£113,193	0.55	0.92	£205798
Suni	£75,069	1.46	2.45	£129,652	0.55	0.91	£237872
Cabo	£158,308	2.07	3.46	£46,413	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 41: Scenario analysis 29 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£208,302	2.04	3.22				
Pazo	£69,003	1.64	2.62	£139,299	0.40	0.60	£345056
Tivo	£89,085	1.61	2.56	£119,217	0.43	0.66	£277159
Suni	£68,246	1.61	2.58	£140,056	0.43	0.65	£328141
Risk population: Favourable risk							
Cabo+nivo	£250,960	2.63	4.43				
Pazo	£83,998	2.19	3.65	£166,961	0.44	0.78	£378766
Tivo	£114,957	2.16	3.57	£136,003	0.47	0.86	£287097
Suni	£83,098	2.16	3.59	£167,862	0.47	0.84	£358258
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,400	1.97	3.27				
Nivo+ipi	£137,491	1.43	2.37	£66,909	0.54	0.91	£124475
Pem+lenv	£229,376	2.20	3.55	£-24,976	-0.23	-0.28	SW quadrant £108092
Pazo	£75,751	1.45	2.42	£128,649	0.52	0.85	£248854
Tivo	£91,215	1.42	2.35	£113,185	0.55	0.92	£206185
Suni	£74,756	1.42	2.37	£129,644	0.54	0.91	£238296
Cabo	£158,007	2.04	3.38	£46,393	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 42: Scenario analysis 41 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£268,610	2.22	3.71				
Pazo	£90,005	1.69	2.84	£178,604	0.53	0.88	£338401
Tivo	£109,214	1.66	2.76	£159,396	0.56	0.95	£284507
Suni	£89,347	1.67	2.78	£179,262	0.56	0.93	£322902
Risk population: Favourable risk							
Cabo+nivo	£306,185	2.67	4.52				
Pazo	£96,409	2.23	3.73	£209,776	0.44	0.78	£476487
Tivo	£127,052	2.19	3.66	£179,133	0.47	0.86	£378536
Suni	£96,091	2.20	3.68	£210,095	0.47	0.84	£448933
Risk population: Intermediate / poor risk							
Cabo+nivo	£243,568	2.00	3.36				
Nivo+ipi	£155,814	1.46	2.44	£87,754	0.54	0.92	£161965
Pem+lenv	£241,554	2.23	3.62	£2,014	-0.23	-0.26	Cabo+nivo dominated
Pazo	£87,071	1.49	2.50	£156,497	0.52	0.85	£302129
Tivo	£101,745	1.45	2.43	£141,823	0.55	0.92	£257852
Suni	£86,286	1.46	2.45	£157,282	0.55	0.91	£288565
Cabo	£185,797	2.07	3.46	£57,771	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 43: Scenario analysis 50 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,847	2.55	3.71				
Pazo	£78,649	2.00	2.84	£145,198	0.55	0.88	£264436
Tivo	£98,517	1.96	2.76	£125,329	0.58	0.95	£214404
Suni	£77,675	1.97	2.78	£146,172	0.58	0.93	£251752
Risk population: Favourable risk							
Cabo+nivo	£251,276	3.05	4.52				
Pazo	£84,321	2.60	3.73	£166,955	0.46	0.78	£366224
Tivo	£115,279	2.56	3.66	£135,997	0.49	0.86	£276478
Suni	£83,420	2.57	3.68	£167,856	0.49	0.84	£344088
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.30	3.36				
Nivo+ipi	£137,774	1.72	2.44	£66,947	0.59	0.92	£113978
Pem+lenv	£229,649	2.53	3.62	£-24,928	-0.23	-0.26	SW quadrant £110626
Pazo	£76,064	1.77	2.50	£128,656	0.54	0.85	£239324
Tivo	£91,528	1.73	2.43	£113,193	0.57	0.92	£197686
Suni	£75,069	1.74	2.45	£129,652	0.57	0.91	£227953
Cabo	£158,308	2.41	3.46	£46,413	-0.10	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 44: Scenario analysis 58 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,034	2.25	3.71				
Pazo	£78,651	1.70	2.84	£144,383	0.55	0.88	£263634
Tivo	£98,356	1.67	2.76	£124,679	0.58	0.95	£214585
Suni	£77,542	1.67	2.78	£145,492	0.57	0.93	£253249
Risk population: Favourable risk							
Cabo+nivo	£250,469	2.69	4.52				
Pazo	£84,321	2.23	3.73	£166,148	0.46	0.78	£361257
Tivo	£115,115	2.20	3.66	£135,354	0.49	0.86	£274122
Suni	£83,285	2.20	3.68	£167,184	0.49	0.84	£343219
Risk population: Intermediate / poor risk							
Cabo+nivo	£203,908	2.03	3.36				
Nivo+ipi	£137,656	1.47	2.44	£66,252	0.56	0.92	£118043
Pem+lenv	£229,179	2.24	3.62	£-25,271	-0.22	-0.26	SW quadrant £116423
Pazo	£76,068	1.49	2.50	£127,841	0.54	0.85	£237664
Tivo	£91,368	1.46	2.43	£112,541	0.57	0.92	£197150
Suni	£74,938	1.46	2.45	£128,971	0.56	0.91	£228494
Cabo	£158,236	2.08	3.46	£45,673	-0.05	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 45: Scenario analysis 73 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,847	2.22	3.71				
Pazo	£78,649	1.69	2.84	£145,198	0.53	0.88	£275106
Tivo	£98,517	1.66	2.76	£125,329	0.56	0.95	£223701
Suni	£77,675	1.67	2.78	£146,172	0.56	0.93	£263297
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£208,542	2.05	3.42				
Nivo+ipi	£177,056	1.86	3.03	£31,486	0.19	0.40	£166830
Pem+lenv	£229,649	2.23	3.62	£-21,106	-0.18	-0.20	SW quadrant £114914
Pazo	£76,064	1.49	2.50	£132,478	0.56	0.92	£236606
Tivo	£91,528	1.45	2.43	£117,014	0.59	0.99	£197678
Suni	£75,069	1.46	2.45	£133,473	0.59	0.98	£227392
Cabo	£162,131	2.13	3.50	£46,412	-0.08	-0.08	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 46: Scenario analysis 74 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£229,417	2.35	3.95				
Pazo	£78,649	1.69	2.84	£150,768	0.66	1.12	£229908
Tivo	£98,517	1.66	2.76	£130,900	0.69	1.19	£190195
Suni	£77,675	1.67	2.78	£151,742	0.68	1.17	£222122
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£213,547	2.16	3.65				
Nivo+ipi	£171,494	1.82	3.06	£42,053	0.34	0.59	£124853
Pem+lenv	£229,649	2.23	3.62	£-16,101	-0.07	0.03	SW quadrant £237882
Pazo	£76,064	1.49	2.50	£137,483	0.68	1.15	£203410
Tivo	£91,528	1.45	2.43	£122,019	0.71	1.22	£172361
Suni	£75,069	1.46	2.45	£138,478	0.70	1.20	£196994
Cabo	£163,435	2.14	3.54	£50,112	0.02	0.10	£2359677

