Single Technology Appraisal

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

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

1. **Company submission from Merck Serono:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Action Kidney Cancer
   b. Kidney Cancer UK
   c. British Uro-Oncology Group
   d. National Disease Registration Service SACT report

4. **Expert personal perspectives** from:
   a. Dr Ricky Frazer – clinical expert, nominated by Merck Serono
   b. Dr Naveen Vasudev – clinical expert, nominated by Action Kidney Cancer
   c. Christopher Hallworth – patient expert, nominated by Action Kidney Cancer

   Hazel Jackson – patient expert, nominated by Kidney Cancer UK (*see document 3b.*)

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

6. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab in combination with axitinib for advanced renal cell carcinoma (MA review of TA645) [ID6294]

Document B

Company evidence submission

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ID6294_Avelumab-axitinib_aRCC_Document-B_250221_[redacted]	**3.0**	**No**	**21 February 2025**

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Tables and Figures

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Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
aRCC	Advanced renal cell carcinoma
ASCO	American Society of Clinical Oncology
ASR	Age-standardised rate
BD	Twice per day
BICR	Blinded independent central review
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organization of Medical Sciences
CR	Complete response
CSR	Clinical study report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cutoff
DCR	Disease control rate
DoR	Duration of response
EAMS	Early Access to Medicines Scheme
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FA	Final analysis
FAS	Full analysis set
GCP	Good clinical practice
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IgG1	Immunoglobulin G1
IL	Interleukin
IMDC	International Metastatic RCC Database Consortium
IO	Immunotherapy
IV	Intravenous
LCI	Lower limit of the confidence interval
LLN	Lower limit of normal
LLQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MAA	Marketing authorisation application
mAb	Monoclonal antibody
mRCC	Metastatic renal cell carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
mTORi	Mammalian target of rapamycin inhibitor
NCCN	National Comprehensive Cancer Network
NDRS	National Disease Registration Service
NE	Not evaluable

NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PD-L1	Programmed cell death-ligand-1
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Orally
PP	Per protocol
PR	Partial response
PS	Performance status
Q2W	Every two weeks
QALY	Quality-adjusted life year
RCC	Renal cell carcinoma
RCI	Repeated confidence interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Cancer Therapy
SAF	Safety analysis set
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ class
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumour-Node-Metastasis
TTR	Time to response
UCI	Upper limit of the confidence interval
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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

In September 2020, following a single technology appraisal (STA), the National Institute for Health and Care Excellence (NICE) recommended avelumab + axitinib for use within the Cancer Drugs Fund (CDF) as an option for untreated, unresectable locally advanced or metastatic renal cell carcinoma (aRCC) in adults (TA645).[1,2] The recommendation covered the technology's full marketing authorisation for this indication. At the time of the submission, there were no immunotherapy (IO)-based combination agents routinely recommended for use in first-line by the NHS – nivolumab with ipilimumab was recommended for use within the CDF – and except for cabozantinib, tyrosine kinase inhibitors (TKIs) were recommended for use without regard to disease risk stratification. [3–7]

Since the recommendation of avelumab + axitinib within the CDF, there has been a significant evolution in the treatment pathway for aRCC. Evidence supporting the role of IO agents in the management of previously untreated patients with aRCC has been accepted into international clinical practice guidelines, and greater relevance has been placed on identifying subgroups of patients according to disease risk factors that influence treatment decisions.[8–11] In UK clinical practice, the International Metastatic RCC Database Consortium (IMDC),[12] also known as Heng criteria, is the most common prognostic model used to categorise patients into risk groups for survival. When considering first-line treatments, clinicians consider two main IMDC subgroups: (i) favourable-risk and (ii) intermediate-/poor-risk. The increasing use of IMDC risk categorisation in clinical trials has translated into an increasing number of IO+IO or IO+TKI therapies recommended by NICE for the first-line treatment of patients with intermediate-/poor-risk, but not favourable-risk aRCC. The availability of new treatments has also resulted in additional comparators for avelumab + axitinib in the intermediate-/poor-risk subgroup (but not the favourable-risk subgroup) since the September 2020 original NICE decision.[13–15]

The current submission is a managed access review of TA645 based on new data from the final analysis of overall survival (OS) from the pivotal Phase 3 JAVELIN 101 study (data cut of 31 August 2023) and the Systemic Anti-Cancer Therapy (SACT) dataset, collected by NHS England as part of the managed access agreement for CDF entry for avelumab + axitinib. The submission covers the technology's full marketing authorisation for this indication. Aligned with the evolution of the treatment pathway, evidence is presented for subgroups of particular interest: people with favourable-IMDC risk disease and people with intermediate-/poor-IMDC risk disease.

B.1.1 Decision problem

A summary of the decision problem is provided in Table 1. The company submission is consistent with the final NICE scope regarding population, comparators, and outcomes.[16] Differences in the intervention and subgroups are outlined in Table 1.

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	Adults with untreated aRCC	Adults with untreated aRCC with IMDC favourable-risk disease and intermediate-/poor-risk disease	Aligned with the evolution of the treatment pathway, evidence is additionally presented as subgroups of particular interest: people with favourable-risk disease and people with intermediate-/poor-risk disease.
Intervention	Avelumab with axitinib	Avelumab with axitinib	In line with the NICE final scope.
Comparator(s)	Favourable-risk disease as defined in the IMDC criteria: • Pazopanib • Sunitinib • Tivozanib Intermediate-/poor-risk disease as defined in the IMDC criteria: • Cabozantinib • Nivolumab with ipilimumab • Lenvatinib with pembrolizumab • Cabozantinib with nivolumab • Pazopanib • Sunitinib • Tivozanib	Favourable-risk disease as defined in the IMDC criteria: • Pazopanib • Sunitinib • Tivozanib Intermediate-/poor-risk disease as defined in the IMDC criteria: • Cabozantinib • Nivolumab with ipilimumab • Lenvatinib with pembrolizumab • Cabozantinib with nivolumab • Pazopanib • Sunitinib • Tivozanib	In line with the NICE final scope.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates	As per the final scope, the submission considers the following outcomes: • overall survival • progression-free survival • response rates	In line with the NICE final scope.

	• duration of response • time on treatment/time to next treatment • adverse effects of treatment • health-related quality of life.	• duration of response • time on treatment/time to next treatment • adverse effects of treatment • health-related quality of life.	
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 and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The cost-effectiveness analysis takes into consideration commercial arrangements for the following treatments: • avelumab • pazopanib There are commercial arrangements for the following treatments that could not be taken into consideration since the volume of any Patient Access Scheme (PAS) discounts are unknown: • axitinib • tivozanib • cabozantinib • nivolumab • ipilimumab • pembrolizumab • lenvatinib	The cost-effectiveness analysis is in line with the NICE final scope, except for the specification of PAS discounts which are confidential.
Subgroups to be considered	If the evidence allows the following subgroup will be considered: • Favourable-risk advanced metastatic RCC as defined in the IMDC criteria	• IMDC favourable-risk subgroup • IMDC intermediate-/poor-risk subgroup • PD-L1 status	In line with the NICE final scope. Evidence is presented for the PD-L1 positive (+) subgroup; however, clinical opinion suggests that PD-L1 status is not relevant to systemic treatment decision-making for aRCC and

	• Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • PD-L1 status		hence it has not been explored in cost-effectiveness analyses.[1,17]

Abbreviations: aRCC, advanced renal cell carcinoma; IMDC, international metastatic renal cell cancer database consortium; PD-L1, programmed cell death-ligand-1.

B.1.2 Description of the technology being appraised

Renal cell carcinoma

- Kidney cancer is the sixth most common cancer in the UK, accounting for 4% of all cancer cases.[18]
- Renal cell carcinoma (RCC) is the most common kidney cancer, accounting for approximately 85–90% of all renal malignancies.[10,19,20]
- There are five major histological subtypes of RCC; clear-cell RCC is the most common accounting for approximately [redacted]% of cases.[21]
- As kidney cancers often remain asymptomatic until later stages, cases are often diagnosed as advanced or metastatic disease (31.4% at stage III or IV).[22]
- In the UK, the IMDC (also known as Heng criteria) is the most common prognostic risk model used at diagnosis to categorise people into favourable- or intermediate-/poor-risk groups for survival according to multiple prognostic factors, and to inform first-line treatment decisions.[12,23]
  - Although published incidence rates specific to RCC are lacking, it is estimated that 3,652 cases of advanced RCC (aRCC) were diagnosed in England in 2020, of which 16.1% (588) had favourable-risk disease and 80.8% (2,951) had intermediate-/poor-risk disease.[19,22,24,25]

Burden of disease

- Outcomes for advanced kidney cancer are poor, with prognosis significantly correlated with the stage at diagnosis.
- Five-year survival rates in England decrease from 88.3% at stage I to 14.0% at stage IV[22]
  - In stage IV RCC, median OS according to IMDC risk categorisation with favourable-, intermediate- or poor-risk groups is equivalent to 40.9 months, 24.1 months and 10.2 months, respectively ($p<0.0001$).[26]
  - While survival for favourable-risk patients appears comparatively longer relative to intermediate-/poor-risk aRCC, the disease remains life-limiting and is still incurable with current treatment options.
- Due to the symptom burden and poor prognosis associated with aRCC, there is a considerable negative impact on patients' health-related quality of life (HRQoL). Baseline utility scores in clinical trials range from 0.69 to 0.76.[27–30]

Clinical pathway of care

- Patient-centred treatment is an important consideration in the management of people with aRCC.[8,9,31]
- As aRCC is usually incurable, the goal of treatment is to prevent disease progression, maintain HRQoL, provide relief from cancer symptoms and extend life.[32]
- In previously untreated patients, the choice of regimen is determined by IMDC risk categorisation and individual patient factors such as histology, comorbidities and performance status.
- International clinical practice guidelines recognise the importance of giving the most effective treatments from the outset, and consider combination therapy with IO with either of the vascular endothelial growth factor receptor (VEGFR) TKIs or another IO as standard of care irrespective of IMDC risk category.[8,9,31] Single-agent VEGFR TKIs are an alternative option for first-line treatment for the favourable-risk disease, although with a weaker grade of evidence.[8,9,11,33]

NICE technology appraisals

Favourable-risk disease

- No IO combinations are recommended by NICE for first-line treatment in people with favourable-risk disease in routine commissioning. [14,15]
- The only available treatments recommended by NICE in this setting are the VEGFR TKIs sunitinib, pazopanib, tivozanib (which are recommended irrespective of IMDC risk categorisation).[4–6]

Intermediate-/poor-risk disease

- Nivolumab with ipilimumab, lenvatinib with pembrolizumab and cabozantinib with nivolumab and cabozantinib monotherapy have optimised recommendations only in people with intermediate-/poor-risk aRCC.[7,13–15]
- The VEGFR TKIs sunitinib, pazopanib, tivozanib can also be used in this setting as they are recommended irrespective of IMDC risk categorisation.[4–6]

Unmet need

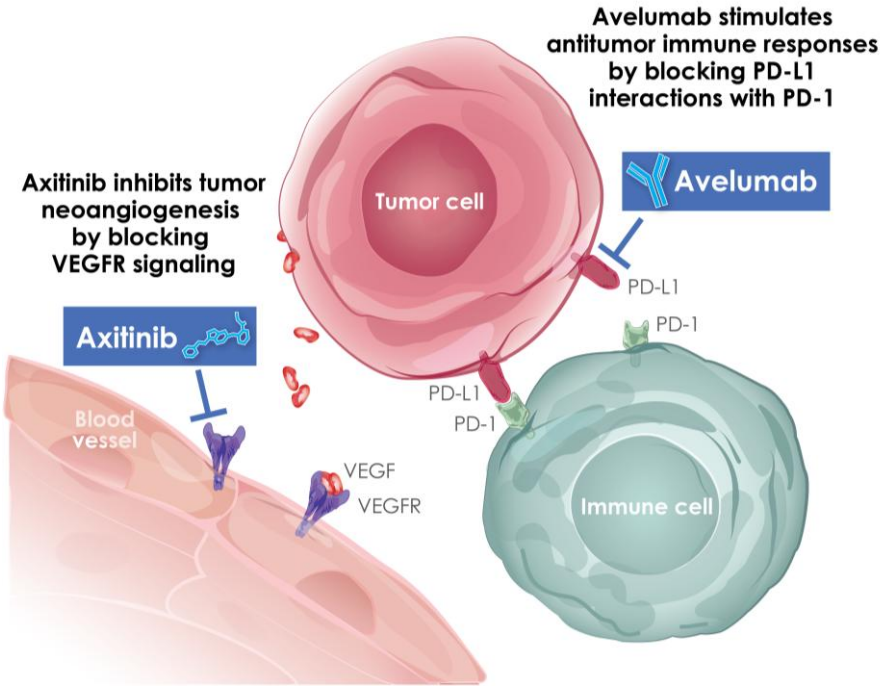
- Despite the improvements in patient outcomes since the introduction of targeted therapies, median progression free survival (PFS) fails to reach one year across all IMDC risk groups, and overall outcomes remain poor in people treated with current first-line TKI monotherapies.[34,35]
- Real-world studies have identified a high unmet need associated with currently available first-line TKI monotherapy in aRCC, with respect to OS, time to next treatment (TTNT) and time to treatment discontinuation (TTD).[36]
- Furthermore, given that less than 50% of all people treated in the first-line setting (regardless of IMDC risk group) receive second-line therapies (typically due to a lack of fitness for treatment)[26,37], it is important to ensure that people are treated with the most effective therapies in the first-line setting.
- The poor survival outcomes and durability of response in people across all IMDC risk groups treated with first-line TKI monotherapy highlight an unmet need for an effective treatment approach with manageable tolerability that increases patient and physician choice, offers greater disease control and extends survival.[36]
- Outside of the CDF, NICE only routinely recommends TKI monotherapy in the first-line setting for favourable-risk disease.[4–6] This is inconsistent with the evolution of international clinical practice guidelines which recommend IO-containing regimens as first-line treatment options in favourable-risk people. This is also inconsistent with recommendations of the Scottish Medicines Consortium (SMC) where avelumab + axitinib (as well as pembrolizumab and axitinib) is recommended for the first-line treatment of aRCC (irrespective of IMDC risk group).[8,9,31,38]
- UK treatment patterns show 44.2% of favourable-risk patients do not receive IO therapy at any line of treatment.[26] This highlights an unmet need for the availability of an IO-containing first-line regimen for people with favourable-risk disease in England and Wales.

Avelumab in combination with axitinib

- Avelumab is a human immunoglobulin G1 monoclonal antibody directed against the programmed cell death-ligand-1 (PD-L1) molecule expressed by tumour cells and a number of different immune cells,[39] while axitinib is a potent and selective TKI of VEGFRs 1, 2 and 3 with a short plasma half-life (2.5 to 6.1 hours).[40]
- Avelumab + axitinib builds on the established efficacy of TKI monotherapy in aRCC through the added benefit of an IO. Together, the combination has the potential for complementary and synergistic mechanisms of action,[41,42] which may lead to durable responses across all risk groups.
- Recognising the importance of giving the most effective treatments from the outset, it is important that all patients, regardless of IMDC risk group, have access to an IO containing regimen at first-line treatment.
- While the licence allows use of avelumab + axitinib in aRCC irrespective of IMDC risk groups, it provides an individualised treatment option for people with IMDC favourable-and intermediate-/poor-risk groups:
  - If recommended by NICE, avelumab + axitinib would be the first IO+TKI combination treatment option routinely recommended for untreated favourable-risk aRCC, providing people with favourable-risk disease continued access to an IO combination, outside of the context of the CDF.
  - In intermediate-/poor-risk aRCC, avelumab + axitinib could provide an alternative to existing reimbursed IO+TKI/IO+IO combinations that allows flexibility of dosing with a manageable tolerability profile.[43,44]

Detailed descriptions of avelumab and axitinib are provided in Table 2 and the summary of product characteristics (SmPC) for each are included in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Avelumab (Bavencio®) + axitinib (Inlyta®)
Mechanism of action	Avelumab is a human immunoglobulin G1 monoclonal antibody directed against the programmed cell death-ligand-1 (PD-L1) molecule expressed by tumour cells and a number of immune cells, while axitinib is a potent and selective TKI of VEGFRs 1, 2 and 3 with a short plasma half-life (2.5 to 6.1 hours).[40] The mechanisms of action of avelumab and axitinib are shown in Figure 1. **Figure 1: Avelumab and axitinib mechanisms of action**  Abbreviations: PD-L1, programmed death-ligand 1; VEGFR, vascular endothelial growth factor receptor. Source: Motzer et al. 2018.[45] Avelumab binds PDL1 and blocks the interaction between PDL1 and the PD1 and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumour T-cell responses. Avelumab has also been shown to induce natural killer cell-mediated direct tumour cell lysis via ADCC *in vitro*.[39] The ADCC activity of avelumab may directly destroy tumour vasculature,[46] notable for favourable-risk disease treatment given the enrichment in angiogenic tumour profiles.[47] . Axitinib is an oral, small molecule, second-generation TKI selective for VEGFR1, 2, and 3, which have been implicated in tumour angiogenesis, growth, and metastasis. Axitinib inhibits VEGF-mediated endothelial cell proliferation and survival,[40] thereby preventing the formation of new blood vessels in tumours. Inhibition of VEGF promotes an immune-stimulatory tumour microenvironment through increased T-cell infiltration, reduced accumulation and activity of immune suppressor cells, and a reduction in

	inflammatory signalling.[48–50] The combination of avelumab and axitinib may exhibit synergistic effects by targeting two critical hallmarks of cancer: evading immune destruction and promoting angiogenesis.[46]
Marketing authorisation	The European Commission granted marketing authorisation for avelumab + axitinib for the first-line treatment of adult patients with advanced RCC on 24th October 2019.[51]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Avelumab in combination with axitinib is indicated for the first-line treatment of adult patients with aRCC. Additionally, avelumab is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma; and as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy.
Method of administration and dosage	Avelumab: 800 mg IV Q2W Axitinib: 5 mg PO BD
Additional tests or investigations	None
List price and average cost of a course of treatment	The list price of avelumab is £768.00 per 200 mg vial The list prices of axitinib are £703.40 for the 1 mg strength, £2,110.20 for the 3 mg strength, £3,517.00 for the 5 mg strength and £4,923.80 for the 7 mg strength (all strengths will be provided in packs of 56 tablets)
Patient access scheme (if applicable)	A confidential, simple Patient Access Scheme (PAS) discount of [redacted]% is in place for avelumab.

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; aRCC, advanced renal cell carcinoma; BD, twice daily; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IgG1, immunoglobulin G1; IV, intravenous; mAb, monoclonal antibody; MAA, marketing authorisation application; PD-1, programmed death-1; PD-L1, programmed death-ligand-1; PO, orally; Q2W, every 2 weeks; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

B.1.2.1 Dosing of avelumab

The licensed dose for avelumab is 800 mg every 2 weeks (Q2W). The avelumab dose evaluated in the pivotal Phase 3 study was 10 mg/kg Q2W (see Section B.2.3.2.1). Pharmacology data support a flat dosing regimen. Furthermore, a flat dosing regimen provides more consistent dosing across body weights, reduces drug wastage, facilitates preparation and administration, and reduces pharmacy errors (consistent with the NHS's recommended dose banding).[52] During the original appraisal of avelumab + axitinib for untreated aRCC (TA654), the committee accepted that the licensed dose of avelumab would have similar efficacy to the weight-based dose used in the pivotal Phase 3 JAVELIN 101 study, and concluded it would use the licensed dose for decision-making.[1] As such, the licensed dose of avelumab has been used in this submission.