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Table 47: Scenario analysis 75 pairwise comparison table

Technologies	Costs (£)	QALYs	LYG	Inc. Costs	Inc. QALYs	Inc. LYG	ICER cabo + nivo vs comparator
Risk population: All-risk							
Cabo+nivo	£223,847	2.22	3.71				
Pazo	£78,649	1.69	2.84	£145,198	0.53	0.88	£275106
Tivo	£98,517	1.66	2.76	£125,329	0.56	0.95	£223701
Suni	£77,675	1.67	2.78	£146,172	0.56	0.93	£263297
Risk population: Favourable risk							
Cabo+nivo	£251,276	2.67	4.52				
Pazo	£84,321	2.23	3.73	£166,955	0.44	0.78	£379222
Tivo	£115,279	2.19	3.66	£135,997	0.47	0.86	£287383
Suni	£83,420	2.20	3.68	£167,856	0.47	0.84	£358676
Risk population: Intermediate / poor risk							
Cabo+nivo	£204,721	2.00	3.36				
Nivo+ipi	£137,774	1.46	2.44	£66,947	0.54	0.92	£123562
Pem+lenv	£229,628	2.23	3.62	£-24,907	-0.23	-0.26	SW quadrant £110406
Pazo	£76,064	1.49	2.50	£128,656	0.52	0.85	£248380
Tivo	£91,528	1.45	2.43	£113,193	0.55	0.92	£205798
Suni	£75,069	1.46	2.45	£129,652	0.55	0.91	£237872
Cabo	£158,308	2.07	3.46	£46,413	-0.07	-0.11	Cabo+nivo dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; inc. incremental; LYG, life-years gained; QALY, quality-adjusted life-year