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

B.1.3.1 Disease overview

Kidney cancer is the sixth most common cancer in the UK, accounting for 4% of all cancer cases.[18] RCC is a heterogeneous form of kidney cancer that arises from the renal tubule

epithelium.[19] It is the most common kidney cancer, accounting for approximately 85–90% of all renal malignancies.[10,19,20]

There are five major histological subtypes of RCC; of which clear-cell RCC (ccRCC) is the most common (approximately [redacted]% of cases). Other subtypes, considered as non-clear-cell RCC, include papillary ([redacted]%), chromophobe ([redacted]%), and collecting duct ([redacted]%).[21]

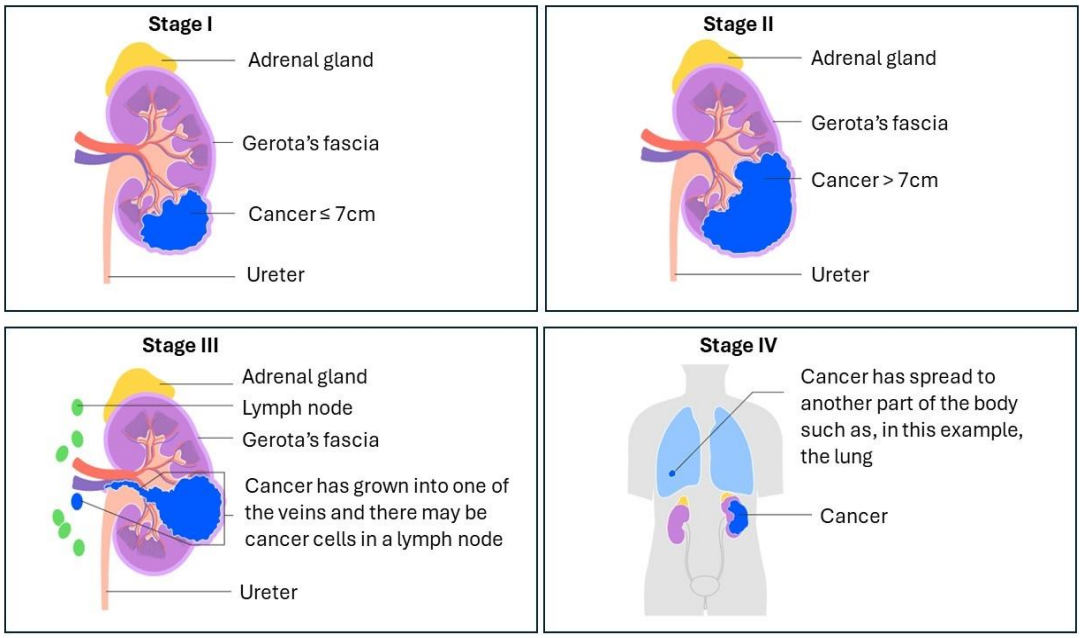
While the causes of RCC are not completely understood, a number of risk factors have been identified, including increasing age, male sex, obesity, hypertension and smoking.[19,53,54] In addition to these risk factors, four major, autosomal-dominant, heritable RCC syndromes have been identified (von Hippel-Lindau syndrome, hereditary leiomyomatosis and RCC, Birt-Hogg-Dubé syndrome and hereditary papillary renal carcinoma), which account for 5–8% of RCC cases.[55]

B.1.3.1.1 Staging and prognostic risk factors

RCC is generally staged using the Tumour-Node-Metastasis (TNM) system of the American Joint Committee on Cancer and the Union for International Cancer Control (8th edition), which is based on local tumour growth (T), lymph node involvement (N) and the presence or absence of distant metastases (M).[8] The TNM system can be grouped into the following four stages (Figure 2):[8]

- Stage I: The tumour is ≤7 cm in the greatest dimension and confined to the kidney (T1, N0, M0)
- Stage II: The tumour is >7 cm in the greatest dimension and confined to the kidney (T2, N0, M0)
- Stage III: The tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia (T3, N0, M0), and/or has metastasised to a single regional lymph node (T1–3, N1, M0)
    - Stage III disease is also described as locally advanced disease.[56] This stage can be further divided into resectable disease which can be surgically removed with curative intent, and unresectable disease which cannot be completely removed by surgery.
- Stage IV: The tumour extends beyond Gerota's fascia (T4, Any N, M0), or has metastasised to distant site(s) (Any T, Any N, M1)

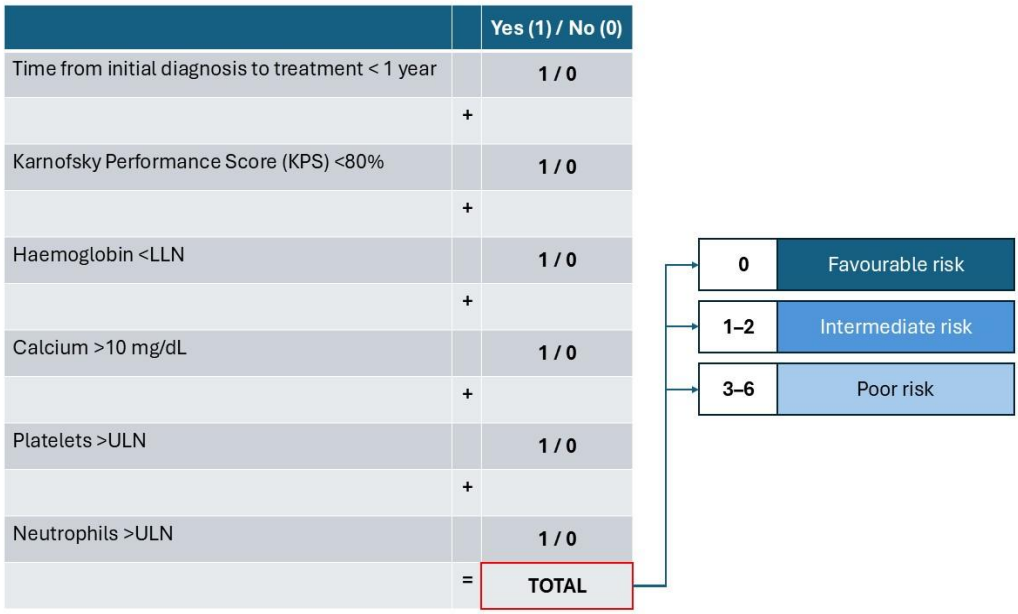
Figure 2: Stages of RCC



Abbreviations: RCC, renal cell carcinoma.
Source: Cancer Research UK.[56]

Multiple prognostic risk models have been developed to characterise prognosis in RCC, including the IMDC and Memorial Sloan Kettering Cancer Center (MSKCC) systems. The IMDC risk score, also known as Heng Criteria, was developed for people treated with targeted therapies, in contrast to the MSKCC, which used data from people receiving cytokine therapy.[57] As such, the IMDC risk categorisation is the most relevant prognostic model for this submission. IMDC is most commonly used in UK clinical practice at presentation to categorise patients into favourable-, intermediate- and poor-risk groups for survival according to multiple prognostic factors: Karnofsky performance status, time from diagnosis to treatment, haemoglobin, platelet and neutrophil levels, and corrected calcium concentration (Figure 3).[12,23] This baseline prognostic score and categorisation is used to determine first-line treatment options[1] and has been used in previous NICE submissions (see Table 4). As shown in Table 4, the treatment options for intermediate- and poor-risk aRCC are the same, and these categories are therefore combined into a single intermediate-/poor-risk group. This was established during a multiple technology appraisal including pembrolizumab and lenvatinib, when the assessment group reported that, in line with NICE guidance clinical advice, treatment decisions in aRCC are based on the combined intermediate-/poor-risk disease category (one category, not two categories). If a patient does not have intermediate-/poor-risk disease then, by definition, the patient has favourable-risk disease.[14] This is also consistent with expert advice received by the company during the preparation of this submission.

Figure 3: IMDC criteria for aRCC



Abbreviations: LLN, lower limit of normal; ULN, upper limit of normal.
Source: Heng, 2009.[12]

B.1.3.2 Epidemiology

The overall worldwide age-standardised rate (ASR) of kidney cancer is 4.4 cases per 100,000 population, with the highest incidence in North America (12.6 per 100,000) and Europe (9.7 per 100,000). Kidney cancer is more common in males, with 63% and 37% of cases in the UK for males and females, respectively.[58] The incidence of kidney cancer is strongly associated with age, with incidence rates rising steeply from 65 to 69 years of age, and the highest rates observed among those aged between 85 and 89 years, for both men and women.[58]

In England and Wales in 2020 there were an estimated 4,321 people newly diagnosed with aRCC at stage I-II and 3,320 newly diagnosed at stage III-IV.[22] Of people with aRCC, an international analysis including UK patients estimates that 16.1% have favourable-risk disease and 80.8% have intermediate-/poor-risk disease at diagnosis according to the IMDC staging system.[25]

SACT data collected by the National Disease Registration Service (NDRS) to inform the NICE Appraisal Committee for the review of TA645, identified [redacted] unique CDF patients and [redacted] unique early-access to medicines scheme (EAMS) patients.[21] In the CDF cohort [redacted]% (n=[redacted]) had favourable-risk disease and [redacted]% had intermediate-/poor-risk disease (n=[redacted]). IMDC risk groups were not recorded in the EAMS cohort.[21]

Table 3: Estimated incidence of aRCC (stage III–IV) in England and Wales in 2020

	Parameter	Value	Source/calculation
A	Number newly diagnosed at stage I–II	4,321	CRUK Early diagnosis data hub [22]
B	Number newly diagnosed at stage III–IV	3,320	CRUK Early diagnosis data hub[22]
C	Proportion who progress from stage I–II to stage III–IV	22.6%	Dabestani et al. 2018[24]
D	Number who progress from stage I–II to stage III–IV	977	A x C
E	Total number of advanced (stage III–IV) kidney cancer	4,297	B + D
F	Percentage of stage III–IV RCC	85.0%	Nabi et al. 2018[19]
G	Total number of aRCC cases (85–90% of kidney cancer cases)[10,19,20]	3,652-3,867	E x F
H	Proportion of people with favourable-risk disease at diagnosis	16.1%	Esterberg 2024[25]
I	Proportion of people with intermediate-/poor-risk disease at diagnosis	80.8%	Esterberg 2024[25]
K	Total number of stage III–IV aRCC cases with IMDC favourable-risk disease	588-623	G x H
L	Total number of people with IMDC intermediate-/poor-risk disease	2,951-3,124	G x I

As the last year of complete data reported from Wales was 2020, the equivalent year of data from England was reported here.
Abbreviations: aRCC, advanced renal cell carcinoma; ONS, Office for National Statistics; RCC, renal cell carcinoma.

B.1.3.3 Symptomatology and clinical presentation

Kidney cancers often remain asymptomatic until the advanced stage[20] and the distinctive triad of flank pain, visible haematuria and palpable abdominal mass is rare (6–10% of cases).[8,59] When present, the most common symptoms reported are nonspecific and include loss of appetite, fatigue and nausea with increasing loss of appetite, back pain/pressure and anaemia.[60] Paraneoplastic symptoms, such as hypercalcaemia, erythrocytosis, amyloidosis,

hepatic dysfunction, unexplained fever and weight loss are found in approximately 30% of patients with symptomatic RCC.[8,59] The most common initial symptoms of metastatic disease may include bone pain and persistent cough.[8]

B.1.3.4 Burden of aRCC to patients, carers, and society

B.1.3.4.1 Mortality burden

Specific common cancer statistics for the UK are reported by Cancer Research UK on the Cancer Statistics Data Hub.[61] This source reports data for kidney cancer as a whole, rather than RCC specifically, but given RCC accounts for 85%-90% of kidney cancers, the results are indicative to this submission and hence are presented here. There are an estimated 3,859 deaths/year due to kidney cancer equating to an ASR of 7.3 (95% CI: 7.2, 7.4) per 100,000 population.[62] Current one-, five-, and ten-year kidney cancer survival rates for England are 81%, 66.6% and 51.8%, respectively.[61]

Kidney cancer mortality is strongly related to age; with the ASR increasing from 0.73 deaths per 100,000 population among people ages 40–49 years, to 14.9 per 100,000 for those aged ≥70 years.[63] The mortality burden is also significantly associated with stage at diagnosis; one- and five-year survival rates in England decrease from 96.3% and 88.3%, respectively, for patients diagnosed at stage I, to 92.3%/75.9% at stage III, and 40.3%/14.0% at stage IV.[22] A UK multicentre analysis of real-world patterns of treatment and response in stage IV patients reported significant differences in median OS according to IMDC risk categorisation with favourable-, intermediate- or poor-risk groups equivalent to 40.9 months, 24.1 months and 10.2 months respectively ($p<0.0001$).[26] While survival for favourable-risk patients appears comparatively longer relative to intermediate- and poor-risk aRCC, the disease is still incurable with current treatment options.

B.1.3.4.2 Humanistic burden

As well as high levels of mortality, aRCC is associated with a significant humanistic burden on patients and carers. Due to the symptom burden and poor prognosis associated with aRCC, there is a considerable negative impact on HRQoL. Among patients with newly diagnosed aRCC with no prior chemotherapy, baseline EuroQol 5-Dimension (EQ-5D) utility scores in clinical trials range from 0.69 to 0.76.[27–30] Compared with the population normal utility score of 0.86, these scores represent a clinically meaningful decrease in HRQoL (≥0.05).[64] There is also a considerable psychosocial impact on patients with aRCC, as a result of being diagnosed with a cancer with a poor prognosis and a lack of curative treatments (see Section B.1.3.5.2).

HRQoL continues to deteriorate as the disease progresses and patients receive multiple lines of treatment.[28,65] In a UK study, people with aRCC who experienced disease progression had a greater reduction in HRQoL compared with those with stable disease.[66] Deterioration in HRQoL is largely driven by the symptoms of aRCC, which worsen with disease progression. In a similar UK real-world population who had received two or more lines of treatment for aRCC, the mean EQ-5D-5L index score was 0.56 (SD 0.37) with over half of people reporting problems on pain/discomfort (75%) and usual activities (69%) dimensions.[65] As such, treatments which delay progression could in turn help to delay deterioration in HRQoL.[67]

The burden on caregivers is also significant. A systematic review of 192 articles focused on cancer caregiving (1990-2008) found that the most prevalent problems for caregivers

included sleep disturbance, fatigue, pain, loss of physical strength, loss of appetite, and weight loss.[68]

B.1.3.4.3 Economic burden

The majority of direct medical costs associated with aRCC are related to hospital care, accounting for approximately 85% of total costs.[69] While UK cost or healthcare resource utilisation data specific to RCC are not available, NHS Digital data report 20,654 finished consultant episodes, 17,520 admissions and 53,775 bed-days for malignant neoplasm of the kidney (excluding renal pelvis cancer) in England in 2017–2018.[70]

Kidney cancer is also associated with indirect costs, in part due to the time spent supporting patients by informal carers, which represents time not spent pursuing usual activities, including work. Although UK-specific data are not available, in a US study, carers spent an average of 11.4 months providing care to patients with kidney cancer. The average value of informal carer time over two years following diagnosis was $53,541 (2006 US$; equivalent to £29,051 [2006 UK£][71]).[72]

B.1.3.5 Current aRCC treatment pathway and proposed positioning of avelumab + axitinib

B.1.3.5.1 Diagnostic pathway

At present, there is no screening programme in place for detecting kidney cancer in the UK,[73] and there is no national UK-specific diagnostic guidance, other than the NICE guideline on suspected cancer: recognition and referral (NICE guideline NG12), published in 2015 and last updated in October 2023.[31] Due to the vague presentation of signs and symptoms and sometimes asymptomatic nature of RCC, the majority of cases of RCC are identified incidentally.[8,9,59]

While physical examination has a limited role in RCC diagnosis, the presence of a palpable abdominal mass, palpable cervical lymphadenopathy, and non-reducing varicocele and bilateral lower extremity oedema should prompt radiological examination. Common laboratory parameters assessed on suspicion of RCC include serum creatinine, glomerular filtration rate, complete cell blood count, lactate dehydrogenase, C-reactive protein and serum-corrected calcium.[8,9]

The majority of cases of RCC are diagnosed by the use of diagnostic imaging tests, such as abdominal ultrasound, computer tomography (CT) and magnetic resonance imaging.[8,9] According to European Society for Medical Oncology (ESMO) guidelines, contrast-enhanced chest, abdominal and pelvic CT is mandatory for accurate staging,[9] and a renal tumour biopsy may be used to determine the histological subtype.[8,9] PD-L1 is not routinely tested for in RCC, and clinical opinion suggests that it is not relevant to systemic treatment decision-making.[1,17]

B.1.3.5.2 Treatment pathway

As aRCC is usually incurable, the goal of treatment is to prevent disease progression, maintain HRQoL, provide relief from cancer symptoms and extend life.[32] Patient-centred treatment is an important consideration in the management of people with aRCC.

Prior to the development of targeted therapies, immunotherapy with interleukins (ILs) and interferons (IFNs) was the only systemic therapy indicated for aRCC. However, their use was limited by low response rates, modest survival gains and significant toxicity.[74] Targeted

therapies were first approved in 2005, and act on two of the most commonly affected pathways in RCC, the VEGF (TKIs) and mammalian target of rapamycin (mTOR) pathways (TKIs and everolimus respectively).[75,76] Subsequently, the treatment landscape changed further with the introduction of IO agents targeting the PD1/PD-L1 checkpoint pathway, which had already demonstrated efficacy across a number of cancer types.[77]

The treatment pathway has evolved since the time of the original submission. Guidelines from ESMO, the European Association of Urology (EAU), the American Society of Clinical Oncology (ASCO) and the US National Comprehensive Cancer Network (NCCN),[8–11,33] have all been updated since the September 2020 STA. As there are still no national UK-specific clinical guidelines for the treatment of RCC, clinical practice in England and Wales continues to reflect the above international guidelines, along with NICE technology appraisal recommendations.

Clinical practice guidelines

First-line

In previously untreated patients, the choice of regimen is determined by IMDC risk categorisation and individual patient factors, such as histology, comorbidities and performance status. The EAU, ESMO, ASCO and NCCN guidelines recognise combination therapy with PD-1/PD-L1 inhibitor IO with either of the VEGFR TKIs or another IO as standard of care for untreated people with aRCC, irrespective of risk category, i.e., in people with favourable- and intermediate-/poor-risk aRCC.[8,9,31] The EAU, ESMO and ASCO guidelines consider monotherapy VEGFR TKIs – sunitinib or pazopanib – as an alternative option for first-line treatment for people with favourable-risk disease, although with a weaker grade of evidence.[8,9,11,33] ESMO guidelines additionally include a recommendation for tivozanib in this setting.[9]

Second and subsequent lines

Second- and subsequent line treatment options depend on the first-line treatment approach for an individual patient, but for the most part include TKI monotherapy, or nivolumab as options. The guidelines do not recommend use of an IO therapy in patients who have received IO as first-line treatment.[8–10,33] Instead, in patients who have received IO+TKI or IO+IO combinations at first-line, the EAU and ASCO guidelines recommend any approved VEGFR targeted therapy that has not been used previously in combination with the IO used for first-line treatment. In patients who have been previously treated with a TKI monotherapy at first-line, second-line treatment options include cabozantinib, nivolumab or axitinib.[8,33] ESMO recommends the use of a systemic therapy that has not previously been given, such as axitinib, cabozantinib, lenvatinib + everolimus, pazopanib, sunitinib, tivozanib or bezultifan in the second and subsequent line settings.[9] The EAU panel considered, even in the absence of conclusive data, that everolimus may present a therapeutic option in patients who were intolerant to, or previously failed, immune- and VEGFR-targeted therapies.[8]

NICE technology appraisals

For the first-line treatment of aRCC, there are no IO combinations recommended for use in people with favourable-risk disease in routine commissioning. Avelumab + axitinib is currently available in this setting within the CDF.[1] The only available treatments routinely recommended by NICE in this setting are the VEGFR TKIs sunitinib, pazopanib, tivozanib (which are recommended irrespective of IMDC risk categorisation).[4–6] Relative to axitinib, sunitinib and pazopanib are less selective for VEGF1-3.[78,79] Cabozantinib monotherapy and nivolumab with ipilimumab are recommended within their marketing authorisation for use in people with intermediate-/poor-risk disease, while lenvatinib with pembrolizumab and

cabozantinib with nivolumab have optimised recommendations in the intermediate-/poor-risk aRCC population.[7,13–15]

A summary of current NICE guidance for first-line treatment is shown in Table 4.

Table 4: Summary of NICE guidance for first-line treatment of aRCC

Treatment (TA)	Year	Guidance/population
Recommended		
Sunitinib (TA169)[4]	2009	Recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1. This recommendation is irrespective of IMDC group.
Pazopanib (TA215)[5]	2011	Recommended as a first-line treatment option for people with aRCC who have not received prior cytokine therapy and have an ECOG PS of 0 or 1. This recommendation is irrespective of IMDC group.
Tivozanib (TA512)[6]	2018	Recommended as an option for treating aRCC in adults, only if they have had no previous treatment. This recommendation is irrespective of IMDC group.
Cabozantinib (TA542)[7]	2018	Recommended, within its marketing authorisation, for adults with untreated aRCC **that is intermediate- or poor-risk** as defined in the IMDC criteria
Nivolumab with ipilimumab (TA780)[13]	2022	Nivolumab with ipilimumab is recommended, within its marketing authorisation, as an option for untreated aRCC in adults whose disease is **intermediate- or poor-risk** as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria
Lenvatinib with pembrolizumab (TA858)[14]	2023	Recommended as an option for untreated aRCC in adults, only if: • their disease is **intermediate- or poor-risk** as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria • nivolumab with ipilimumab would otherwise be offered
Cabozantinib with nivolumab (TA964)[15]	2024	Cabozantinib with nivolumab is recommended as an option for untreated aRCC in adults, only if: • their disease is **intermediate- or poor-risk** as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria • nivolumab with ipilimumab or lenvatinib with pembrolizumab would otherwise be offered
Cancer Drugs Fund		
Avelumab with axitinib (TA645)[1]	2020	Recommended for use within the CDF as an option for untreated aRCC in adults. It is recommended only if the conditions in the managed access agreement for avelumab + axitinib are followed. This recommendation is irrespective of IMDC group.
Not recommended		
Sorafenib (TA178)[80]	2009	
Temsirolimus (TA178)[80]		

Bevacizumab (TA178)[80]		Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma
Pembrolizumab with axitinib (TA650)[81]	2020	Pembrolizumab with axitinib is not recommended, within its marketing authorisation, for untreated aRCC in adults. The committee noted that short-term clinical trial evidence shows that pembrolizumab with axitinib is more effective than sunitinib for people with untreated renal cell carcinoma, but it is uncertain if there is a long-term benefit. This means the cost-effectiveness estimates are uncertain but are higher than NICE normally considers acceptable use of NHS resources.

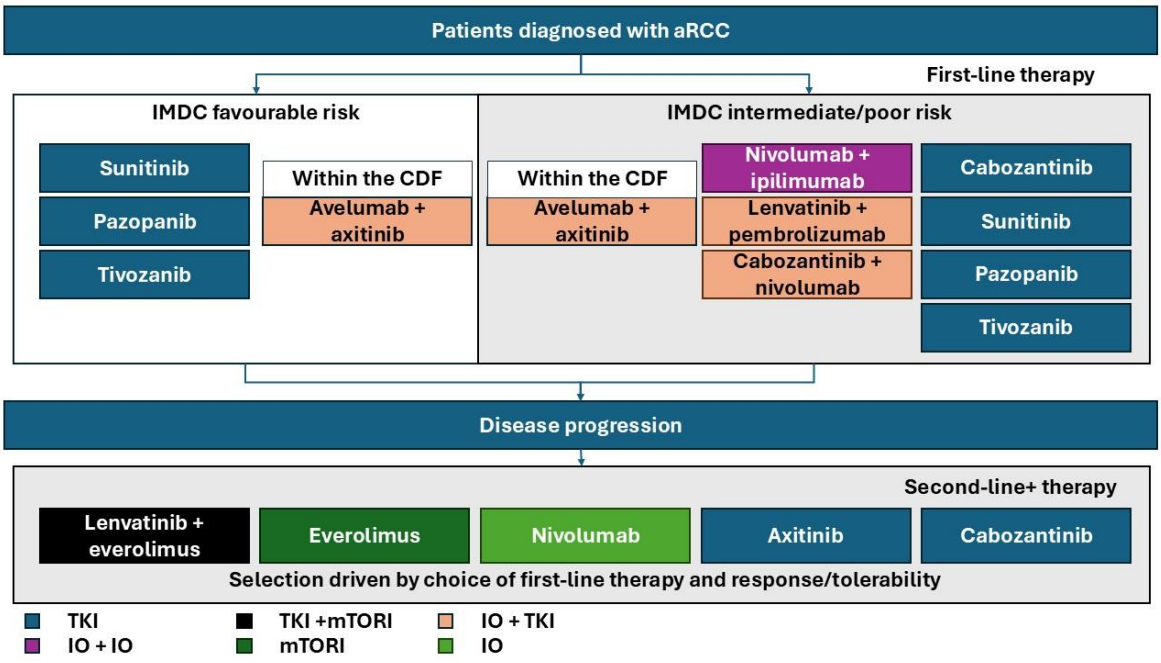
Abbreviations: aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PS, performance status; TA, technology appraisal.

NICE recommendations for previously treated people with aRCC all predate the introduction of PD-1/PD-L1 IO in the first-line setting. Recommendations for previously treated patients do not differentiate between IMDC risk categories.[8–11,33]

Since the initial submission for avelumab + axitinib, NICE have recommended pembrolizumab, within its marketing authorisation, as an option for the adjuvant treatment of renal cell carcinoma at increased risk of recurrence after nephrectomy, with or without metastatic lesion resection, in adults (TA830).[82] This population does not overlap with the population in this submission.

The clinical pathway of care for managing untreated aRCC, including the current CDF positioning of avelumab + axitinib, is presented in Figure 4.

Figure 4: Current clinical pathway of care for aRCC in England and Wales

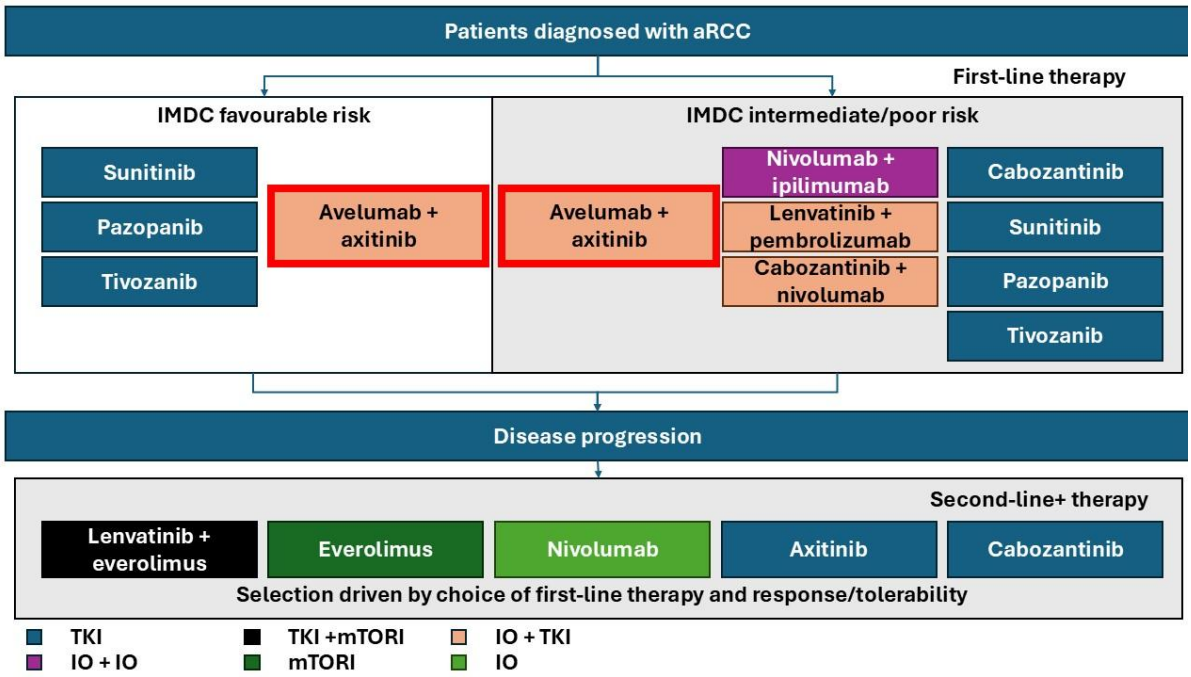


Abbreviations: aRCC, advanced renal cell cancer; CDF, cancer drugs fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; mTORI, mammalian target of rapamycin inhibitor; TKI, tyrosine kinase inhibitor.
Source: NICE.[4,7,14–16,83–87]

B.1.3.6 Place of avelumab + axitinib in the treatment pathway

The anticipated place in therapy for avelumab + axitinib is shown in Figure 5. It is anticipated that avelumab + axitinib will be used in accordance with its proposed marketing authorisation (first-line treatment of aRCC in adult patients). This is supported by data from the systemic anti-cancer treatment CDF cohort – collected as a condition of entry into the CDF – which shows that clinicians recognise a role for avelumab + axitinib in the favourable-risk group and as an alternative treatment option for people in the intermediate-/poor-risk categories.[21]

Figure 5: Clinical pathway of care including the anticipated place for avelumab + axitinib in the treatment pathway



Abbreviations: aRCC, advanced renal cell cancer; CDF, cancer drugs fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; mTORI, mammalian target of rapamycin inhibitor; TKI, tyrosine kinase inhibitor.
Source: NICE.[4,7,14–16,83–87]

If recommended by NICE, avelumab + axitinib would be the first IO+TKI combination treatment option routinely recommended for untreated favourable-risk aRCC, alongside the TKI monotherapies sunitinib, pazopanib, tivozanib. As such, avelumab + axitinib would provide people with favourable-risk disease continued access to an IO combination, outside of the context of the CDF. An IO+TKI combination is consistent with the recommendations of international clinical practice guidelines which recognise the importance of giving the most effective treatments from the outset.[8–11,33,37]

In intermediate-/poor-risk aRCC, avelumab + axitinib would provide an alternative treatment option to existing reimbursed IO+TKI/IO+IO combinations that allows flexibility of dosing with a manageable tolerability profile.[43,44]

B.1.3.7 Real-world UK treatment patterns

Real-world treatment patterns in aRCC in the UK have been identified in a retrospective multi-institutional review of patients conducted with the UK Renal Oncology Collaborative (UK ROC) real-world evidence dataset.[26,37] Patients with a clinical, radiological or pathological diagnosis of mRCC who started first-line systemic anti-cancer treatment between 1 January 2018 and 30 June 2021 were included from 17 NHS centres across the UK.[26,37] Of the 1,319 patients who met the eligibility criteria, 22.3% were favourable-risk, 52.7% were intermediate-risk and 24.3% were poor-risk.[26,37]

When considering all patients of all risk groups as defined by IMDC criteria collectively, in 2018, TKI was the main treatment choice, with 93.9% of patients prescribed this in the first-line setting. This evolved in the 2021 cohort, where increasing use of combination IO was observed: TKI use in the first-line setting dropped to 28%, and 69% of patients started combination IO (32% IO/IO and 37% IO/TKI). Despite several trials demonstrating OS advantages for IO-based combinations in the IMDC intermediate- and poor-risk groups, 28% of patients in these two groups had still received TKI as first-line therapy as of 2021.[26] Across the review period (2018 to 2021), of the 294 favourable patients in the analysis, 206 (70%) had TKI therapy, 66 (22.4%) had IO+TKI and 22 (7.4%) had other therapy.[37]

The three most common TKIs used in the first-line setting in the favourable-risk group were sunitinib (50.5%), pazopanib (31.6%) and tivozanib (15%). 95.5% of patients in the favourable-risk group treated with IO+TKI received avelumab + axitinib. For people with favourable-risk who received a TKI at first-line therapy, 42.5% were rechallenged at second line with a further TKI agent, with the majority receiving cabozantinib (31%).[37] However, a proportion (44.2% [130/294]) of favourable-risk patients did not receive immunotherapy at any stage in their treatment.[26] Furthermore, of the 97 favourable-risk patients (33%) who died during the follow-up period, 50 (51.5%) had never received immunotherapy as part of their SACT therapy.[37]

Across all risk groups, among the 778 patients who received first-line TKI monotherapy, 400 received second-line treatment. Of these 400 patients, the second-line treatment option chosen was nivolumab in 229 (57.3%) and cabozantinib in 107 (26.8%).[37]

Irrespective of IMDC risk category, only 47.8% (632/1,319) of patients who started first-line treatment went on to receive a second-line of therapy, after progression.[26] The proportions were similar for favourable- and intermediate-/poor-risk patients (49.0% [144/294] and 47.4% [482/1,016] respectively). Attrition rates across lines of treatment were significant, with only 16.2% (214/1,319) of all patients starting third-line therapy.[26]

B.1.3.8 Unmet need

While survival rates for kidney cancer have improved over recent decades, five-year age-standardised survival rates in the UK remain below 70% (66% for men and 67.8% for women during 2016–2020, compared with 29% and 28% during 1971–1972 for men and women, respectively).[18,88] Historically, outcomes for patients with aRCC have been poor, with response rates of just 12–13% with IL or IFN therapy.[74] Despite the improvements seen since the introduction of targeted therapies, patients in all IMDC risk groups treated with current first-line TKI monotherapies often fail to achieve PFS of longer than 1 year and outcomes remain poor.[34,35] Real-world studies have identified high unmet need associated with currently available first-line monotherapy in aRCC, with respect to OS, time to next treatment and time to treatment discontinuation.[36] Furthermore, given that less than 50% of all patients (regardless of IMDC risk group) treated in the first-line setting (including patients with favourable-risk disease) go on to receive second-line therapies – typically due to a lack

of fitness for treatment[26,37] – it is important to ensure that patients are treated with the most effective first-line therapies. The poor survival outcomes and durability of response in patients across all IMDC risk groups treated with first-line TKI monotherapy highlight an unmet need for an effective treatment approach with manageable tolerability that increases patient and physician choice, offers greater disease control and extends survival.[36]

B.1.3.8.1 IMDC favourable-risk aRCC

Progress has been made with more treatment options that improve patient outcomes following the development of IO agents in combination with VEGFR targeted TKIs, which are now considered first-line standard of care, irrespective of IMDC risk group, according to multiple international clinical practice guidelines.[8–11,33] Additionally, in Scotland, the SMC recommends avelumab + axitinib as well as pembrolizumab + axitinib for the first-line treatment of aRCC, irrespective of IMDC risk group.[38,89] However, there remains a high unmet need for patients with IMDC favourable-risk disease in England and Wales, given no IO containing regimens are routinely recommended by NICE for use in these patients. As such, TKI monotherapy with sunitinib, pazopanib or tivozanib are the only available treatments routinely commissioned for favourable-risk patients in England and Wales. Complete responses to TKI monotherapy remain uncommon in this population and almost all patients eventually progress.[90,91]

According to international clinical practice guidelines, patients initially treated with a TKI monotherapy should be treated subsequently with an IO therapy. This approach is seen in UK clinical practice, with real-world data showing approximately 58% of favourable-risk patients treated at first-line with TKIs receive an IO as second-line therapy.[37] However, the data also show that a proportion (44.2%) of favourable-risk patients did not receive an IO at any stage during their treatment.[26] Furthermore, of the 97 favourable-risk patients (33%) who died during the follow-up period, 50 (51.5%) had never received immunotherapy as part of their SACT therapy.[37] Considering the benefits of IO therapies and their availability through routine commissioning for patients in the intermediate-/poor-risk group, there is a high unmet need for a first-line IO-containing regimen as a treatment option for patients in the favourable-risk group outside of the CDF. Real-world evidence has demonstrated an OS and PFS benefit with IO+TKI versus TKI monotherapy in the IMDC favourable-risk group.[37]

In favourable-risk patients, avelumab + axitinib builds on the established efficacy of TKI monotherapy through the added benefit of an IO. Irrespective of the IMDC risk category, combining avelumab + axitinib has the potential for complementary and synergistic mechanisms of action (see Section B.1.2),[41,42] which may lead to improved disease control and extended survival than currently available first-line therapies recommended by NICE.

Prognosis in favourable-risk patients may be comparatively longer relative to intermediate-/poor-risk patients, but their disease remains life-limiting and incurable with current treatment. As such, extending PFS and OS, and minimising toxicity are important treatment goals.[92] As demonstrated in the pivotal Phase 3 JAVELIN 101 study, avelumab + axitinib resulted in a numerically favourable improvement in PFS vs sunitinib (B.2.6.1.1) and has a well-characterised safety and tolerability profile, with a low rate of discontinuations due to treatment-emergent adverse events (TEAEs; B.2.11.1). This finding is supported by real-world data from UK patients treated with avelumab + axitinib via the EAMS and CDF.[93,94] Furthermore, the potent VEGFR inhibition observed with axitinib may improve effectiveness and ease dose adjustment without compromising safety,[95] and the short half-life prevents substantial accumulation, ensuring that dose interruption or reduction can rapidly resolve any toxicities and help determine the cause of an AE (e.g. immune or TKI-mediated).[44]

As such, avelumab + axitinib could fulfil the unmet need for a safe and effective IO-containing first-line regimen for people with favourable-risk disease in England and Wales.

B.1.3.8.2 IMDC intermediate-/poor-risk aRCC

The use of IO is associated with immune-related AEs that can impact multiple organ systems and are often caused by nonspecific activation of the immune system.[43] These immune-related AEs require management with immunosuppressants such as systemic corticosteroids, and may be complicated by the complex interplay with similar TKI-mediated AEs.[43,44]

Unlike other IO+TKI combinations used for the treatment of intermediate-/poor-risk aRCC, both axitinib and avelumab have a short half-life.[43,95–97] The short half-life of axitinib prevents substantial accumulation, ensuring that dose interruption or reduction can rapidly resolve any toxicities and help determine the cause of an AE (e.g. immune or TKI-mediated).[44] Most immune-related adverse reactions associated with avelumab are reversible and managed with temporary or permanent discontinuation of avelumab, administration of corticosteroids, and/or supportive care.[39] Again, the ease of axitinib dose adjustment without compromising safety,[95] combined with the range of available tablet strengths, provides clinicians with dosing flexibility, allowing them to increase or decrease the dose according to an individual's tolerance.[40] As such, avelumab + axitinib could potentially provide an additional treatment option with a manageable tolerability profile for patients and physicians for intermediate-/poor-risk disease.

B.1.4 Equality considerations

It is important to consider equity of access to treatments across IMDC risk groups. Prognosis in favourable-risk patients may be comparatively longer relative to intermediate-/poor-risk patients, but their disease remains life-limiting and incurable with current treatment. Presently, no IO containing regimens are routinely recommended by NICE for first-line treatment in favourable-risk patients, only in intermediate-/poor-risk patients.

According to the UK ROC RWE dataset, approximately 58% of favourable-risk patients treated at first-line with TKIs receive an IO as second-line therapy.[37] However, a proportion (44.2%) of favourable-risk patients did not receive an IO at any stage during their treatment.[26] Furthermore, of the 97 favourable-risk patients (33%) who died during the follow-up period, 50 (51.5%) had never received immunotherapy as part of their SACT therapy.[37]

The EAU, ESMO, ASCO and NCCN guidelines recognise combination therapy with PD-1/PD-L1 inhibitor IO + either of the VEGFR TKIs or another IO as standard of care for untreated patients with aRCC, irrespective of risk category, i.e., in patients with favourable and intermediate-/poor-risk aRCC.[8,9,31] In Scotland, the SMC recommends avelumab + axitinib as well as pembrolizumab + axitinib for the first-line treatment of aRCC, across all IMDC risk groups, which means patients with favourable risk aRCC in Scotland have access to IO-containing treatment options.[38,89]

Recognising the importance of giving the most effective treatments from the outset, it is important that all patients, especially those in the favourable risk IMDC sub-group where there is a clear unmet need, have access to an IO containing regimen at first-line treatment.

B.2 Clinical effectiveness

Overview of data presented in the initial submission (TA645) and this current submission

The initial submission (TA645) was primarily based on the results of interim analysis (IA) 1 (data cutoff [DCO] 20 June 2018) from the pivotal Phase 3 JAVELIN Renal 101 trial, together with a summary of the results of IA2 (DCO 28 January 2019) where available.[1]

Since the recommendation of avelumab + axitinib within the CDF, and consistent with the requirements of the managed access agreement, this current submission is based on:

- **New data from the final analysis (FA) of JAVELIN 101 (DCO 31 August 2023).**[98–100]
- **Data from the SACT database (collected by NHS England as part of the managed access agreement for CDF entry for avelumab + axitinib) and real-world evidence (RWE) from UK clinical practice (n=4) identified as part of a systematic literature review (SLR) of data on avelumab +axitinib use in routine clinical practice (9 studies).**[21]

This submission covers the technology's full marketing authorisation for avelumab + axitinib as an option for untreated locally advanced or metastatic RCC in adults.

Aligned with the evolution of the treatment pathway, efficacy data from the FA of JAVELIN Renal 101 in this submission are presented separately for the (i) favourable-risk and (ii) intermediate-/poor-risk groups according to IMDC (Heng) prognostic criteria.

Results are presented irrespective of PD-L1 status as per the overall patient population specified in the NICE scope; however, sub-group results for patients with IMDC favourable and intermediate-/poor-risk and PD-L1+ tumours are presented in Section B.2.7 in line with the NICE scope.

Summary of clinical efficacy and safety

The efficacy and safety of avelumab + axitinib in patients with aRCC has been demonstrated in an extensive clinical trial programme, which includes the completed Phase 3 JAVELIN Renal 101 (minimum 68 months follow up in all patients),[98–100] **as well as in real-world studies, which have included patients from the UK:**

- JAVELIN Renal 101 was a Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised study in treatment-naïve adult patients with histologically or cytologically confirmed aRCC with clear cell component and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (N=886).[98,99]
- The trial provides the longest follow-up for an immunotherapy (IO) and tyrosine kinase inhibitor (TKI) combination treatment in aRCC from a Phase 3 trial reported to date (median follow-up of >6 years).[98] The DCO for the FA was 31 August 2023.
- Aligned with the evolution of the UK treatment pathway, efficacy data from the FA (DCO 31 August 2023) are presented separately in this submission for:[98,100]
    - The favourable-risk group (n=190) according to IMDC (Heng) prognostic criteria (irrespective of PD L1 expression status).
    - The intermediate-/poor-risk group (n=691) according to IMDC (Heng) prognostic criteria (irrespective of PD L1 expression status).
        - 5 patients in the avelumab + axitinib arm full analysis set (FAS) did not have a recorded IMDC risk group at baseline.

The Phase 3 JAVELIN Renal 101 trial demonstrated that avelumab + axitinib is associated with long-term efficacy benefits and a manageable safety profile in patients with aRCC.[98]

In patients with IMDC favourable-risk, patients receiving avelumab + axitinib had numerically favourable progression-free survival (PFS) (by investigator assessment), higher objective response rate (ORR) and higher median overall survival (OS) compared with those receiving sunitinib.[98,100]

- There was a numerical 27% reduction in risk of death with avelumab + axitinib compared with sunitinib (stratified HR=0.73 [95% CI: 0.48, 1.10]; stratified p=0.1290). Median OS was 14 months longer in the avelumab + axitinib arm (79.4 months; 95% CI: 59.4, ND) than the sunitinib arm (65.5 months; 95% CI: 53.4, 78.6).
- Patients who received avelumab + axitinib had a 25% reduction in the risk of progression or death, compared with those who received sunitinib (HR=0.75; 95% CI: 0.53, 1.07; log rank, primary, stratified p-value=0.1109). Median PFS (by investigator assessment) was 20.7 months (95% CI: 16.6, 26.2) in the avelumab + axitinib arm and 13.8 months (95% CI: 11.1, 23.5) in the sunitinib arm.
- The ORR for avelumab + axitinib was almost 30% higher than for sunitinib (75.5% and 45.8%, respectively). The proportion of patients with a complete response (CR) was numerically higher in the

avelumab + axitinib combination arm (9.6%) compared with the sunitinib arm (5.2%) and more patients in the avelumab + axitinib arm attained disease control ([redacted]%) compared with those in the sunitinib arm ([redacted]%).

- In patients with a response to avelumab + axitinib, median duration of response (DoR) was 23.4 months (95% CI, 16.6, 29.2); and in those with a response to sunitinib, median DoR was 20.8 months (95% CI, 14.5 to 24.9).

Similarly, in patients with IMDC intermediate-/poor-risk, patients receiving avelumab + axitinib had numerically favourable PFS (by investigator assessment), higher ORR and higher median OS compared with those receiving sunitinib[98,100]

- Median OS was longer in the avelumab + axitinib arm (37.8 months; 95% CI: 31.2, 42.6) than in the sunitinib arm (29.5 months; 95% CI: 24.8, 36.1).
- Patients who received avelumab + axitinib had a 36% reduction in the risk of progression or death, compared with those who received sunitinib (HR=0.64; 95% CI: 0.54, 0.76; log rank, primary, stratified p<0.0001). Median PFS (by investigator assessment) was 11.1 months (95% CI: (9.8, 14.6) in the avelumab + axitinib arm and 8.1 months (95% CI: 6.9, 8.4) in the sunitinib arm.
- The ORR for avelumab + axitinib was almost double the ORR for sunitinib, with a 27.5% difference in rates (55.7% and 28.2%, respectively). The proportion of patients with a CR was marginally higher in the avelumab + axitinib combination arm compared with the sunitinib arm (4.7% and 3.2%, respectively) and more patients in the avelumab + axitinib arm attained disease control ([redacted]%) compared with those in the sunitinib arm ([redacted]%).
- In patients with a response to avelumab + axitinib, median DoR was 19.4 months (95% CI, 14.1, 22.3); and in those with a response to sunitinib, median DoR was 9.8 months (95% CI, 7.0, 15.3).

Patient-reported outcomes demonstrated that HRQoL was generally maintained during treatment with avelumab + axitinib, until just before the end of the treatment period, and was similar to that reported during treatment with sunitinib.[99]

UK real-world data sources (4 studies identified through the RWE SLR plus data from the SACT database) demonstrate that the outcomes observed in the JAVELIN Renal 101 trial translate into real-world treatment benefits for patients with aRCC, including those with favourable and intermediate-/poor-risk disease.[21,37,93,94]

- In analysis of the CDF cohort from the SACT dataset, the median OS was [redacted] for patients with a favourable-risk score, [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days) for patients with an intermediate-risk score, and [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days) for patients with a poor-risk score.[21]

The safety profile of avelumab + axitinib as a first line treatment for patients with aRCC is well characterised and is generally tolerable, manageable, and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies.[98,99]

The long-term safety profile of avelumab + axitinib in JAVELIN Renal 101 was consistent with previous analyses[98,99]

- In the FA (DCO 31 August 2023) of the safety analysis set (SAF), the avelumab + axitinib and sunitinib arms had similar incidences of TEAEs, including Grade ≥3 TEAEs and treatment-related TEAEs.
- A larger proportion of patients experienced a serious TEAE in the avelumab + axitinib arm (53.2% versus 37.8% in the sunitinib arm).
- In the avelumab + axitinib arm, the most common TEAEs (reported by >40% of patients) were diarrhoea, hypertension, fatigue, and nausea.

Overall, the results show that avelumab + axitinib provides an effective and well-tolerated additional treatment option for patients and physicians in the treatment of aRCC. In favourable-risk patients – who currently only have access through routine NHS commissioning to TKI monotherapies – it builds on the established efficacy of TKI monotherapy through the added benefit of immunotherapy, as shown by numerically improved PFS, ORR, DoR and OS versus sunitinib TKI monotherapy.