Appendix F: Implied Hazard Ratio Plots

Figure 30: Implied hazard ratio over time: all-risk population, OS

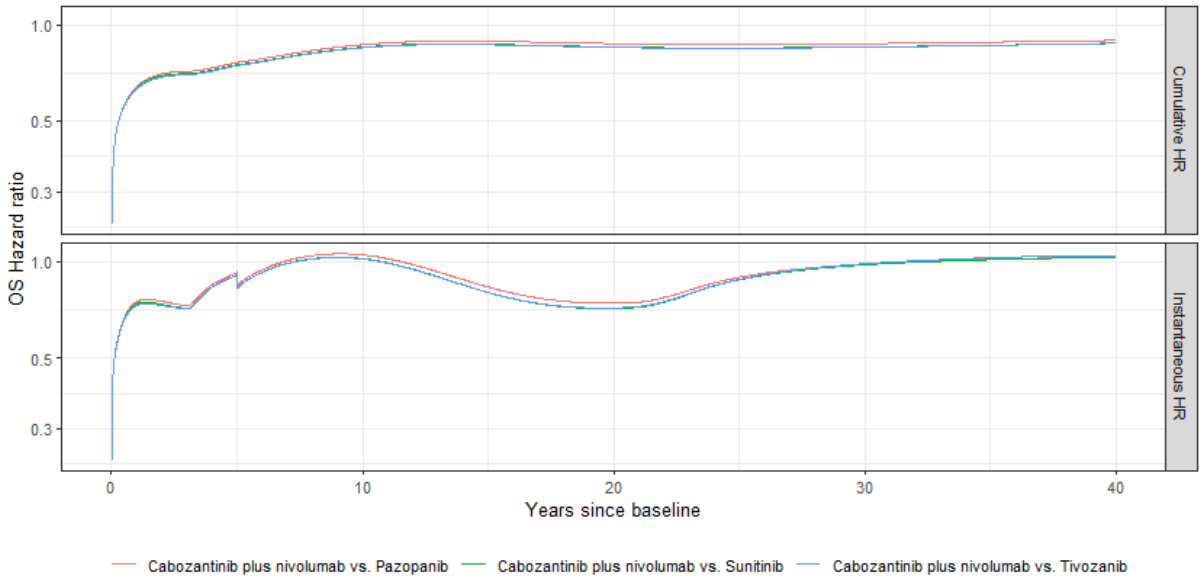


Figure 31: Implied hazard ratio over time: favourable risk population, OS

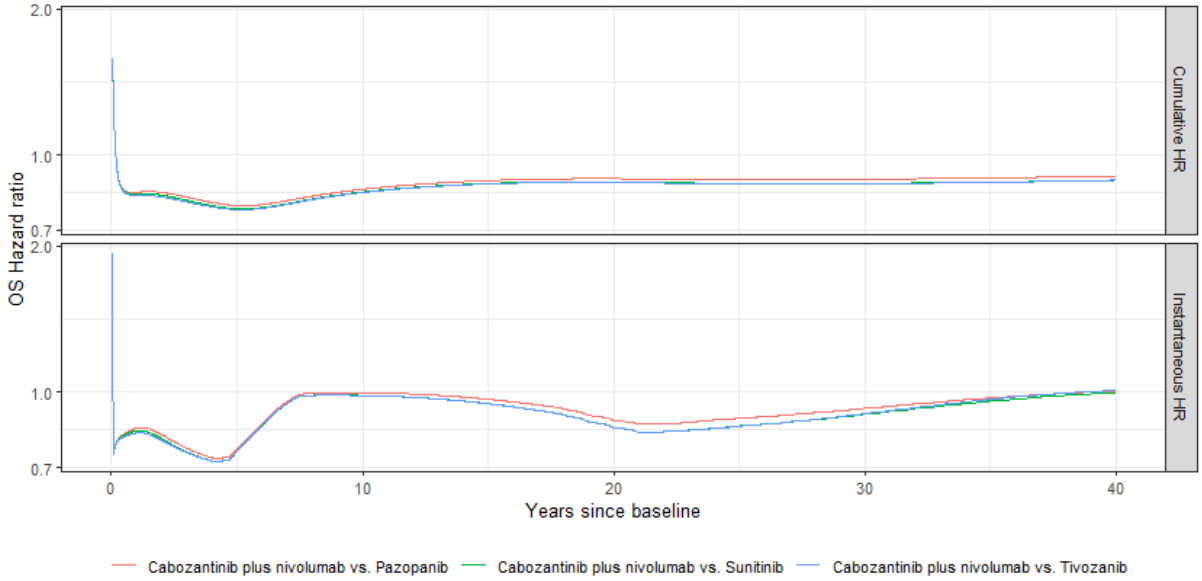


Figure 32: Implied hazard ratio over time: intermediate / poor risk population, OS