B.2.1 Identification and selection of relevant studies

Systematic literature reviews (SLRs) were conducted to identify the available randomised controlled trial (RCT) evidence (conducted 4 June 2024) for established clinical management in untreated aRCC and real-world evidence (RWE) (conducted 29 July 2024) for patients treated with avelumab + axitinib. Full details of the methodology and the results of the SLRs are detailed in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

This submission is based on efficacy data from the Phase 3 Study B9991003 (JAVELIN Renal 101; NCT02684006). Data are presented for the final analysis (data cutoff [DCO] 31 August 2023).[99]

Data from the open-label, dose-finding Phase 1b trial B9991002 (JAVELIN Renal 100; NCT02493751) were used in original submission. These data have now been superseded by the final analysis (DCO 31 August 2023) from JAVELIN Renal 101, and by RWE from UK clinical practice, and are therefore not included in this submission.

Table 5: Clinical effectiveness evidence

Study	Study B9991003 (JAVELIN Renal 101, NCT02684006)
Study design	Multicentre, randomised, open-label, parallel-arm phase 3 trial
Population	Treatment-naïve adult patients with histologically or cytologically confirmed aRCC with clear cell component and an ECOG PS of 0 or 1
Intervention(s)	Avelumab + axitinib
Comparator(s)	Sunitinib
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	Pivotal phase 3 trial supporting this indication
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rates • Duration of response • Time on treatment/time to next treatment • Adverse events • Health-related quality of life
All other reported outcomes	• Objective response rate • Time to response

Key publications	FA: Motzer *et al.* Abstract 4508, ASCO 2024[98] IA3: Haanen *et al. ESMO Open*. 2023 Jun;8(3):101210[101] IA2: Choueiri *et al. Ann Oncol*. 2020 Aug;31(8):1030-1039[102] IA1: Motzer *et al. N Engl J Med*. 2019 Mar 21;380(12):1103-1115[103]
Secondary sources	• DoF JAVELIN Renal 101 CSR (final analysis, DCO 31 August 2023)[99] • DoF JAVELIN Renal 101 CSR (IA3, DCO 28 April 2020)[104] • DoF JAVELIN Renal 101 CSR (IA2, DCO 28 January 2019)[105] • DoF JAVELIN Renal 101 CSR (IA1, DCO 20 June 2018)[106]

Abbreviations: aRCC, advanced renal cell carcinoma; CSR, clinical study report; DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; FA, final analysis; IA, interim analysis.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

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

B.2.3.1 Trial design

JAVELIN Renal 101 was a Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised study conducted across 20 countries.[99] Out of 886 patients enrolled, 32 were from the UK. The study population consisted of treatment-naïve adult patients with histologically or cytologically confirmed aRCC with clear cell component and an ECOG performance status of 0 or 1.[99]

Patients were randomised (1:1) to receive either avelumab + axitinib (n=442) or sunitinib monotherapy (n=444).[99] Randomisation was stratified according to ECOG performance status (0 or 1) and region (United States, Canada/Western Europe, or rest of the world). Crossover between treatment arms was not permitted.[99]

The study included the following periods:[99]

- Screening (up to 28 days before randomisation)
- Study treatment
- Short-term follow-up for 90 days after the last dose of study treatment
- Long-term follow-up until death, end of study, or withdrawal of consent, whichever occurred first.

JAVELIN Renal 101 provides the longest follow-up to date for an immune checkpoint inhibitor + TKI combination treatment from a Phase 3 trial in aRCC (minimum of 68 months in all patients).[98] Four pre-specified analyses were conducted:

- Interim analysis (IA)1: Planned for after approximately 235 PFS events (70% of the expected 336 events from the power calculation, Table 10) had occurred in the PD-L1-positive population (IA for PFS and IA1 for OS).[107] The DCO for this analysis was 20 June 2018, when 253 PFS events had occurred in the PD-L1-positive population.[106]
- IA2: Planned for after 336 PFS events had occurred in the PD-L1-positive population (primary analysis for PFS and IA2 for OS).[107] The DCO for this analysis was 28 January 2019, when 309 PFS events had occurred in the PD-L1-postive population.[105]
- IA3: Planned for 15 months after the primary analysis for PFS (IA3 for OS).[107] The DCO for this analysis was 28 April 2020.[104]
- Final analysis: Planned for after 368 deaths had occurred in the PD-L1-positive population (primary analysis for OS).[107] The DCO for this analysis was 31 August 2023 when 375 deaths had occurred in the PD-L1-positive population.[99]

The submission for TA645 was primarily based on the results of IA1, and a summary of the results of IA2 were also presented where available at the time of submission.[1] This submission presents the final analysis for OS of the completed JAVELIN Renal 101 trial (DCO 31 August 2023), supplemented by RWE from UK clinical practice.[99] Since the recommendation of avelumab + axitinib within the CDF, there has been a significant

evolution in the treatment pathway for untreated aRCC. In UK clinical practice, the IMDC prognostic model is used to categorise patients into risk groups for survival to inform treatment selection based on NICE recommendations: (i) favourable-risk and (ii) intermediate-/poor-risk.[12] This baseline prognostic categorisation is used to determine first-line treatment options.[1] Aligned with the evolution of the treatment pathway, efficacy data from the final analysis (FA) (DCO 31 August 2023) of JAVELIN Renal 101 in this submission are presented separately for the (i) favourable-risk and (ii) intermediate-/poor-risk groups according to IMDC (Heng) prognostic criteria.

B.2.3.2 Trial methodology

A summary of the methodology of JAVELIN Renal 101 is provided in Table 6.

Table 6: Summary of JAVELIN Renal 101 trial methodology

Trial design	Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised (1:1) study
Duration of study	Median follow-up in the avelumab + axitinib arm: 73.2 months Median follow-up in the sunitinib arm: 73.0 months
Locations (number of patients recruited)	Australia (32), Austria (5), Belgium (9), Canada (74), Denmark (5), France (70), Germany (7), Hungary (2), Israel (41), Italy (15), Japan (67), Mexico (12); Netherlands (38), New Zealand (9), Republic of Korea (48), Romania (20), Russia (138), Spain (1), UK (32), US (261)
Participant eligibility criteria	**Key inclusion criteria** • Age ≥18 years (≥20 years in Japan) • Histologically or cytologically confirmed aRCC* with a clear cell component • At least one measurable lesion (as defined by RECIST version 1.1) that had not been previously irradiated • Estimated life expectancy of ≥3 months • ECOG performance status 0 or 1 • Adequate bone marrow, renal and liver functions
	Key exclusion criteria • Evidence of uncontrolled hypertension • Prior therapies, including systemic therapy for advanced or metastatic RCC, adjuvant or neoadjuvant therapy for RCC, immunotherapy and VEGF pathway inhibitors • Newly diagnosed brain metastases or known symptomatic brain metastases requiring steroids • Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomisation
Trial drugs	**Intervention (n=444):** Avelumab 10 mg/kg as a 1-hour intravenous infusion every 2 weeks in a 6-week cycle Axitinib 5 mg taken orally twice daily, with or without food, on a continuous dosing schedule
	Comparator (n=442): Sunitinib 50 mg taken orally once daily for 4 consecutive weeks followed by a 2-week -off treatment period (Schedule 4/2 in a 6-week cycle)

Concomitant medication	**Permitted concomitant medication:** • Medications intended solely for supportive care • G-CSF • Local radiotherapy of isolated lesions with palliative intent • Systemic steroids (short-term administration) • Topical and inhaled steroids **Prohibited concomitant medication:** • Anti-cancer therapy (other than avelumab, axitinib or sunitinib) • Vaccine therapies ≤4 weeks prior to the start of study treatment (except inactive influenza vaccine) • Bisphosphonate or denosumab (unless initiated >14 days prior to the first dose of study treatment) • Other experimental pharmaceutical products • Herbal remedies with immune-stimulating properties or with the potential to interfere with major organ function
Primary outcomes	• PFS (according to RECIST version 1.1) by BICR assessment in patients with PD-L1-positive tumours (≥1% staining in tumour-associated immune cells) • OS in patients with PD-L1-positive tumours
Other outcomes used in the model/specified in scope	**Secondary endpoints:** • **PFS** (according to RECIST version 1.1) by BICR assessment in patients unselected for PD L1 expression • **OS** in patients unselected for PD-L1 expression • ORR (BOR of CR or PR based on BICR assessment, according to RECIST version 1.1) DCR (BOR of CR, PR, non-CR/non-PD or stable disease based on BICR assessment, according to RECIST version 1.1) • TTR • DoR • PFS2
Other outcomes	**Patient-reported outcomes** – Time to deterioration in FKSI-DRS – FKSI-19 – **EQ-5D-5L** • **Safety outcomes** – **Adverse events** – **TTD** – Vital signs – Physical examination – 12-lead ECG – Laboratory assessments – ECOG performance status – Verification of concomitant medication use
Pre-planned subgroups	*Note: Heng/IMDC prognostic criteria subgroups have emerged as key subgroups across the long-term follow-up of the trial, and we therefore present results across favourable and intermediate-poor subgroups in*

	Section B.2.6, alongside a short summary of the ITT population results for completeness. Pre-planned subgroup analysis was in PFS, OS, ORR, and DoR by: • PD-L1 expression (PD-L1-positive vs unselected for PD-L1 expression) • ECOG performance status (0 vs 1) • Geographical region (US vs Canada/Western Europe vs RoW) • Age (<65 years vs ≥65 years) • Gender (male vs female) • Race (Caucasian/white vs Asian vs Black/African American vs other) • Ethnicity (Hispanic/Latino vs non-Hispanic/Latino) • Pooled geographical region (North America vs Europe vs Asia vs RoW) • Nephrectomy at baseline (yes vs no) • MSKCC prognostic criteria at baseline (favourable vs intermediate vs poor) • IMDC (Heng) prognostic criteria at baseline (favourable vs intermediate vs poor)

Outcomes listed in bold are included in the economic model.
*aRCC included unresectable locally advanced and metastatic disease.
Abbreviations: aRCC, advanced renal cell carcinoma; BICR, blinded independent central review; BOR, best overall response; CR, complete response, DCR, disease control rate; DoR, duration of response, ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FKSI-19, Functional Assessment of Cancer Therapy – Kidney Symptom Index-19; FKSI-DRS, Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; G-CSF, granulocyte colony stimulating factor; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, progression-free survival on next-line therapy; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; RoW, rest of the world; TTD, time to treatment discontinuation; TTR, time to response; UK, United Kingdom; US, United States; VEGF, vascular endothelial growth factor.
Source: DoF JAVELIN Renal 101 FA CSR;[99] DoF JAVELIN Renal 101 protocol.[107]

B.2.3.2.1 Study treatments

All investigational products were administered on an outpatient basis.[99] Patients in the avelumab + axitinib arm received avelumab 10 mg/kg as a 1-hour intravenous infusion every 2 weeks in a 6-week cycle. Patients in this arm also received axitinib 5 mg twice daily, administered orally on a continuous dosing schedule. Patients in the sunitinib arm received sunitinib 50 mg once daily, administered orally in 6-week cycles (4 consecutive weeks of treatment followed by a 2-week off treatment period).[99]

Patients received study treatment until confirmed disease progression, global deterioration of health status requiring discontinuation, or unacceptable toxicity.[107] Treatment with single-agent avelumab, single-agent axitinib or avelumab + axitinib, or sunitinib monotherapy could continue beyond confirmed disease progression if the patient was experiencing clinical benefit. Crossover between treatment arms was not permitted.[107]

No avelumab dose modifications were permitted, but infusions could be omitted due to persisting toxicity.[107] Infusion of avelumab was to be stopped in case of Grade ≥2 infusion-related, allergic or anaphylactic reactions, and the infusion rate reduced in case of Grade 1 reactions.[107]

In the event of toxicity, axitinib dose modifications (including dosing interruption and/or dose reduction to 3 mg or 2 mg twice daily) were allowed.[107] Dose modifications of axitinib and infusion omissions of avelumab could occur independently, and patients who stopped either

avelumab or axitinib for reasons other than confirmed disease progression could continue on single-agent treatment until disease progression. Axitinib dose escalation to 7 mg twice daily and 10 mg twice daily was allowed if patients tolerated the current dose without axitinib-related Grade 3 or higher adverse events (AEs) for two consecutive weeks. As with axitinib, sunitinib treatment could be adjusted by dosing interruption and/or dose reduction to 37.5 mg or 25 mg once daily for the management of toxicities.[107]

B.2.3.2.2 Trial outcomes

Trial endpoints and their definitions are shown in Table 7.

Table 7: JAVELIN Renal 101 | Summary of key endpoints

Endpoint/assessment	Definition
Primary endpoints	
PFS in patients with PD-L1-positive tumours	• PFS defined as the time from date of randomisation to the date of the first documentation of objective disease progression (according to RECIST version 1.1 and based on BICR assessment) or death due to any cause, whichever occurred first – PFS was assessed by BICR for the preplanned interim and primary analyses only (IA1 [DCO 20 June 2018] and IA2 [DCO 28 January 2019]). BICR activities subsequently ended and PFS was assessed by the investigator for later analyses • PD-L1-positive tumours defined as those with PD-L1 staining of any intensity in tumour-associated immune cells covering ≥1% of tumour area
OS in patients with PD-L1-positive tumours	• OS defined as the time from date of randomisation to the date of death due to any cause • PD-L1-positive tumours defined as above
Secondary endpoints	
PFS in patients unselected for PD-L1 expression	Defined as above
OS in patients unselected for PD-L1 expression	Defined as above
Objective response	BOR of CR or PR according to RECIST version 1.1, from randomisation until disease progression assessed by BICR or death due to any cause
Disease control	BOR of CR, PR, non-CR/non-PD or SD according to RECIST version 1.1, from randomisation until disease progression assessed by BICR or death due to any cause
Time to response	Time from randomisation to first documentation of objective response (CR or PR)
Duration of response	Time from the first documentation of objective response to the first documentation of PD or death due to any cause, whichever occurs first
PFS on next-line therapy (PFS2)	Time from randomisation to discontinuation of next-line treatment after first objective disease progression (by investigator assessment) after initiation of next-line treatment or death due to any cause, whichever occurs first
Patient-reported outcomes	

Time to deterioration in the FKSI-DRS	Time from randomisation to the first ≥3-point decrease from baseline in the FKSI-DRS subscale
FKSI-19 total score	Stand-alone instrument to measure symptoms and quality of life in patients with advanced kidney cancer
EQ-5D-5L scores	6-item patient-completed questionnaire, with a Health State Profile and a Visual Analogue Scale
Safety endpoints	
Adverse events, serious adverse events, vital signs, physical examination, 12-lead electrocardiogram, laboratory assessments, ECOG performance status, and verification of concomitant medication use	• Adverse events classified using the MedDRA classification system • Severity of toxicities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCO, data cutoff; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FKSI-19, Functional Assessment of Cancer Therapy – Kidney Symptom Index-19; FKSI-DRS, Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MedDRA, Medical Dictionary for Regulatory Activities; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.
Source: DoF JAVELIN Renal 101 SAP.[108]

B.2.3.3 Patient baseline demographic and disease characteristics

Table 8 presents key patient baseline demographic and disease characteristics for the full analysis set (all randomised patients) and for the subgroups with IMDC (Heng) favourable and intermediate-/poor-risk.

All baseline characteristics were well balanced between the treatment arms in the full analysis set (FAS) population. Baseline characteristics were also balanced between the treatment arms within the favourable-risk subgroup and the intermediate-/poor-risk subgroup, with the exception of the sunitinib arm containing a greater proportion of male patients ([redacted]%) versus the avelumab + axitinib arm ([redacted]%) in the favourable-risk subgroup.[100,106]

Differences between the two subgroups include:[100]

- A greater proportion of patients with an ECOG performance status of 0 in the favourable-risk subgroup versus the intermediate-/poor-risk subgroup ([redacted]% versus [redacted]% in the avelumab + axitinib arm and [redacted]% versus [redacted]% in the sunitinib arm)
- A greater proportion of patients with previous nephrectomy in the favourable-risk subgroup versus the intermediate-/poor-risk subgroup ([redacted]% versus [redacted]% in the avelumab + axitinib arm and [redacted]% versus [redacted]% in the sunitinib arm)
- A greater proportion of patients with one target tumour site and fewer patients with 3 and ≥4 target tumours sites in the favourable-risk subgroup versus the intermediate-/poor-risk subgroup
- A slightly smaller proportion of patients with positive PD-L1 expression in the favourable-risk subgroup versus the intermediate-/poor-risk subgroup, albeit with a more pronounced difference in the avelumab + axitinib arm ([redacted]% versus [redacted]% in the avelumab + axitinib arm and [redacted]% versus [redacted]% in the sunitinib arm).

Table 8: Patient baseline demographic and disease characteristics | Full analysis set and IMDC (Heng) prognostic risk groups

	Avelumab + axitinib			Sunitinib		
	FAS (n=442)*	IMDC (Heng) prognostic risk group		FAS (n=444)	IMDC (Heng) prognostic risk group	
		Favourable (n=94)*	Intermediate/ poor (n=343)*		Favourable (n=96)	Intermediate/ poor (n=348)
Age, median (range), years	62.0 (29.0, 83.0)	[redacted]	[redacted]	61.0 (27.0, 88.0)	[redacted]	[redacted]
Sex, n (%)						
Male	316 (71.5)	[redacted]	[redacted]	344 (77.5)	[redacted]	[redacted]
Female	126 (28.5)	[redacted]	[redacted]	100 (22.5)	[redacted]	[redacted]
ECOG PS, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous nephrectomy, n (%)						
Yes	352 (79.6)	[redacted]	[redacted]	355 (80.0)	[redacted]	[redacted]
No	90 (20.4)	[redacted]	[redacted]	89 (20.0)	[redacted]	[redacted]
Number of target tumour sites at baseline (RECIST, BICR), n (%)						
0	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
1	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
2	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
3	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
≥4	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
Number of target tumour sites at baseline (RECIST, INV), n (%)						
0	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
1	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
2	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]

	Avelumab + axitinib			Sunitinib		
	FAS (n=442)*	IMDC (Heng) prognostic risk group		FAS (n=444)	IMDC (Heng) prognostic risk group	
		Favourable (n=94)*	Intermediate/ poor (n=343)*		Favourable (n=96)	Intermediate/ poor (n=348)
3	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
≥4	Not reported	[redacted]	[redacted]	Not reported	[redacted]	[redacted]
PD-L1 status, n (%)						
Positive	270 (61.1)	[redacted]	[redacted]	290 (65.3)	[redacted]	[redacted]
Negative	132 (29.9)	[redacted]	[redacted]	120 (27.0)	[redacted]	[redacted]
Unknown	40 (9.0)	[redacted]	[redacted]	34 (7.7)	[redacted]	[redacted]

*Five patients in the avelumab + axitinib arm FAS did not have a recorded IMDC risk group at baseline.
Abbreviations: BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; IMDC, International Metastatic RCC Database Consortium; INV, investigator; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: DoF JAVELIN Renal 101 IA1 CSR;[106] DoF JAVELIN Renal 101 FA - additional analyses.[100]

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

B.2.4.1 Analysis sets

Table 9 describes the populations included in JAVELIN Renal 101. As previously described, since the recommendation of avelumab + axitinib within the CDF, there has been a significant evolution in the treatment pathway for untreated aRCC in the UK. This baseline prognostic categorisation is used to determine first-line treatment options.[1] Aligned with the evolution of the treatment pathway, efficacy data from the final analysis (FA) (DCO 31 August 2023) of JAVELIN Renal 101 in this submission are presented separately for the (i) favourable-risk and (ii) intermediate-/poor-risk groups according to IMDC (Heng) prognostic criteria (unselected for PD-L1 expression status).

For completeness, data for the full (intention-to-treat) population across the different analysis time points are summarised in Section B.2.6.

Table 9: Summary of JAVELIN Renal 101 analysis sets

Analysis set	Definition	Avelumab + axitinib, n (%)	Sunitinib, n (%)	Total, n (%)
Subgroup analysis sets (relevant to the decision problem)				
Favourable-risk	Subset of the FAS to include patients with no risk factors according to the IMDC (Heng) criteria	94 (21.3)*	96 (21.6)	190 (21.4)*
Intermediate-/ poor-risk	Subset of the FAS to include patients with any risk factor(s) according to the IMDC (Heng) criteria	343 (77.6)*	348 (78.4)	691 (78.0)*
Prespecified analysis sets**				
FAS	All randomised patients	442 (100)	444 (100)	886 (100)
SAF	All patients who received ≥1 dose of study drug	434 (98.2)	439 (98.9)	873 (98.5)
PP for OS	Subset of the FAS to include all patients who meet none of the following criteria: • Did not receive ≥1 dose of study treatment • ECOG status >1 • Prior therapies for aRCC • OS assessments not per protocol	434 (98.2)	439 (98.9)	873 (98.5)
PP for PFS	As above for OS but with PFS assessments not per protocol	405 (91.6)	405 (91.2)	810 (91.4)
Avelumab PK concentration	Subset of the SAF to include patients with ≥1 post-dose concentration measurement above LLQ for avelumab	405 (91.6)	NA	405 (45.7)
Axitinib PK concentration	As above for avelumab but with measurement above LLQ for axitinib	407 (92.1)	NA	407 (45.9)

Immunogenicity	Subset of the SAF to include patients with ≥1 ADA/nAb sample collected for avelumab	426 (96.4)	NA	426 (48.1)
Biomarker	Subset of the SAF to including patients with ≥1 screening biomarker assessment	397 (89.8)	407 (91.7)	804 (90.7)

*Five patients in the avelumab + axitinib arm FAS did not have a recorded IMDC risk group at baseline. ** For some endpoints, analyses were also performed on the subset of PD-L1+ patients.
Abbreviations: ADA, anti-drug antibodies; aRCC, advanced renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; LLQ, lower limit of quantitation; nAb, neutralising antibody; PFS, progression-free survival; PK, pharmacokinetics; PP, per protocol; SAF, safety analysis set.
Source: DoF JAVELIN Renal 101 SAP;[108] DoF JAVELIN Renal 101 IA1 CSR;[106] DoF JAVELIN Renal 101 FA CSR;[99] DoF JAVELIN Renal 101 FA - additional analyses.[100]

B.2.4.2 Statistical analyses

Statistical analysis methods for JAVELIN Renal 101 are summarised in Table 10.

Table 10: Summary of JAVELIN Renal 101 statistical analyses

Hypothesis objective	• The primary null hypotheses were that there was no difference in PFS or OS (in patients with PD-L1-positive tumours) between the two treatments of avelumab + axitinib and sunitinib. The alternative hypothesis was that avelumab + axitinib improves PFS and/or OS relative to sunitinib. • Key secondary null hypotheses were that there was no difference in PFS or OS (in patients unselected for PD-L1 expression) between the two treatments. • Hypotheses for the additional secondary endpoints were also tested.
Statistical analysis	**Randomisation** Patients were randomised using an interactive response technology system. Randomisation was stratified by ECOG performance status (0 or 1) and region (United States, Canada/Western Europe, or rest of the world). **Primary endpoints: PFS and OS in patients with PD-L1-positive tumours** Final analysis of PFS was performed when 446 PFS events and 375 OS events had occurred (Note: PFS was assessed by BICR for the preplanned interim and primary analyses only (IA1 [DCO 20 June 2018] and IA2 [DCO 28 January 2019]). BICR activities subsequently ended and PFS was assessed by the investigator for later analyses). The study was considered positive if the stratified log-rank test was significant at the respective α levels for either of these two endpoints. One-sided stratified log rank tests, stratified by randomisation stratification factors, were performed for both endpoints. Duration of PFS and OS were summarised by treatment arm using the Kaplan–Meier (KM) method. The treatment effect was estimated using a Cox proportional hazard model stratified by the randomisation stratification factors to calculate the HR. In order to account for the group sequential design in this study, the repeated CI (RCI) method was used to construct the two-sided RCI for the HR. **Key secondary endpoints: PFS and OS in patients unselected for PD-L1 expression** The methodology used for the primary analyses of PFS and OS in patients with PD-L1 positive tumours was followed for the analyses of PFS and OS in patients unselected for PD-L1 expression.

	Other secondary endpoints: **Objective response** The ORR was calculated for each treatment arm along with the two-sided 95% CI using the Clopper–Pearson method. **Disease control** The DCR was summarised by frequency counts and percentages. **Time to response and duration of response** TTR was summarised using simple descriptive statistics and DoR was analysed using KM methodology. KM estimates were presented by treatment arm together with a summary of associated statistics, including the median DoR time with two-sided 95% CI calculated according to the Brookmeyer and Crowley method. **PFS2** PFS2 was summarised by treatment arm using KM methodology. KM estimates were presented by treatment arm together with a summary of associated statistics, including the median PFS2 time with two-sided 95% CI calculated according to the Brookmeyer and Crowley method. **PROs (EQ-5D-5L and FKSI-19)** Statistical methods applied to these data included calculating completion rates and reasons for non-completion. Descriptive summaries of the scores, including absolute values and changes from baseline, were calculated - specifically, mean, SD, median, first and third quartiles, and range.
Sample size, power calculation	For the primary analysis of PFS in patients with PD-L1-positive tumours, 336 events would provide 90% power to detect a HR of 0.65 using a one-sided log-rank test at a significance level of 0.004, with a two-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. For the primary analysis of OS in patients with PD L1 positive tumours, 368 events would provide 90% power to detect a HR of 0.70 using a one-sided log-rank test at a significance level of 0.021, with a four-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. The sample size of approximately 830 patients was based on the following: 1. A median PFS with sunitinib of 11 months and a median PFS with avelumab + axitinib of 16.9 months for PD-L1-positive patients and 15.7 months for patients unselected for PD-L1 expression; this corresponds to a HR of 0.65 and 0.7, respectively, under the exponential model assumption; 2. A median OS with sunitinib of 26.4 months and a median OS with avelumab + axitinib of 37.7 months for PD-L1-positive patients and 35.2 months for patients unselected for PD-L1 expression; this corresponds to a HR of 0.7 and 0.75, respectively, under the exponential model assumption; 3. PFS and OS drop-out rates of approximately 15% and 5%, respectively; 4. 70% of the randomised patients PD-L1-positive; 5. non-uniform patient accrual accomplished over a 21-month period. The sample size of approximately 830 patients would also allow an assessment of PFS and OS in patients unselected for PD-L1 expression.
Data management, patient withdrawals	Unless otherwise specified, all data were evaluated as observed, and no imputation method for missing values was used.

Statistical analysis timepoints	There were four planned analyses: • IA1: Planned for after approximately 235 PFS events (70% of the expected 336 events) had occurred in the PD-L1-positive population (IA for PFS and IA1 for OS). The DCO for this analysis was 20 June 2018, when 253 PFS events had occurred in the PD-L1-positive population. • IA2: Planned for after 336 PFS events had occurred in the PD-L1-positive population (primary analysis for PFS and IA2 for OS). The DCO for this analysis was 28 January 2019, when 309 PFS events had occurred in the PD-L1-postive population. • IA3: Planned for 15 months after the primary analysis for PFS (IA3 for OS). The DCO for this analysis was 28 April 2020. • FA: Planned for after 368 deaths had occurred in the PD-L1-positive population (primary analysis for OS). The DCO for this analysis was 31 August 2023 when 375 deaths had occurred in the PD-L1-positive population.

Abbreviations: CI, confidence interval; DCO, data cutoff; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FKSI-19, Functional Assessment of Cancer Therapy – Kidney Symptom Index-19; FA, final analysis; HR, hazard ratio; IA, interim analysis; KM, Kaplan–Meier; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, progression-free survival on next-line therapy; PRO, patient-reported outcome; RCI, repeated confidence interval; SD, standard deviation; TTR, time to response.
Source: DoF JAVELIN Renal 101 SAP;[108] DoF JAVELIN Renal 101 IA3 CSR;[104] DoF JAVELIN Renal 101 FA CSR.[99]

B.2.4.3 Patient flow in JAVELIN Renal 101

Of the 1,155 patients who were screened, 886 patients were randomised to avelumab + axitinib (n=442) or sunitinib (n=444). Of the 886 randomised patients, 873 received at least one dose of study treatment (434 patients in the avelumab + axitinib arm and 439 patients in the sunitinib arm). At the final analysis (DCO 31 August 2023), 418 (94.6%) patients had discontinued avelumab, 415 (93.9%) had discontinued axitinib, and 434 (97.7%) patients had discontinued sunitinib. Disease progression was the primary reason for discontinuation of avelumab and axitinib (46.6% and 50.2%, respectively) and sunitinib (59.9%). Patient disposition is summarised in Table 11.[99] For summaries of patient disposition in the interim analyses (IA1, IA2 and IA3) please refer to the corresponding CSRs.[99,104–106]

Table 11: Summary of patient disposition | Full analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants	Avelumab + axitinib (n=442)		Sunitinib (n=444)
	Avelumab	Axitinib	
Discontinued	418 (94.6)*	415 (93.9)*	434 (97.7)
Death	25 (5.7)	28 (6.3)	22 (5.0)
Progressive disease	206 (46.6)	222 (50.2)	266 (59.9)
Adverse event	109 (24.7)	77 (17.4)	65 (14.6)
Non-compliance with study drug	[redacted]	[redacted]	[redacted]
Physician decision	21 (4.8)	20 (4.5)	9 (2.0)
Protocol deviation	[redacted]	[redacted]	[redacted]
No longer meets eligibility criteria	[redacted]	[redacted]	[redacted]
Global deterioration of health status	18 (4.1)	23 (5.2)	20 (4.5)

Withdrawal by participant	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Other	7 (1.6)	9 (2.0)	6 (1.4)
Ongoing	24 (5.4)	27 (6.1)	10 (2.3)

*In the avelumab + axitinib arm, 7 (1.6%) patients discontinued avelumab but not axitinib, 4 (0.9%) patients discontinued axitinib but not avelumab, and 411 (93%) patients discontinued both treatments.
Abbreviations: DCO, data cutoff.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

Patients who discontinued treatment and continued in the study could proceed into the follow-up phase or directly into long-term follow-up phase (if the patient initiated subsequent anti-cancer therapy at the end of treatment or by patient request). As of the DCO date, there were 185 (41.9%) and 332 (75.1%) patients in the avelumab + axitinib arm, and 151 (34.0%) and 359 (80.9%) patients in the sunitinib arm, ongoing in the follow-up and long-term follow-up phases, respectively.[99]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of JAVELIN Renal 101 was conducted using the NICE checklist (based on Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care [University of York Centre for Reviews and Dissemination]) and is described further in Appendix D.[109] This assessment concluded that JAVELIN Renal 101 was methodologically robust and had low risk of bias overall, with an appropriate randomisation scheme, well-balanced patient characteristics between the treatment arms, no unexpected imbalances in dropouts between treatment arms, and good quality assurance for the trial (Table 12).

Although JAVELIN Renal 101 was a high-quality trial, as evidenced in Table 12, patients were not randomised to the trial according to IMDC (Heng) prognostic subgroups. Subgroup analyses (for PFS, OR and DoR per blinded independent central review [BICR] assessment and OS based on the FAS) according to Heng prognostic criteria at baseline (favourable, intermediate, and poor) were pre-specified in the SAP, but were exploratory with no adjustment for multiplicity, and the intermediate and poor subgroups were pooled in a *post hoc* analysis.[108] This approach has been accepted by NICE in appraisals for other IO-based therapies.[7,13–15]

Table 12: JAVELIN Renal 101 | Critical appraisal

Question	JAVELIN Renal 101
Was the randomisation method adequate?	Yes. Patients were centrally assigned to randomised in a 1:1 ratio to treatment with avelumab + axitinib or sunitinib, via an interactive response technology system. Randomisation was stratified by ECOG performance status and region. However, subgroups were not stratified by baseline characteristics and there were minor differences between the subgroups, although baseline characteristics were generally balanced between the treatment arms within the risk subgroups (see Section B.2.3.3).
Was the allocation adequately concealed?	Due to the different routes of administration, concealment of treatment allocation was not possible. For PFS, BICR was used to minimise bias (see below).

Were the groups similar at the outset of the study in terms of prognostic factors?	In patients irrespective of PD-L1 expression as well as in patients with PD-L1-positive tumours, similar distributions of ECOG performance status, MSKCC and IMDC (Heng) prognostic criteria at baseline were observed in both treatment arms. Baseline characteristics were balanced between the treatment arms within the risk subgroups, with the exception of the sunitinib arm containing a greater proportion of male patients ([redacted]) vs the avelumab + axitinib arm ([redacted]) in the favourable-risk subgroup.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Although JAVELIN Renal 101 was an open-label study, BICR was used to minimise bias that could be introduced into the assessment by the investigator, based on the knowledge of treatment assignment at randomisation. To mitigate the potential for bias in determining disease progression, expedited BICR review was performed for investigator-assessed disease progression. All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory. All patients' files and radiologic images must be available for source verification and peer review.
Were there any unexpected imbalances in drop-outs between groups?	No. Patients discontinued avelumab (94.6%), axitinib (93.9%), and sunitinib (97.7%) in comparable proportions.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the clinical study report.
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. Efficacy analyses were performed using the full analysis set, defined as all randomised patients. Unless otherwise specified, all data were evaluated as observed, and no imputation method for missing values was used.
Was there good quality assurance for this trial?	Yes. The trial was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki Council and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, applicable ISO 14155 guidelines, medical device guidelines, and other applicable laws and regulations, including privacy laws. A quality assurance audit was conducted.

Abbreviations: BICR, blinded independent central review; CIOMS, Council for International Organization of Medical Sciences; ECOG, Eastern Cooperative Oncology Group; GCP, good clinical practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMDC, International Metastatic RCC Database Consortium; ISO, International Organization for Standardization; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death ligand 1; PFS, progression-free survival.
Sources: DoF JAVELIN Renal 101 protocol;[107] DoF JAVELIN Renal 101 FA CSR.[99]

A discussion around the strengths and limitations of JAVELIN Renal 101 is presented in Section B.2.13.2.

B.2.6 Clinical effectiveness results of the relevant trials

As previously discussed, since the recommendation of avelumab + axitinib within the CDF, there has been a significant evolution in the treatment pathway for untreated aRCC. In UK clinical practice, the IMDC prognostic model is used to categorise patients into risk groups for survival: (i) favourable-risk and (ii) intermediate-/poor-risk.[12] This baseline prognostic categorisation is used to determine first-line treatment options.[1] Aligned with the evolution of the treatment pathway, efficacy data from the final analysis (FA) (DCO 31 August 2023) of

JAVELIN Renal 101 in this submission are presented separately for the (i) favourable-risk and (ii) intermediate-/poor-risk groups according to IMDC (Heng) prognostic criteria (unselected for PD-L1 expression status).

Avelumab + axitinib is licensed across all risk populations based on IMDC (Heng) prognostic criteria. JAVELIN Renal 101 reports numerically improved efficacy results in favourable-risk patients. Avelumab + axitinib is also efficacious in the pooled intermediate-/poor-risk group, which has the highest number of patients (please note, the study was not powered to show significance within these subgroups). The distribution of IMDC risk subgroups within the study is in line with the proportion of patients within each IMDC risk group observed in England.[25]

For completeness, data for the full (intention-to-treat) population across the different analysis points are summarised in Table 13 below, and more detailed information is available in the FA CSR.[99]

Table 13: Summary of PFS (by investigator assessment) and OS results in the ITT population | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=442)	Sunitinib (n=444)
PFS in the overall population		
Median follow up, months (95% CI)	Not reported	Not reported
Median PFS, months (95% CI)	13.9 (11.1, 16.6)	8.5 (8.2, 9.7)
HR (95% CI); 1 sided p value	0.66 (0.565, 0.768) <0.0001	
OS in the overall population		
Median follow-up, months (95% CI)	73.7 (72.3, 74.6)	73.6 (72.0, 75.5)
Deaths, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	44.8 (39.7, 51.1)	38.9 (31.4, 45.2)
HR (95% CI); 1-sided p-value	0.88 (0.749, 1.039) 0.0669	

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: DoF JAVELIN Renal 101 FA CSR;[99] Motzer *et al.* Abstract 4508, ASCO (2024).[98]

The submission for TA645 was primarily based on the results of IA1 (the primary analysis for PFS in PD-L1 positive patients, and a summary of the results of IA2 were also presented where available at the time of submission.[1] As shown in the summary table in Appendix M.1, the PFS and OS results of the FA were consistent with those of the previous three interim analyses.[99,104]

Results are presented irrespective of PD-L1 status as per the overall patient population specified in the NICE scope; however, sub-group results for patients with IMDC favourable and intermediate-/poor-risk and PD-L1+ tumours are presented in Section B.2.7 in line with the NICE scope.

B.2.6.1 JAVELIN Renal 101 | Favourable-risk according to IMDC (Heng) prognostic criteria

B.2.6.1.1 Overall survival

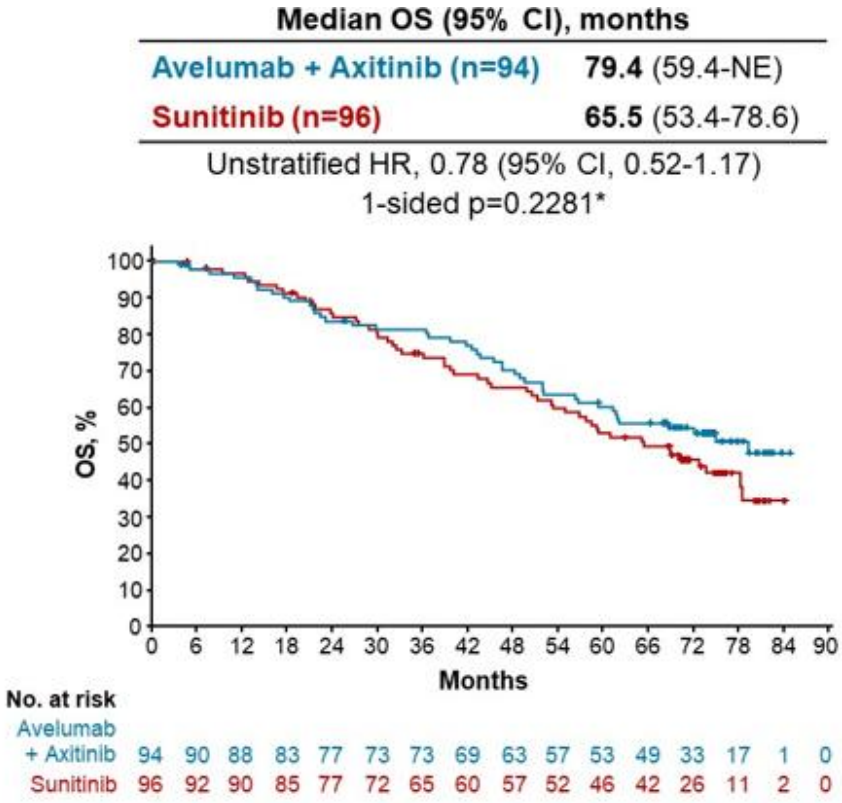
At FA, 96 deaths had occurred (44 [46.8%] in the avelumab + axitinib arm and 52 [54.2%] in the sunitinib arm), resulting in a numerical 27% reduction in risk with avelumab + axitinib compared with sunitinib (stratified HR=0.73 [95% CI: 0.48, 1.10]; p=0.1290; unstratified HR=0.78 [95% CI: 0.52, 1.17]; p=0.2281;Table 14).[98,100] Median OS was 14 months longer in the avelumab + axitinib arm (79.4 months [95% CI: 59.4, not estimable]) than the sunitinib arm (65.5 months [95% CI: 53.4, 78.6]).[98] The numerical risk reduction was evidenced by a clear separation of survival curves from approximately 30 months, which continued to the end of follow-up (Figure 6).[98]

Table 14: Summary of OS for patients with favourable-risk disease | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=94)	Sunitinib (n=96)
Events (deaths), n (%)	44 (46.8)	52 (54.2)
HR (stratified)	0.73	
95% CI	0.48, 1.10	
p-value (Log rank, stratified)	0.1290	
HR (unstratified)	0.78	
95% CI	0.52, 1.17	
p-value (Log rank, unstratified)	0.2281	
Median OS (95% CI), months	79.4 (59.4, NE)	65.5 (53.4, 78.6)
Survival rate, % (95% CI)		
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
72 months	[redacted]	[redacted]
84 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DCO, data cutoff; HR, hazard ratio; NE, not estimable; OS, overall survival.
Source: Motzer *et al.* Abstract 4508, ASCO (2024);[98] DoF JAVELIN Renal 101 FA - additional analyses.[100]

Figure 6: Kaplan–Meier plot of OS for patients with favourable-risk disease | Final analysis (DCO 31 August 2023)



Abbreviations: HR, hazard ratio; LCI, lower limit of the confidence interval; NA, not applicable; OS, overall survival; UCI, upper limit of the confidence interval.
Source: Motzer *et al.* Abstract 4508, ASCO (2024).[98]

B.2.6.1.2 Progression-free survival

PFS was only assessed by BICR for the preplanned interim and primary analyses for PFS (IA1 and IA2 with DCO dates of 20 June 2018 and 28 January 2019, respectively).[105,106] BICR activities subsequently ended and PFS was assessed by the investigator for IA3 and for the FA presented in this submission.[99]

Although the trial was not powered to determine statistical significance within IMDC subgroups, at the FA, PFS (by investigator assessment) in the avelumab + axitinib was numerically favourable compared with sunitinib in patients with favourable-risk according to IMDC prognostic criteria, irrespective of PD-L1 status (Table 15; Figure 7).[100] The median PFS was 20.7 months (95% CI: 16.6, 26.2) and 13.8 months (95% CI: 11.1, 23.5) in the avelumab + axitinib and sunitinib arms, respectively. Therefore, patients who received avelumab + axitinib had a 25% reduction in the risk of progression or death, compared with those who received sunitinib (stratified HR=0.75; 95% CI: 0.53, 1.07; log rank, p-value=0.1109). The event-free rate was higher for avelumab + axitinib than with sunitinib at Months 12 through to 72.[100]

A KM plot of PFS (by investigator assessment) in patients with favourable-risk irrespective of PD-L1 status is shown in Figure 7. The effect of avelumab + axitinib compared with sunitinib was apparent at the time of the first tumour assessment and remained throughout the follow-up period.[100]

Table 15: Summary of PFS by investigator assessment for patients with favourable-risk disease | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=94)	Sunitinib (n=96)
Events, n (%)	76 (80.9)	69 (71.9)
Death	2 (2.1)	2 (2.1)
Progressive disease	74 (78.7)	67 (69.8)
HR (stratified)	0.75	
95% CI	0.53, 1.07	
p-value (Log rank, stratified)	0.1109	
HR (unstratified)	0.75	
95% CI	0.54, 1.04	
p-value (Log rank, unstratified)	0.0873	
Median PFS (95% CI), months	20.7 (16.6, 26.2)	13.8 (11.1, 23.5)
Event-free rate, % (95% CI)		
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
72 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

Figure 7: Kaplan–Meier plot of PFS by investigator assessment for patients with favourable-risk disease | Final analysis (DCO 31 August 2023

Abbreviations: HR, hazard ratio; LCI, lower limit of the confidence interval; PFS, progression-free survival; UCI, upper limit of the confidence interval.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

B.2.6.1.3 Objective response

A summary of best overall response, objective response and disease control rates is shown in Table 16. The ORR for avelumab + axitinib was almost 30%-points higher than for sunitinib (75.5% and 45.8%, respectively).[100] The proportion of patients with a CR was also numerically higher in the avelumab + axitinib arm compared with the sunitinib arm (9.6% and 5.2%, respectively), while the proportion of patients with a best response of PD was lower in the avelumab + axitinib arm ([redacted]%) compared with the sunitinib arm ([redacted]%). In addition, a larger proportion of patients in the avelumab + axitinib arm attained disease control ([redacted]%) compared with those in the sunitinib arm ([redacted]%).[100]

Table 16: Summary of objective response by investigator assessment for patients with favourable-risk disease | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=94)	Sunitinib (n=96)
Confirmed best overall response, n (%)		
Complete response (CR)	9 (9.6)	5 (5.2)
Partial response (PR)	[redacted] ([redacted])	[redacted] ([redacted])

Stable disease (SD)	[redacted]	[redacted]
Non-CR/non-PD	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Not evaluable (NE)	[redacted]	[redacted]
Reason for NE, n (%)		
No adequate BL assessment	[redacted]	[redacted]
No post-BL assessments due to early death	[redacted]	[redacted]
No post-BL assessments due to other reasons	[redacted]	[redacted]
All post-BL assessments have OR of NE	[redacted]	[redacted]
New anti-cancer therapy started before first post-BL assessment	[redacted]	[redacted]
SD too early (<6 weeks after randomisation)	[redacted]	[redacted]
Objective response (CR + PR), n (%)	71 (75.5)	44 (45.8)
95% CI	65.6, 83.8	35.6, 56.3
Disease control (CR + PR + SD + non CR/non-PD), n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

*Clopper-Pearson method used.
Abbreviations: BL, baseline; CI, confidence interval; CR, complete response; DCO, data cutoff; NE, not evaluable; OR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