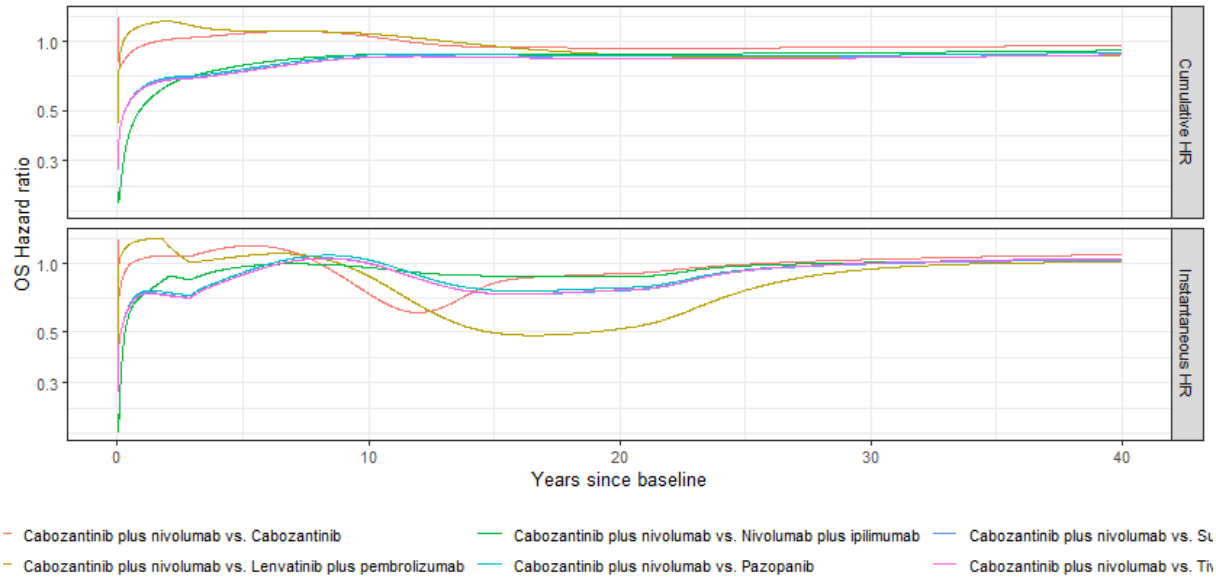


Figure 33: Implied hazard ratio over time: all-risk population, PFS

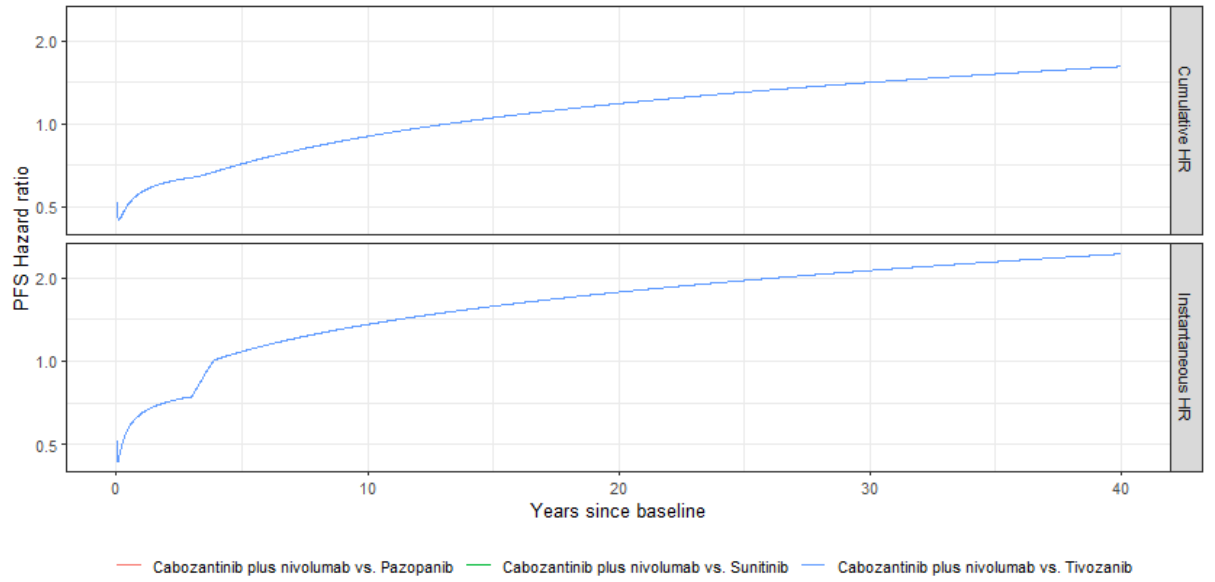
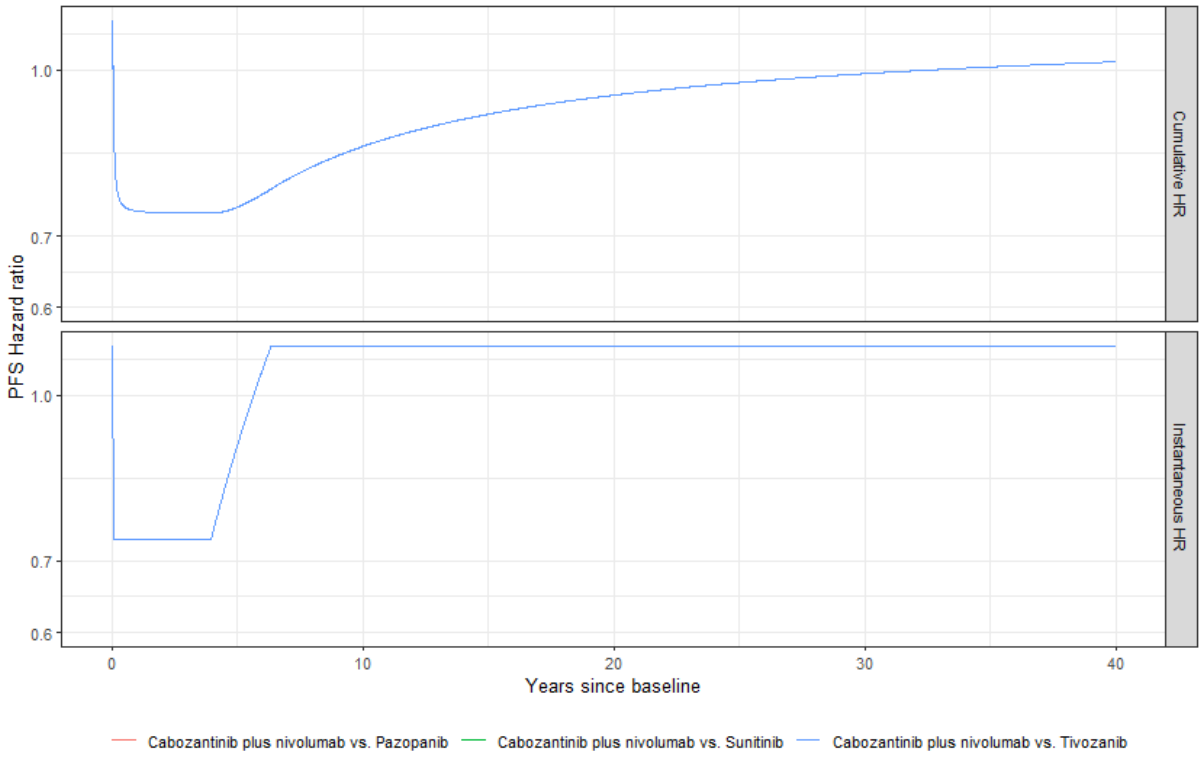


Figure 34: Implied hazard ratio over time: favourable risk population, PFS



Note: proportional hazards NMA applies in the favourable risk population

Figure 35: Implied hazard ratio over time: intermediate / poor risk population, PFS