B.2.6.1.4 Time to response and duration of response

Median time to response (TTR) was [redacted] months ([redacted] to [redacted] months) in the 71 patients with confirmed CR/PR to avelumab + axitinib.[100] In the 44 patients with a response to sunitinib, the median TTR was [redacted] months ([redacted] to [redacted] months).[100]

Among the 71 patients with a response to avelumab + axitinib, median DoR was 23.4 months (95% CI, 16.6 to 29.2). In the sunitinib arm, DoR among the 44 patients with a response was 20.8 months (95% CI, 14.5 to 24.9).[99]

B.2.6.2 JAVELIN Renal 101 | Intermediate-/poor-risk according to IMDC (Heng) prognostic criteria

B.2.6.2.1 Overall survival

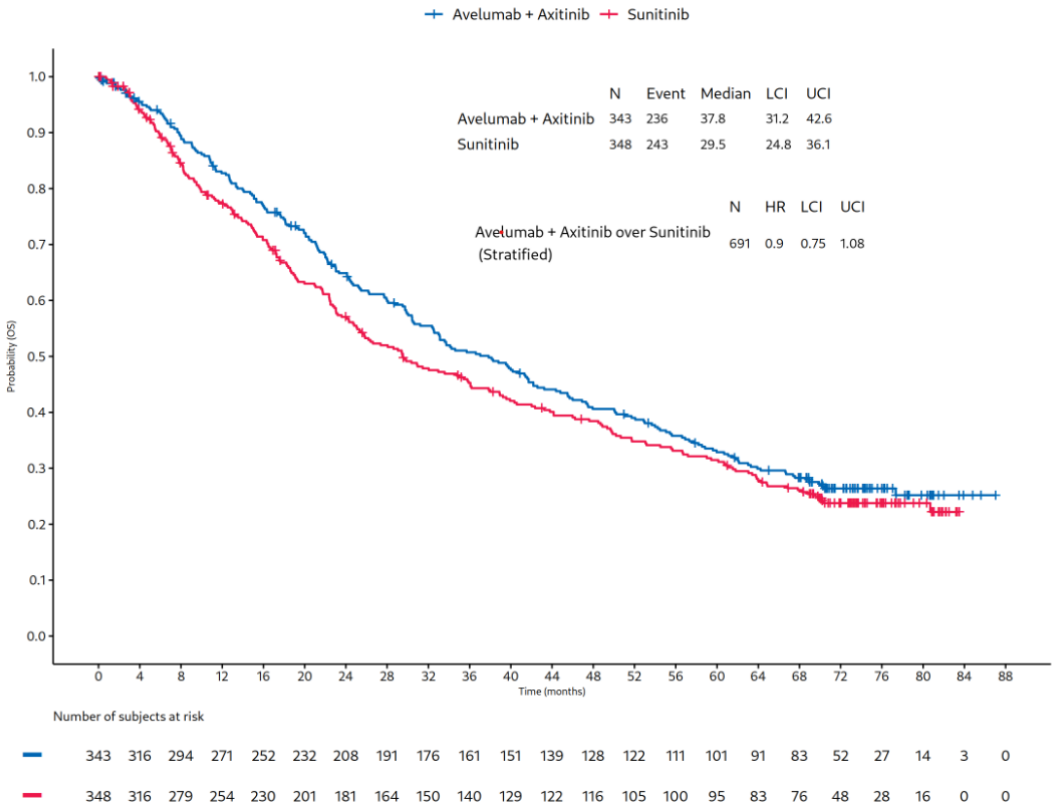
By FA, 479 deaths were observed in the trial (236 [68.8%] in the avelumab + axitinib arm and 243 [69.8%] in the sunitinib arm.[100] Median OS was 37.8 months (95% CI: 31.2, 42.6) in the avelumab + axitinib arm, and 29.5 months (95% CI: 24.8, 36.1) in the sunitinib arm (Table 17), the results indicate a trend in OS favouring avelumab + axitinib compared with sunitinib (stratified HR=0.90 [95% CI: 0.75, 1.08] log rank, primary p=0.2471).[100]

Table 17: Summary of OS for patients with intermediate-/poor-risk disease | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=343)	Sunitinib (n=348)
Events (deaths), n (%)	236 (68.8)	243 (69.8)
HR (primary, stratified)	0.90	
95% CI	0.75, 1.08	
p-value (Log rank, primary)	0.2471	
HR (primary, unstratified)	0.88	
95% CI	0.74, 1.06	
p-value (Log rank, primary)	0.1739	
Median OS (95% CI), months	37.8 (31.2, 42.6)	29.5 (24.8, 36.1)
Survival rate, % (95% CI)		
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
72 months	[redacted]	[redacted]
84 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DCO, data cutoff; HR, hazard ratio; ND, not evaluable; OS, overall survival.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

Figure 8: Kaplan–Meier plot of OS for patients with intermediate-/poor-risk disease | Final analysis (DCO 31 August 2023)



Abbreviations: HR, hazard ratio; LCI, lower limit of the confidence interval; OS, overall survival; UCI, upper limit of the confidence interval.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

B.2.6.2.2 Progression-free survival

At FA, though the trial was not powered to detect statistical significance in IMDC subgroups, PFS by investigator assessment favoured treatment with avelumab + axitinib compared with sunitinib (Table 18).[100] The median PFS was 11.1 months (95% CI: 9.8, 14.6) and 8.1 months (95% CI: 6.9, 8.4) in the avelumab + axitinib and sunitinib arms, respectively.[100] Therefore, patients who received avelumab + axitinib had a 36% reduction in risk of progression or death (stratified HR=0.64; 95% CI: 0.54, 0.76; log rank, primary p<0.0001).[100] The probability of being event free was higher for avelumab + axitinib than sunitinib at all timepoints assessed from 12 months, with the survival curves of the Kaplan–Meier continuing to show separation up to the end of follow-up (Figure 9).[100]

Table 18: Summary of PFS by investigator assessment for patients with intermediate-/poor-risk disease | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=343)	Sunitinib (n=348)
Events, n (%)	263 (76.7)	276 (79.3)
Death	22 (6.4)	16 (4.6)
Progressive disease	241 (70.3)	260 (74.7)

HR (primary, stratified)	0.64	
95% CI	0.54, 0.76	
p-value (Log rank, primary, stratified)	<0.0001	
HR (primary, unstratified)	0.64	
95% CI	0.54,0.76	
p-value (Log rank, primary, unstratified)	<0.0001	
Median PFS (95% CI), months	11.1 (9.8, 14.6)	8.1 (6.9, 8.4)
Event-free rate, % (95% CI)		
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
72 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

Figure 9: Kaplan–Meier plot of PFS by investigator assessment for patients with intermediate-/poor-risk disease | Final analysis (DCO 31 August 2023)

Abbreviations: HR, hazard ratio; LCI, lower limit of the confidence interval; PFS, progression-free survival; UCI, upper limit of the confidence interval.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

B.2.6.2.3 Objective response

A summary of best overall response, objective response and disease control is shown in Table 19. The ORR for avelumab + axitinib was almost double the ORR for sunitinib, with a 27.5%-point difference in rates (55.7% and 28.2%, respectively).[100] The proportion of patients with a CR was marginally higher in the avelumab + axitinib arm compared with the sunitinib arm (4.7% and 3.2%, respectively) and the proportion with PR was more than double the proportion for sunitinib (51.0% and 25.0%, respectively). The proportion of patients with PD was lower in the avelumab + axitinib arm (10.2%) compared with the sunitinib arm (17.2%).[100]

Table 19: Summary of objective response by investigator assessment for patients with intermediate-/poor-risk disease | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=343)	Sunitinib (n=348)
Confirmed best overall response, n (%)		
Complete response (CR)	16 (4.7)	11 (3.2)
Partial response (PR)	[redacted]	[redacted]

Stable disease (SD)	[redacted]	[redacted]
Non-CR/non-PD	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Not evaluable (NE)	[redacted]	[redacted]
Reason for NE, n (%)		
No adequate BL assessment	[redacted]	[redacted]
No post-BL assessments due to early death	[redacted]	[redacted]
No post-BL assessments due to other reasons	[redacted]	[redacted]
All post-BL assessments have OR of NE	[redacted]	[redacted]
New anti-cancer therapy started before first post-BL assessment	[redacted]	[redacted]
SD too early (<6 weeks after randomisation)	[redacted]	[redacted]
Objective response (CR + PR), n (%)	191 (55.7)	98 (28.2)
95% CI	50.3, 61.0	23.5, 33.2
Disease control (CR + PR + SD + non-CR/non-PD), n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: BL, baseline; CI, confidence interval; CR, complete response; DCO, data cutoff; NE, not evaluable; OR, overall response; PD, progressive disease; PR, partial response; SD, stable disease.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

B.2.6.2.4 Time to response and duration of response

Median TTR was [redacted] months ([redacted] to [redacted] months) in the 191 patients with confirmed CR/PR to avelumab + axitinib.[100] In the 98 patients with a response to sunitinib, the TTR was [redacted] months ([redacted] to [redacted] months).[100]

Among the 191 patients with a response to avelumab + axitinib, median DoR was 19.4 months (95% CI, 14.1 to 22.3). In the sunitinib arm, DoR among the 98 patients with a response was 9.8 months (95% CI, 7.0 to 15.3).[99]

B.2.6.3 JAVELIN Renal 101 | Subsequent treatment | Favourable-risk and intermediate-/poor-risk according to IMDC (Heng) prognostic criteria

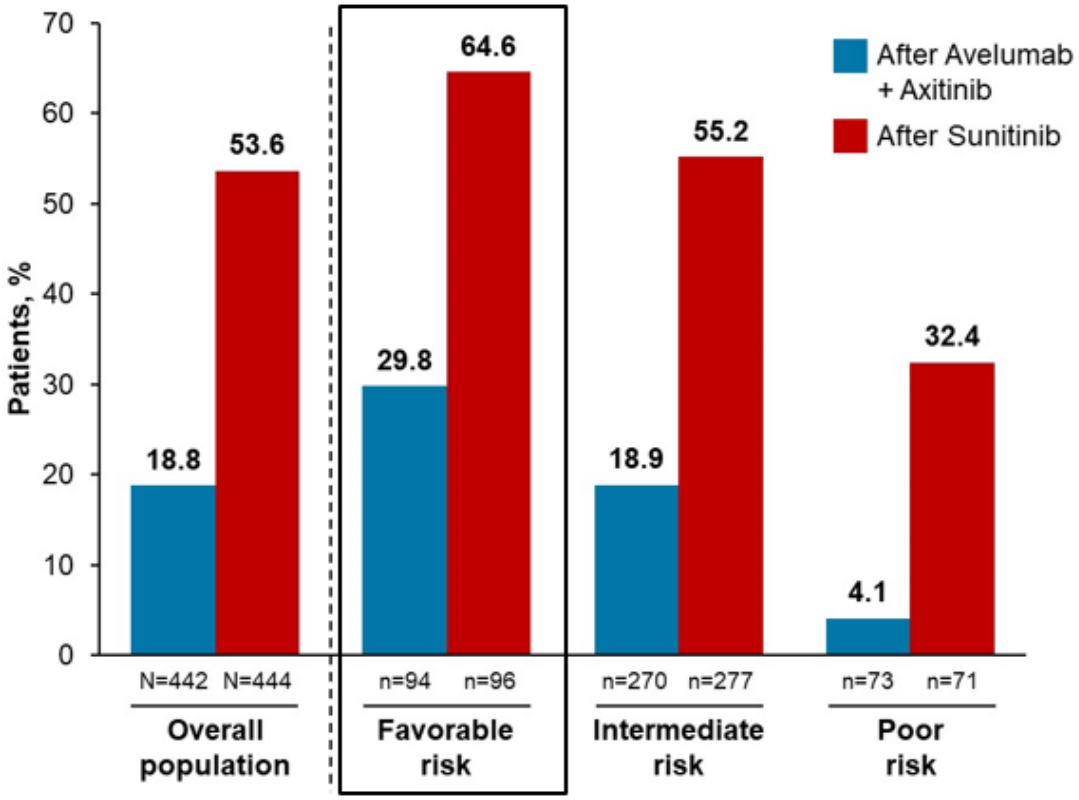
The long duration of follow-up in the final OS analysis of JAVELIN Renal 101 means that outcomes also reflect the impact of subsequent (second and later-line) treatments in both arms.

In the IMDC favourable-risk subgroup, more patients in the sunitinib arm (79.2%) received follow-up anticancer treatment than in the avelumab + axitinib arm (67.0%).[98] Moreover, fewer patients in the avelumab + axitinib arm received subsequent PD-1 or PD-L1 treatment (29.8% of patients) than in the sunitinib arm (64.6%).

For patients with intermediate-/poor-risk, more patients in the sunitinib treatment arm received follow-up anticancer treatment after discontinuation of study treatment compared with the avelumab + axitinib treatment arm (66.7% patients versus 56.3% patients).[98] For patients with intermediate prognostic risk, 55.2% and 18.9% of patients received subsequent PD-1/PD-L1 therapy in the sunitinib and avelumab + axitinib arms, respectively (Figure 10).

For patients with poor prognostic risk, 32.4% and 4.1% of patients received subsequent PD-1/PD-L1 therapy in the sunitinib and avelumab + axitinib arms, respectively.

Figure 10: Subsequent PD-1 or PD-L1 inhibitor treatment | ITT population and in IMDC risk groups | Final analysis (DCO 31 August 2023)



Abbreviations: PD-1, programmed death-1, PD-L1, programmed death-ligand 1.
Source: Motzer *et al.* Abstract 4508, ASCO (2024).[98]

B.2.6.4 JAVELIN Renal 101 | PROs | Overall population

The JAVELIN Renal 101 trial used the EuroQol 5-Dimension 5-Level (EQ-5D-5L) and Functional Assessment of Cancer Therapy – Kidney Symptom Index-19 (FKSI-19) questionnaires to assess PROs .[108] In both treatment arms, EQ-5D-5L index scores and FKSI-19 total scores remained relatively stable over time until approaching end of treatment, whereas slight improvement was observed for the EQ-VAS.[99] PROs were similar between the treatment arms, suggesting that adding avelumab to TKI treatment had no adverse impact on HRQoL.

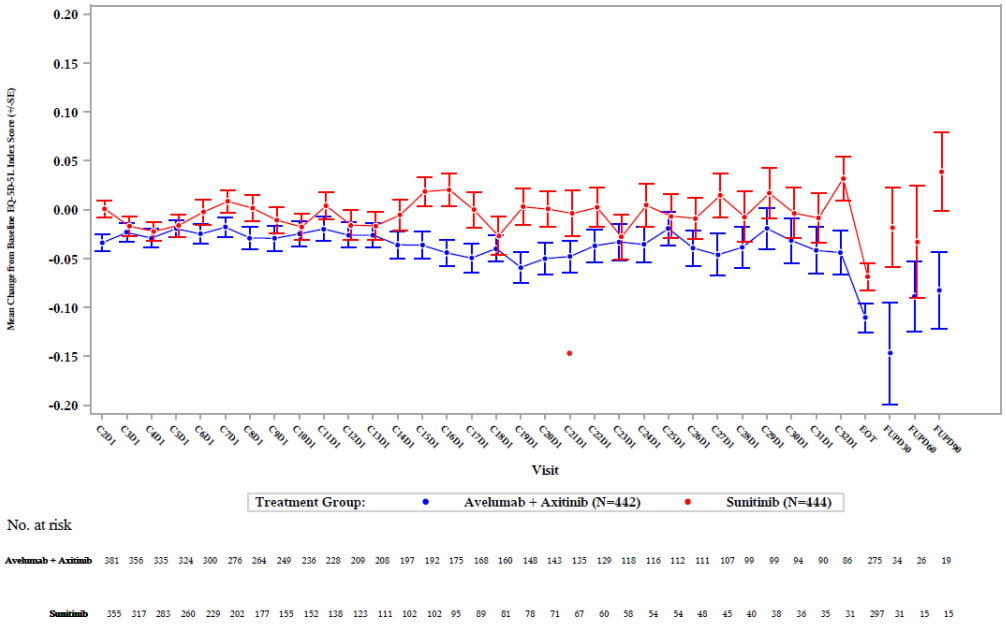
B.2.6.4.1 EQ-5D-5L

In the FAS, patients treated with avelumab + axitinib (N=442) had EQ-5D-5L questionnaire completion rates of 95.4% at baseline, which remained above 90.0% through to Cycle 60 Day 1 and were 72.2% at the end of treatment visit.[99] Equivalent rates in the sunitinib arm (N=444) were 94.4%, above 90.0% through to Cycle 58, and 74.5% at end of treatment visit.[99]

EQ-5D-5L index scores

In the FAS, both treatment groups had similar baseline EQ-5D-5L index scores, with patients treated with avelumab + axitinib having slightly higher mean index score 0.780 (SD=0.20) compared with those treated with sunitinib (mean index score of 0.750; SD=0.21).[99] Over time, there were small differences in changes from baseline through to the end of treatment visit. In the FAS, the mean change in index score for avelumab + axitinib (n=275) was -0.111 (SD=0.25), whereas for sunitinib (n=297) it was -0.069 (SD=0.24). Line plots comparing the profile of mean changes in index scores for the FAS for avelumab + axitinib versus sunitinib show that the mean index scores for sunitinib remained generally elevated throughout the treatment period, and trends for both treatments were flat until approaching end of treatment (Figure 11).[99]

Figure 11: Summary of EQ-5D-5L index scores change from baseline by visit (FAS) | Final analysis (DCO 31 August 2023)

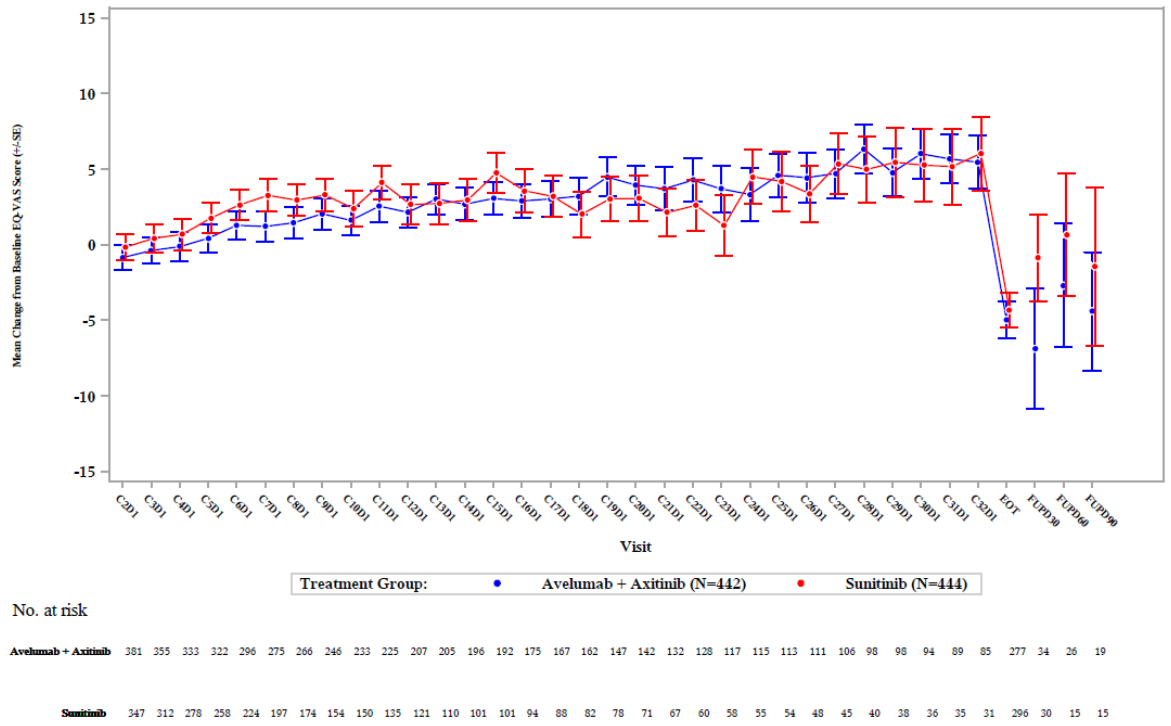


Baseline is the last non-missing measurement prior to randomisation or, if not available, prior to the first dose of study treatment. Unscheduled visits are excluded from the analysis.
Abbreviations: DCO, data cutoff; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FAS, full analysis set.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

EQ-5D-5L VAS

In the FAS, both treatment groups had nearly identical baseline EQ-5D-5L VAS scores, with average VAS scores of 75.9 (SD=19.47) in the avelumab + axitinib arm, and of 74.3 (SD=17.19) the sunitinib arm.[99] Over time, there were small differences in changes from baseline through to the end of treatment visit. The mean change in EQ-5D-5L VAS score for avelumab + axitinib (n=277) was -5.0 (SD=19.92), whereas for sunitinib (n=296) it was -4.3 (SD=19.63). Line plots comparing the profile of mean changes in EQ-5D-5L VAS scores for avelumab + axitinib versus sunitinib show that both treatment groups demonstrated an overlapping pattern of change, with small positive increases in VAS scores until immediately preceding the end of treatment visit (Figure 12).[99]

Figure 12: Summary of EQ-VAS scores change from baseline by visit (FAS) | Final analysis (DCO 31 August 2023) | Final analysis (DCO 31 August 2023)



Baseline is the last non-missing measurement prior to randomisation or, if not available, prior to the first dose of study treatment. Number at risk is the number of participants in the FAS who have EQ-VAS score at baseline and (for the post-baseline visits) at the post-baseline visit. Unscheduled visits are excluded from the analysis.
Abbreviations: DCO, data cutoff; EQ, EuroQol; FAS, full analysis set; VAS, visual analogue scale.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

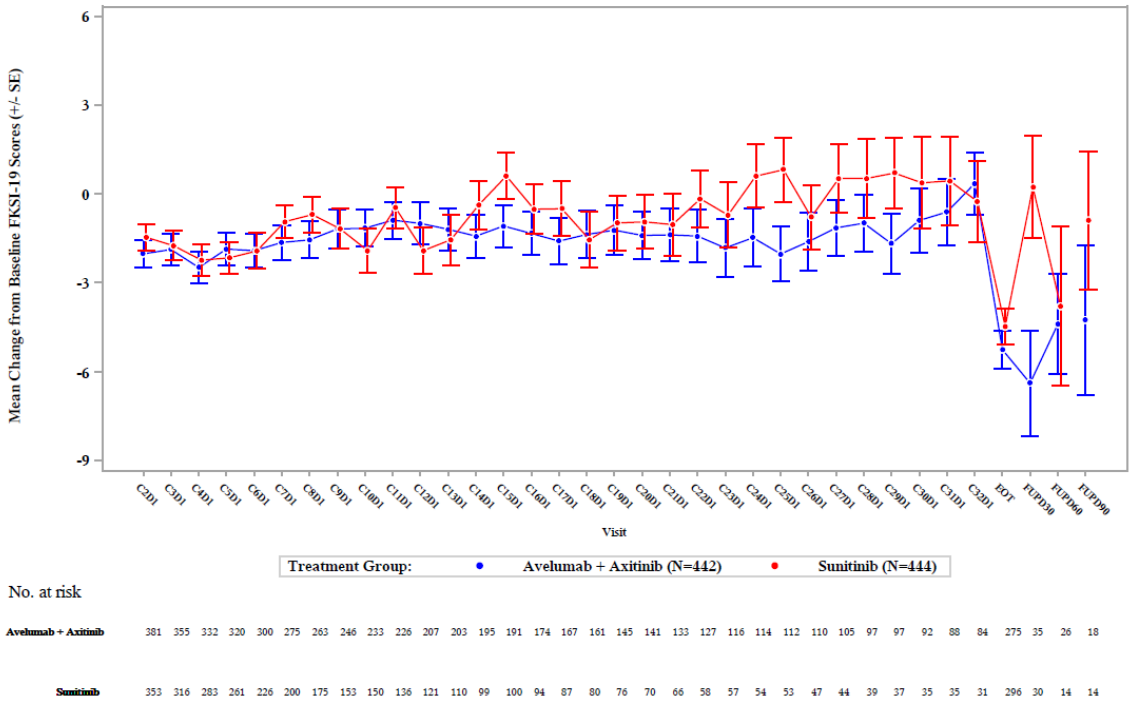
B.2.6.4.2 FKSI-19

In the FAS, patients treated with avelumab + axitinib (N=442) had FKSI-19 questionnaire completion rates of 87.6% at baseline, which remained above 66.7% through to Cycle 60 Day 1, and were 69.8% at end of treatment.[99] Equivalent rates in the sunitinib arm (N=444) were 88.3% at baseline and above this through to Cycle 60 Day 1, and 69.4% at the end of treatment.[99]

In the FAS, both treatment groups had nearly identical baseline FKSI-19 total scores, with average total scores of 58.9 (SD=9.96) in the avelumab + axitinib arm, and 57.9 (SD=9.27) in the sunitinib arm.[99]

Over time, there were small differences in changes from baseline through the end of treatment visit.[99] In the FAS, the mean change in FKSI-19 score for avelumab + axitinib (n=275) was -5.3 (SD=10.40), whereas for sunitinib (n=296) it was -4.5 (SD=10.40). Line plots comparing the profile of mean changes in FKSI-19 scores for the FAS for avelumab + axitinib versus sunitinib show that average scores were similar between groups up until Cycle 21 Day1, where average scores for sunitinib increased compared with avelumab + axitinib through to Cycle 32 Day 1, where average scores converged before decreasing in both groups at the end of treatment visit (Figure 13).[99]

Figure 13: Summary of FKSI-19 scores change from baseline by visit (FAS) | Final analysis (DCO 31 August 2023)



Baseline is the last non-missing measurement prior to randomisation or, if not available, prior to the first dose of study treatment. Number at risk is the number of participants in the FAS who have FKSI-19 score at baseline and (for the post-baseline visits) at the post-baseline visit. Unscheduled visits are excluded from the analysis.
Abbreviations: DCO, data cutoff; FAS, full analysis set; FKSI-19, Functional Assessment of Cancer Therapy – Kidney Symptom Index-19.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.6.4.3 Q-TWiST

In a post hoc exploratory analysis of quality-adjusted time without symptoms or toxicity (Q-TWiST), avelumab + axitinib treatment resulted in a 3.20-month gain in Q-TWiST versus sunitinib (10.9% relative improvement; established clinically important difference ≥10%); see Appendix M.2.[110]

B.2.7 Subgroup analysis

The results presented above are based on subgroup analysis conducted according to IMDC (Heng) prognostic criteria. Additional subgroup analyses have been conducted for patients with PD-L1-positive tumours (see Table 20).[100] Overall, the PFS, objective response and OS results for the patients with PD-L1-positive tumours were generally similar to the FAS, in both the favourable- and intermediate-/poor-risk groups.

Table 20: Summary of efficacy outcomes for patients with PD-L1+ tumours | Final analysis (DCO 31 August 2023)

	Favourable-risk		Intermediate-/poor-risk	
	Avelumab + axitinib (n=52)	Sunitinib (n=59)	Avelumab + axitinib (n=217)	Sunitinib (n=231)
OS				
Events (deaths), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HR (primary, stratified)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value (Log rank, primary, stratified)	[redacted]		[redacted]	
HR (primary, unstratified)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value (Log rank, primary, unstratified)	[redacted]		[redacted]	
Median OS (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
Survival rate, % (95% CI)				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]
60 months	[redacted]	[redacted]	[redacted]	[redacted]
72 months	[redacted]	[redacted]	[redacted]	[redacted]
84 months	[redacted]	[redacted]	[redacted]	[redacted]
PFS by investigator assessment				
Events (PD/deaths), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
HR (primary, stratified)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value (Log rank, primary, stratified)	[redacted]		[redacted]	
HR (primary, unstratified)	[redacted]		[redacted]	
95% CI	[redacted]		[redacted]	
p-value (Log rank, primary, unstratified)	[redacted]		[redacted]	
Median PFS (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]

	Favourable-risk		Intermediate-/poor-risk	
	Avelumab + axitinib (n=52)	**Sunitinib (n=59)**	**Avelumab + axitinib (n=217)**	**Sunitinib (n=231)**
Event-free rate, % (95% CI)				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]
60 months	[redacted]	[redacted]	[redacted]	[redacted]
72 months	[redacted]	[redacted]	[redacted]	[redacted]
Objective response				
Confirmed best overall response, n (%)				
Complete response (CR)	[redacted]	[redacted]	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Non-CR/non-PD	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable (NE)	[redacted]	[redacted]	[redacted]	[redacted]
Reason for NE, n (%)				
No adequate BL assessment	[redacted]	[redacted]	[redacted]	[redacted]
No post-BL assessments due to early death	[redacted]	[redacted]	[redacted]	[redacted]
No post-BL assessments due to other reasons	[redacted]	[redacted]	[redacted]	[redacted]
All post-BL assessments have overall response of NE	[redacted]	[redacted]	[redacted]	[redacted]
New anti-cancer therapy started before first post-BL assessment	[redacted]	[redacted]	[redacted]	[redacted]
SD too early (<6 weeks after randomisation)	[redacted]	[redacted]	[redacted]	[redacted]
Objective response (CR + PR), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI*	[redacted]	[redacted]	[redacted]	[redacted]
Disease control (CR + PR + SD + non-CR/non-PD), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; CI, confidence interval; CR, complete response; DCO, data cutoff; ND, not determined; OR, overall response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Source: DoF JAVELIN Renal 101 FA - additional analyses.[100]

Among the [redacted] patients with confirmed CR/PR to avelumab + axitinib in the favourable-risk group, median TTR was [redacted] months (range: [redacted] to [redacted] months). In the [redacted] patients with a response to sunitinib, the median TTR was [redacted] months ([redacted] to [redacted] months).[100]

In the intermediate-/poor-risk group, median TTR was [redacted] months ([redacted] to [redacted] months) among the [redacted] patients with a response to avelumab + axitinib, and [redacted] months ([redacted] to [redacted] months) in the [redacted] patients with a response to sunitinib.[100]

B.2.8 Real-world evidence of avelumab + axitinib effectiveness

Since its recommendation for inclusion in the CDF in 2020,[1] further evidence on the effectiveness of avelumab in combination with axitinib for the first-line treatment of patients with aRCC has accumulated from various real-world data sources. A systematic literature review (n=9) was conducted to support this appraisal to identify relevant real-world data (see Appendix D), and this has been supplemented with data collected from the SACT database.

Below we present the real-world evidence most generalisable to UK clinical practice, namely that derived from:

- The SACT dataset,[21] collected by NHS England as part of the managed access agreement for CDF entry for avelumab + axitinib.
- An analysis by Nathan *et al*. (2024) using data from 130 patients who received avelumab + axitinib via an EAMS[93,94]
    - *Note that EAMS patients are included in both the SACT dataset (161 patients, from August 2019 to July 2020) and the Nathan et al. analysis (130 patients, from August 2019 to July 2023).*
- A retrospective review of 1,319 patients from 17 centres in the UK who initiated systemic anti-cancer therapy for the treatment of metastatic RCC between 01 January 2018 and 30 June 2021 (McGrane *et al*. (2024)).[37] Of the 197 patients in the IO+TKI group (across all IMDC risk groups), the majority of patients (85.3%) received avelumab + axitinib.

The analyses presented relate to UK patients with aRCC, and demonstrate that the outcomes observed in the JAVELIN Renal 101 RCT translate into real-world treatment benefits for patients. Briefly:

- In the analysis of real-world data from the SACT dataset, the median OS for all patients was [redacted] months in the CDF cohort (n=[redacted]) and [redacted] months in the EAMS cohort (n=[redacted]).[21] The median treatment duration for all patients in the CDF cohort (n=[redacted]) was [redacted] months and [redacted] months for all patients in the EAMS cohort (n=161).[21]
- For the CDF cohort (IMDC sub-group analysis was not available in EAMS cohort):
    - The median OS for patients with a favourable-risk score was [redacted].[21]

- The median OS for patients with an intermediate-risk score was [redacted] [95% CI: [redacted], [redacted]] ([redacted] days), and the median OS for patients with a poor-risk score was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days).

- OS, PFS, ORR and best responses at 36 months from a UK-based multicentre, retrospective noninterventional cohort study of adults with aRCC (who initiated treatment with avelumab + axitinib via the EAMS) by Nathan *et al*. (2024) are in line with findings from the JAVELIN Renal 101 clinical study and other real-world studies, with no newly emerging AEs.[93,94]

- Data from a multicentre respective review of patients with metastatic RCC conducted across 17 centres in the UK, supports the use of first-line IO+TKI in the favourable-risk group and IO+TKI or IO+IO in the intermediate- and poor-risk groups versus TKI for the treatment of metastatic RCC. The addition of IO for the first-line treatment of metastatic RCC has significant OS and PFS benefits for all patients versus TKI. In the favourable-risk group, there was a significant benefit with IO+TKI versus TKI for OS and PFS.[37]

Overall, real-world studies provide further evidence of the effectiveness of avelumab + axitinib for the first-line treatment of aRCC, including in patients with favourable-risk aRCC, and support the findings from the JAVELIN Renal 101 clinical study, providing validation of the efficacy of avelumab + axitinib in routine clinical practice.

B.2.8.1 RWE SLR overview

A literature review was conducted on 29 July 2024 to support this appraisal to identify relevant real-world data (see Appendix D for more details). The SLR identified nine studies that included real-world treatment of patients with aRCC treated with avelumab + axitinib:

- 4 studies from the UK
  - Nathan *et al* (2024; EAMS 36 months follow-up)[93,94]
  - McGrane *et al*. (2024)[37]
  - Allison *et al* (2021)[111]
  - Fenton *et al* (2023)[112]
- 1 study conducted in Russia (RAVE-Renal)
- 3 studies from Japan – a multicentre retrospective study, prospective multi centre post-marketing surveillance (PMS), and J-DART retrospective medical chart review
- 1 study from the US - Adelphi Disease Specific Programme (DSP) cross sectional study.

Of the four UK studies, the analysis by Nathan *et al*. (2024) using data from 130 patients who received avelumab + axitinib via an EAMS, and the retrospective review by McGrane *et al*. (2024) of 1,319 patients (of whom 168 received avelumab + axitinib) from 17 centres in the UK (UK ROC Study) are discussed in more detail below, together with data collected from the SACT database. The studies by Allison *et al* (2021) and Fenton *et al.* (2023) are not discussed further as they include patients from single centres who were included in the EAMS, so are considered to be already captured in Nathan *et al*. (2024).

The RWE presented shows that the outcomes observed in the JAVELIN Renal 101 RCT translate into real-world treatment benefits for UK patients.

Overview of baseline data from the UK RWE studies

The demographic characteristics of the population assessed across the UK datasets are presented in Table 21. Comparisons of key clinical baseline characteristics from the RWE studies identified with the JAVELIN Renal 101 trial population show that characteristics reported in real-world populations, such as the proportion of patients by age, prior nephrectomy, clear-cell type histology, and IMDC poor-risk, fall within the range observed in the JAVELIN Renal 101 trial, indicating that JAVELIN Renal 101 is generalisable to UK clinical practice.

Table 21: Patient demographics and clinical characteristics at baseline (UK RWE datasets and JAVELIN Renal 101)

Study name (Trial name)	Treatment	Age: median (range)	Sex: n (%) Male Female	Metastatic site: n (%) Lung Liver Bone Brain	Histology: n (%) Clear cell Non-clear cell Other	Prior therapy: n (%) Surgery Radiotherapy	ECOG performance status: n (%) 0 1 2	Risk group (IMDC): n (%) Good/favourable Intermediate Poor/high
NHS England SACT dataset (CDF cohort)[21]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NHS England SACT dataset (EAMS cohort)[21]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nathan 2024[93]	Avelumab + axitinib	67.1 (35.8–87)	96 (73.8) 34 (26.1)	87 (67) 18 (14) 28 (22) 5 (4)	115 (88) 7 (5) 8 (6)	72 (55) NR	61 (47) 61 (47) 6 (5)	51 (39) 52 (40) 25 (19)
McGrane 2024[37] (ROC study)	IO + TKI (85.3% = avelumab + axitinib)	NR (29–86)	142 (72.1) 55 (27.9)	NR NR NR NR	171 (87) NR (6)¥ NR (4)	120 (61) NR	NR NR NR	66 (33) 96 (49) 34 (17)

Study name (Trial name)	Treatment	Age: median (range)	Sex: n (%) Male Female	Metastatic site: n (%) Lung Liver Bone Brain	Histology: n (%) Clear cell Non-clear cell Other	Prior therapy: n (%) Surgery Radiotherapy	ECOG performance status: n (%) 0 1 2	Risk group (IMDC): n (%) Good/favourable Intermediate Poor/high
Motzer 2019 (JAVELIN Renal 101)[103]	Avelumab 10 mg/kg Q2W + axitinib 5 mg bid	62 (29–83)	316 (71.5) 126 (28.5)	NR	All patients had histologically or cytologically confirmed aRCC* with a clear cell component[107]	352 (79.6) NR	284 (64.3) 157 (35.5) 0	94 (21.3) 271 (61.3) 72 (16.3)

*aRCC included unresectable locally advanced and metastatic disease.

¥Study reported papillary RCC (non clear-cell RCC) as next most common subtype (5.6%); however data on other non-clear cell RCC subtypes was not reported.

Abbreviations: BID, twice daily; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IO, immunotherapy; NR, not reported; SACT, Systemic Anti-Cancer Cancer Therapy; TKI, tyrosine kinase inhibitor.

B.2.8.2 NHS England SACT data

NHS England has evaluated the real-world effectiveness of avelumab + axitinib for untreated advanced or metastatic RCC in clinical practice in England using the SACT dataset collected by the NDRS.[21] This data collection was conducted to inform the NICE Appraisal Committee for the review of TA645. OS and treatment duration were evaluated.[21] Treatment duration was not an area of clinical uncertainty in TA645 but was included in the analysis. OS, PFS and treatment duration results were explored by IMDC risk group, in a further sensitivity analysis of the CDF cohort.[21]

B.2.8.2.1 Patient population

Using the NHS England Blueteq® System, [redacted] CDF and [redacted] EAMS applications were identified between 31 July 2020 and 29 February 2024 and August 2019 to July 2020, respectively.[21] To qualify for avelumab + axitinib treatment via the CDF, patients:

- Had unresectable locally advanced or metastatic RCC, either completely treatment-naïve for systemic immune-modulatory therapy for RCC (or if they had received prior systemic immune-modulatory therapy in the context of adjuvant/neoadjuvant therapy, then this was completed ≥12 months previously)
- Had ECOG performance status ≤1
- Had a confirmed risk score assessment
- Were not receiving steroids for symptomatic brain/leptomeningeal metastases.

Requirements were similar for the EAMS, but no use of investigational drug(s)/experimental interventions within 30 days was also stipulated. Following exclusions, [redacted] unique CDF patients and [redacted] unique EAMS patients were included in the final cohorts.[21] Baseline demographics and clinical characteristics are provided in Table 22.

Table 22: Baseline demographics and clinical characteristics

	CDF cohort N=[redacted]	EAMS cohort N=[redacted]
Age, median, years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
ECOG PS at treatment initiation, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]
IMDC status at treatment initiation, n (%)		
0 (favourable-risk disease)	[redacted]	
1 or 2 (intermediate-risk disease)	[redacted]	
3 to 6 (poor-risk disease)	[redacted]	
Not captured	[redacted]	[redacted]
Histological subtype, n (%)		
RCC with clear cell component	[redacted]	
Unclassified RCC	[redacted]	
Xp11 translocation RCC	[redacted]	
Collecting duct RCC (bellini collecting duct RCC)	[redacted]	
Papillary RCC	[redacted]	
Chromophobe RCC	[redacted]	
Medullary RCC	[redacted]	
Mucinous tabular and spindle cell RCC	[redacted]	
Not recorded	[redacted]	[redacted]

Previous systemic therapy for RCC, n (%)		
No previous adjuvant/neoadjuvant systemic therapy of any kind and treatment naïve for the locally advanced/metastatic RCC indication	[redacted]	[redacted]
Prior adjuvant/neoadjuvant therapy for RCC with agents which target VEGF, and the last dose received by the patient was ≥12 months prior to this application and treatment naïve for the locally advanced/metastatic RCC indication	[redacted]	
Not captured	[redacted]	[redacted]

Abbreviations: aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; ECOG PS, Eastern Cooperative Oncology Group performance status; EAMS, Early Access to Medicines Scheme; IMDC, International Metastatic RCC Database Consortium.
Source: DoF (NHS England SACT report, 2024).[21]

B.2.8.2.2 OS | CDF and EAMS cohorts

Median follow-up time (median observed time from the start of treatment to death or censored date) was [redacted] months ([redacted] days) and [redacted] months ([redacted] days) for the CDF and EAMS cohort, respectively.[21]

The maximum follow-up period for survival was [redacted] months and [redacted] months for the CDF and EAMS cohort, respectively.[21] At the end of the follow-up period (2 July 2024), [redacted] patients in the CDF cohort had died and [redacted] patients were alive; in the EAMS cohort [redacted] patients had died and [redacted] patients were alive.[21]

The median OS for all patients in the CDF cohort (n=[redacted]) was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days) and for all patients in the EAMS cohort (n=[redacted]) median OS was [redacted] months ([redacted] days).[21]

A sensitivity analysis was conducted for OS for a cohort with at least 6 months of data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.[21]

OS by IMDC risk group

A secondary sensitivity analysis was performed comparing OS by IMDC risk factors (good [favourable; IMDC score 0], intermediate [IMDC score 1 or 2] and poor [IMDC score 3–6] for the CDF cohort. The median OS for patients with a favourable-risk score was [redacted].[21] The median OS for patients with an intermediate-risk score was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days), and the median OS for patients with a poor-risk score was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days).[21] In comparison, the median OS for favourable-risk patients in JAVELIN Renal 101 was 79.4 months (see Section B.2.6.1.1) and for intermediate-/poor risk patients was 37.8 months (see Section B.2.6.2.1).[100] IMDC risk categorisation was not collected for the EAMS cohort.

OS by RCC histology

A third sensitivity analysis was performed comparing OS by RCC histology (clear cell, non-clear cell) for the CDF cohort. The median OS for patients with clear cell RCC was [redacted] months [95% CI: [redacted] and the median OS for patients who did not have clear cell RCC was [redacted] months [95% CI: [redacted]]. Results were statistically significantly different between the two groups. RCC histology was not collected for the EAMS cohort.[21]

OS over time

OS over time is presented in Table 23. OS was longer in the EAMS cohort than in the CDF cohort. The difference was statistically significant at 18, 24 and 36 months.[21]

Table 23: Landmark OS at 6, 12, 18, 24, 36 and 48-month intervals

Time period	OS CDF cohort, (95% CI)	OS EAMS cohort, (95% CI)
6 months	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
12 months	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
18 months	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
24 months	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
36 months	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
48 months		[redacted] ([redacted], [redacted])

Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; EAMS, Early Access to Medicines Scheme; OS, overall survival; SACT, Systemic Anti-Cancer Cancer Therapy.
Source: DoF (NHS England SACT report, 2024).[21]

B.2.8.2.3 Treatment duration | CDF and EAMS cohorts

Of the [redacted] patients in the CDF cohort, [redacted] patients ([redacted]%) were identified as having completed treatment by 29 February 2024 (latest follow-up in SACT dataset).[21] Of the [redacted] patients in the EAMS cohort, [redacted] patients ([redacted]%) were identified as having completed treatment.[21]

Median follow-up time (median observed time from initiation of treatment to last treatment date in the SACT dataset plus the length of prescription) was [redacted] months ([redacted] days) and [redacted] months ([redacted] days) for the CDF and EAMS cohort, respectively.[21] At the end of the follow-up period (29 February 2024), [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) had ended treatment in the CDF and EAMS cohort, respectively.[21]

Median treatment duration for all patients in the CDF cohort (n=[redacted]) was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days) and for all patients in the EAMS cohort (n=[redacted]) [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days).[21]

A treatment duration sensitivity analysis was conducted for a cohort with at least 6 months of data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.[21]

Treatment duration by IMDC risk group

A secondary sensitivity analysis was performed comparing treatment duration by IMDC risk factors (good, intermediate and poor) for the CDF cohort. The median treatment duration for patients with a favourable-risk score was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days). The median treatment duration for patients with an intermediate-risk score was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days), and the median treatment duration for patients with a poor-risk score was [redacted] months [95% CI: [redacted], [redacted]] ([redacted] days). Results were statistically significantly different between the three risk groups.[21] IMDC risk factors were not collected for the EAMS cohort.

Treatment duration by RCC histology

A third sensitivity analysis was performed comparing treatment duration and OS by RCC histology (clear cell, non-clear cell) for the CDF cohort. Results were statistically significantly different between the two groups.[21] The median treatment duration for patients with clear cell RCC was [redacted] months [95% CI: [redacted], [redacted]] and the median treatment duration for patients who did not have clear cell RCC was [redacted] months [95% CI: [redacted], [redacted]]. RCC histology was not collected for the EAMS cohort.

Treatment duration over time

Treatment duration over time is presented in Table 24 for both cohorts. Treatment duration was longer in the EAMS cohort than in the CDF cohort.[21] The difference was statistically significant at 24 and 36 months.[21]

Table 24: Treatment duration at 6, 12, 18, 24, 36 and 48-month intervals

Time period	Treatment duration CDF cohort, (95% CI)	Treatment duration EAMS cohort (95% CI)

6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months		[redacted]

Abbreviations: CDF, Cancer Drugs Fund; CI: Confidence interval; EAMS, Early Access to Medicines Scheme; SACT, Systemic Anti-Cancer Cancer Therapy.
Source: DoF (NHS England SACT report, 2024).[21]

B.2.8.3 Nathan *et al* | UK real-world observational study of avelumab + axitinib in advanced renal cell carcinoma

A UK-based multicentre, retrospective noninterventional cohort study of adults with aRCC who initiated treatment with avelumab + axitinib via the EAMS on or after 01 August 2019 was conducted to determine treatment outcomes with first-line avelumab + axitinib in clinical practice.[93,94] The primary outcomes were OS, PFS, ORR and best response at 36 months post avelumab + axitinib treatment initiation. Secondary outcomes included baseline demographics and clinical characteristics, history of RCC before treatment initiation, patterns of avelumab + axitinib use and treatment-related AEs. Data were analysed descriptively and results are also reported by IMDC risk group.[93,94]

Note that EAMS patients are included in both the SACT dataset discussed in Section B.2.8.2 (161 patients, from August 2019 to July 2020) and this analysis (130 patients, from August 2019 to July 2023).

B.2.8.3.1 Patient population

A total of 130 patients with 36-month follow-up data from 9 UK sites were included in the analysis.[93,94] Baseline demographics and clinical characteristics are provided in Table 25.

Table 25: Baseline demographics and clinical characteristics

	N=130
Age, median (range), years	67.1 (35.8–87.0)
Sex, n (%)	
Male	96 (74)
BMI at treatment initiation, mean (SD), kg/m^2 (n=117)	28.2 (5.5)
Ethnicity, n (%)	
Asian/Asian British	5 (4)
White	90 (69)
Not recorded	35 (27)
ECOG PS at treatment initiation, n (%)	
0	61 (47)
1	61 (47)
2	6 (5)
Not recorded	2 (2)
IMDC status at treatment initiation	

Favourable	51 (39)
Intermediate	52 (40)
Poor	25 (19)
Not known	2 (2)
Histological subtype, n (%)	
RCC with clear cell component	115 (88)
Unclassified RCC	7 (5)
Xp11 translocation RCC	1 (1)
Collecting duct RCC (bellini collecting duct RCC)	1 (1)
Papillary RCC	3 (2)
Chromophobe RCC	2 (2)
Not recorded	1 (1)
Time between aRCC diagnosis and treatment initiation, median (range), months	2.5 (0.03–115.4)

Abbreviations: aRCC, advanced renal cell carcinoma; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium.
Source: Nathan *et al*. (2024).[93,94]

B.2.8.3.2 Survival outcomes (OS and PFS)

The OS and PFS rates post-treatment initiation at 12, 24 and 36 months are provided in Table 26. The median OS was not estimable.[93,94] At 36 months the OS rate was 53% which is similar to the 57.2% months reported in the JAVELIN Renal 101 trial FA.[93,94,98]

The median PFS was 13.5 months (95% CI: 10.2–17.7 months), in line with the JAVELIN Renal 101 trial FA in which a median PFS of 13.9 months was reported.[93,94,98] OS and PFS rates at 12, 24 and 36 months are provided in Table 27.

Table 26: OS and PFS rates at 12, 24 and 36 months

Time period	OS rate (95% CI, %)	PFS rate (95% CI, %)
12 months	81.5 (75.1–88.5)	53.1 (45.1–62.5)
24 months	65.3 (57.6–74.0)	36.4 (29.0–45.8)
36 months	53.3 (45.2–62.9)	27.0 (20.3–36.0)

Abbreviations: CI, confidence interval; PFS, progression-free survival, OS, overall survival .
Source: Nathan *et al*. (2024).[93,94]

OS and PFS by IMDC risk group

The median OS for the favourable-risk group was [redacted] and [redacted] months for the intermediate-/poor-risk group.[113] The median PFS for the favourable-risk group was [redacted] months and [redacted] months for the intermediate-/poor-risk group.[113] In comparison, the median OS for favourable-risk patients in JAVELIN Renal 101 was 79.4 months (see Section B.2.6.1.1) and for intermediate-/poor risk patients was 37.8 months (see Section B.2.6.2.1).[100] Median PFS in JAVELINE Renal 101 was 20.7 months in the favourable-risk group (see Section B.2.6.1.2) and 11.1 months in the intermediate-/poor-risk group (see Section B.2.6.2.2).[100]

Table 27: OS and PFS rates at 12, 24 and 36 months

Time period	IMDC favourable-risk group N=51	IMDC intermediate-/ poor-risk group N=77	IMDC favourable-risk group N=51	IMDC intermediate-/ poor-risk group N=77	
	OS rate (95% CI, %)		PFS rate (95% CI, %)		
12 months	[redacted]	[redacted]	[redacted]	[redacted]	
24 months	[redacted]	[redacted]	[redacted]	[redacted]	
36 months	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; PFS, progression-free survival, OS, overall survival.
Source: Nathan *et al*. (2024) Merck Serono Ltd, UK: DOF.[113]

B.2.8.3.3 Response rates

The ORR post-treatment initiation was 62% (95% CI: 53.8%–70.6%) at 36 months, including a best response of CR in 5% of patients (n=6) and PR in 57% of patients (n=73).[93,94] The ORR at 36 months is broadly similar to the ORR of 59.7% reported in the JAVELIN Renal 101 trial FA and a UK real-world study which reported an ORR of 60%.[98,111] The best responses within 36 months are provided in Table 28.

Table 28: Best responses within 36 months

Time period	N (%)
Complete response	6 (5)
Partial response	73 (57)
Stable disease	39 (31)
Progressive disease	9 (7)
None recorded	3

Source: Nathan *et al*. (2024).[93,94]

Response rates by IMDC risk group

The IMDC favourable-risk group [redacted] than the IMDC intermediate-/poor-risk group (Figure 14).[113] This is [redacted] JAVELIN Renal 101 trial FA (Section B.2.6.1.3 and Section B.2.6.2.3).

Figure 14: Overall response rate by baseline IMDC risk group in evaluable patients (n=125)

Abbreviations: IMDC, International Metastatic RCC Database Consortium.
Source: Nathan *et al*. (2024) Merck Serono Ltd, UK: DOF.[113]

B.2.8.3.4 Safety and tolerability

Overall, 68% of patients (88/129) had an AE, with a total of 519 treatment-related AEs.[93,94] The most common AEs were diarrhoea (n=49), fatigue (n=33), and oral mucositis (n=24).[93,94] Nine patients discontinued treatment due to AEs, including diarrhoea in three patients.[93,94] SAEs were experienced by 13% of patients (17/129) with a total of 27 SAEs.[94] There were no newly emerging AEs.[93,94]

B.2.8.4 McGrane *et* al | UK real-world retrospective review of first-line immunotherapy for the treatment of metastatic RCC (ROC study)

A multicentre respective review of patients with metastatic RCC was conducted across 17 centres in the UK to evaluate clinical outcomes with the first-line use of systemic anti-cancer therapy.[37] Patients (age ≥18 years) who initiated systemic anti-cancer therapy for the treatment of metastatic RCC between 01 January 2018 and 30 June 2021 were included.[37] Clinical outcomes evaluated were OS and PFS. Survival data were compared using KM curves and statistical differences between groups were evaluated with the log-rank test.[37] Univariable and multivariable Cox proportional hazard modelling was conducted to estimate the HRs for OS and PFS. Subsequent treatments data from this review are presented in Section B.1.3.7.[37]

B.2.8.4.1 Patient population

A total of 1,319 patients met the inclusion criteria.[37] Thirty-three patients had other investigational medication, a total of 1,286 patients were included in the analysis.[37] Baseline demographics and clinical characteristics are provided in Table 29. Of the 197 patients in the IO+TKI group, majority of patients (85.3%; n=168) received avelumab + axitinib.[37]

Table 29: Baseline demographics and clinical characteristics

	Total N=1,319	IO+TKI N=197	IO+IO N=311	TKI N=778
Age, median (range), years	64 (21–84)	NR (29–86)	NR (28–83)	NR (21–84)
Sex, n (%)				
Male	937 (71.0)	142 (72.1)	232 (74.6)	538 (69.2)
Female	382 (29.0)	55 (27.9)	79 (25.4)	240 (30.8)
IMDC group				
Favourable	294 (22.3)	66 (33.5)	15 (4.8)	206 (26.5)
Intermediate	695 (52.7)	96 (49.0)	200 (64.3)	380 (48.8)
Poor	321 (24.3)	34 (17.3)	96 (30.9)	185 (23.8)
N/A	9 (0.7%	-	-	-
First-line systemic anti-cancer therapy regimen, (%)		Ave + Axi (85.3) Pem + Axi (14.2) Lem + Pem (0.5)	Ipi + Nivo (100.0)	Sun (41.6) Paz (30.1) Cabo (14.7) Tivo (13.4) Axi (0.3)

Abbreviations: Axi, axitinib; Ave, avelumab; Cabo, cabozantinib; IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy; Ipi, ipilimumab; Misc, miscellaneous; N/A, not assessed; Nivo, nivolumab; Paz, pazopanib; NR, not reported; Pem, pembrolizumab; Sun, sunitinib; Tivo, tivozanib; TKI, tyrosine kinase inhibitor.
Source: McGrane *et al*. (2024).[37]

B.2.8.4.2 Overall survival

The median OS for all patients receiving first-line therapy was 25.0 months and 23.8 months in the IO+IO group and TKI group, respectively.[37] Median OS was not reached in the IO+TKI group.[37] Extending the results of the log-rank test which showed a statistically significant difference between the groups, the HR for IO+TKI versus TKI was 0.68 (95% CI: 0.52, 0.90), and the HR for IO+IO versus TKI was 0.96 (95% CI: 0.80, 1.16).[37]

In the IMDC favourable-risk group, the median OS for first-line therapy was not reached in the IO+TKI group and 41.1 months in the TKI group.[37] The IO+IO group was not included in the analysis as this combination is not routinely used in UK clinical practice for favourable-risk patients. The log-rank test suggested a statistically significant difference between the two groups, IO+TKI delayed time to death versus TKI (HR=0.42; 95% CI: 0.18, 0.99).[37]

B.2.8.4.3 Progression-free survival

The median PFS for all patients receiving first-line therapy was 11.3 months, 7.6 months and 7.8 months for the IO+TKI, IO+IO and TKI groups, respectively.[37] Extending the results of the log-rank test which suggested a statistically significant difference between the groups, the HR for IO+TKI versus TKI was 0.61 (95% CI: 0.50, 0.75), the HR for IO+IO versus TKI was 0.93 (95% CI: 0.80, 1.08).[37]

In the IMDC favourable-risk group, the median PFS was 25.0 months and 14.6 months in the IO+TKI and TKI groups, respectively.[37] The log-rank test suggested a statistically significant difference between the two groups, IO+TKI delayed time to death or progression versus TKI (HR=0.60; 95% CI: 0.39, 0.91).[37]

B.2.9 Meta-analysis

All efficacy data supporting the use of avelumab + axitinib for people with previously untreated aRCC are provided by a single Phase 3 study (JAVELIN Renal 101). Therefore, a meta-analysis is not required.

B.2.10 Indirect and mixed treatment comparisons

As detailed in Section B.2.3, the JAVELIN Renal 101 trial compared avelumab + axitinib to sunitinib, yet there are no other head-to-head studies comparing the efficacy of avelumab + axitinib to other treatment options.

Based on precedent set in past NICE appraisals in aRCC and aligned with clinical expert opinion received by the company, it was considered reasonable to assume similar efficacy for TKI monotherapies (sunitinib, tivozanib, or pazopanib) which are recommended for untreated aRCC, irrespective of IMDC risk group.[1,6] Therefore, an ITC was not deemed necessary for the favourable-risk or ITT populations, as the comparators for decision-making comprise of single-agent TKIs (sunitinib, pazopanib, and tivozanib) which are expected to have broadly equivalent efficacy (in keeping with precedence set in previous appraisals conducted by NICE in RCC and supported by clinical expert opinion).[1,14] Therefore, in these populations, the within-trial (i.e., from JAVELIN Renal 101) measure of relative effects are considered most suitable for decision making.[1,14]

For people with intermediate-/poor-risk aRCC (defined by IMDC criteria), there are four additional treatment options available in NHS practice (beyond the three single-agents TKIs discussed above): cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib, and nivolumab + cabozantinib (as detailed in the final scope for this appraisal) where head-to-head trial data is not available. To facilitate a comparison to these treatment options, relevant for the intermediate-/poor-risk subgroup, an indirect treatment comparison (ITC) was required.

The ITC for the intermediate-/poor-risk population took the form of a network meta-analysis (NMA), focusing on the key clinical outcomes of OS and PFS. These two outcomes represent the main endpoints used to inform the economic model (see Section B.3 for further details). In the sub-sections that follow, the process of identifying relevant evidence is described, alongside an assessment of the data used to inform the ITC. In addition, a description of the methodology employed to generate the results of the ITC is provided, and the results of the ITC are presented.

B.2.10.1 Identification and selection of studies

A clinical SLR was originally performed in 2018 to inform TA645, and has since been updated five times. The searches for the most recent update were performed on 13 May 2024. A total of 56 unique studies were identified from 273 publications from the original SLR; 19 additional unique studies were identified from 196 publications during the updates of the original SLR. See Appendix D for further details of the SLR.

Five studies directly compared two or more regimens of relevance for the intermediate-/poor-risk subgroup specifically. Table 30 summarises the outcomes available for each of these five studies (in addition to JAVELIN Renal 101), as well as the publication year and treatment arms.

Table 30: Outcome availability by study list (intermediate-/poor-risk)

Study (Year)	Treatment/ comparator	Label	PFS definition	Intermediate-risk		Poor-risk		Intermediate-/poor-risk	
				OS data HR/KM	PFS data HR/KM	OS data HR/KM	PFS data HR/KM	OS data HR/KM	PFS data HR/KM
JAVELIN Renal 101[98]	Avelumab + axitinib	Ave + Axi	IA (BICR available)	HR/KM	HR/KM	HR/KM	HR/KM	HR/KM	HR/KM
	Sunitinib	Sun		HR/KM	HR/KM	HR/KM	HR/KM	HR/KM	HR/KM
CABOSUN (Choueiri 2018)[114]	Cabozantinib 60 mg/d	Cabo	ICR & IA available		HR		HR	HR/KM	HR/KM
	Sunitinib 50 mg/d	Sun			HR		HR	HR/KM	HR/KM
CheckMate 9ER (Choueiri 2021)[11, 12]	Nivolumab 240mg every 2 weeks + Cabozantinib 40mg/d[a]	Nivo + Cabo	BICR	HR/KM	HR/KM	HR/KM	HR/KM	HR/KM	HR/KM
	Sunitinib 50mg 4 weeks[a]	Sun		HR/KM	HR/KM	HR/KM	HR/KM	HR/KM	HR/KM
CheckMate 214 (Motzer 2018) [18, 19]	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W[b]	Nivo 3 + Ipi 1	ICR	HR		HR		HR/KM	HR/KM
	Sunitinib 50 mg/d od[b]	Sun		HR		HR		HR/KM	HR/KM
CLEAR (Motzer 2021)[20, 21]	Lenvatinib 20mg/d + Pembrolizumab 200mg[c]	Pem + Len	ICR	HR	HR	HR	HR	HR/KM	HR/KM
	Sunitinib 50mg/d 4/2 schedule[c]	Sun		HR	HR	HR	HR	HR/KM	HR/KM

Abbreviations: 1L, first-line; BICR, blinded independent central review; HR, hazard ratio; IA, investigator assessed; ICR, independent central review; KM, Kaplan–Meier; od, once daily; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks.

Notes: Studies that include both an HR and a KM are labelled 'HR/KM'; those with a HR only are labelled 'HR'. Subgroup population was based on IMDC risk unless stated.

a Data are based on the latest datacut reported in the Powles et al. 2024 study.[12]

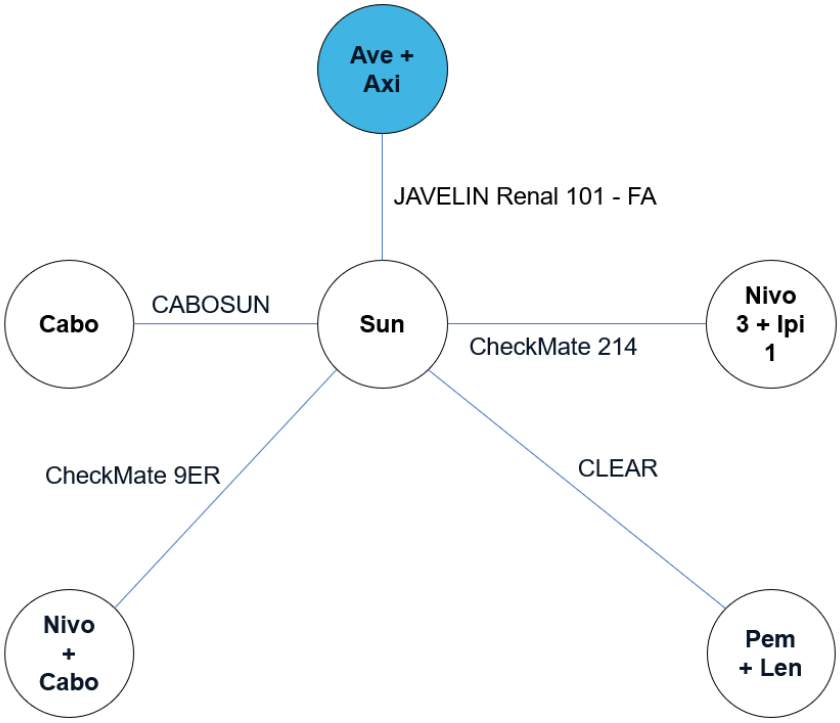
b Data are based on the latest datacut reported in the Tannir et al. 2024 poster presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium.[18]

c Data are based on the latest datacut reported in the Motzer 2023 manuscript.[21]

B.2.10.2 Feasibility analysis and assessment of proportional hazards

To assess the feasibility of the analysis, a network diagram was produced to determine if all connections could be made. The network diagram for both outcomes is presented in Figure 15, which confirmed the viability of the analysis (through connections via sunitinib). In addition, the availability of KM estimates for the intermediate-/poor-risk subgroup allowed the comparison of avelumab + axitinib to sunitinib, cabozantinib, nivolumab + ipilimumab, nivolumab + cabozantinib and pembrolizumab + lenvatinib for both OS and PFS.

Figure 15: Network diagram



Abbreviations: Ave, avelumab; Axi, axitinib; Cabo, cabozantinib; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; Ipi 1, ipilimumab 1 mg/kg; Len, lenvatinib; Nivo 3, nivolumab 3 mg/kg; Pem, pembrolizumab; Sun, sunitinib.

Prior to conducting the NMA, it was first necessary to assess the KM estimates for each endpoint from each study for proportional hazards (PH). For full details of PH assessment, please refer to Appendix N. On balance, the PH assumption was considered reasonable for the purpose of estimating relative effects for the model for this appraisal, owing to the number of comparisons required and the subjectivity associated with assessing the PH assumption.

B.2.10.3 Assessments of heterogeneity and inconsistency

Statistical assessment of heterogeneity based on the I^2 statistic was not applicable in this NMA because this statistic is derived from a direct head-to-head meta-analysis of those treatment comparisons in each network, reported by more than one study. No connections in the network included results from more than one study. In addition, there were no loops in the network, and therefore consistency could not be investigated for this network.

B.2.10.4 Methodology

The NMA was carried out using a Bayesian approach to capture the uncertainty in model parameters while preserving correlation between treatment effects. All PH NMA methods were consistent with NICE Decision Support Unit (DSU) TSDs 2–4.[115–117] Bayesian analyses rely on the use of Markov chain Monte Carlo (MCMC) methods, combining non-informative uniform prior distributions with the data to construct a posterior distribution on which to base summary results. Relative efficacy was estimated using a treatment effect model detailed in NICE DSU TSD 2, which allows direct and indirect evidence to be synthesised in one analysis, while accounting for correlation arising from multi-arm trials.[115] The models were implemented in the *gemtc* package of the software R®.[118–120]

Relative treatment effects were estimated using MCMC methods. An initial number of iterations were discarded as the 'burn-in' period, which was assessed by running three chains using different starting values and checking convergence using the Brooks–Gelman–Rubin statistic and plots of posterior density.[121] As a starting point, the burn-in was 50,000 samples, but was increased where there was evidence that the MCMC simulations had not converged. Once convergence was achieved, a further number of samples (minimum 50,000) were generated from the posterior distribution to estimate treatment effects and 95% credible intervals. A credible interval is the Bayesian counterpart to a frequentist CI. A 95% credible interval has the property that the probability of the true relative treatment effect falling within the interval is 95%.

In the first instance, both fixed- and random-effects models were fitted to the data, and model comparison methods were used to compare the goodness of fit. Preferred models were then identified based on clinical plausibility of the estimated relative treatment effects and goodness-of-fit statistics, such as the deviance information criteria (DIC) (to compare between alternative models) and/or the total residual deviance, which is compared to the number of unique data points.[122]

Autocorrelation was assessed using autocorrelation plots to determine whether samples within each Markov chain were highly correlated. A suitable thinning interval was applied, if needed, to ensure the chain was mixing well and was representative of the posterior distribution.

B.2.10.5 Results

B.2.10.5.1 Overall survival

The fixed-effects model was deemed the most suitable, based on the assessment of DIC (9.99 for both fixed and random effects approaches), and considering the network contained single studies for each connection.

The results of the NMA for OS are provided in Figure 16, with avelumab + axitinib as the reference treatment. All treatments are shown to lead to a reduction in the hazard of death compared with sunitinib in fixed-effects model. Avelumab + axitinib is generally comparable with cabozantinib, but is associated with an increase in the hazard of death compared with nivolumab + ipilimumab, nivolumab + cabozantinib and pembrolizumab + lenvatinib.

Figure 16: OS forest plot for intermediate-/poor-risk population comparing avelumab + axitinib to all other treatments – fixed-effects model

Abbreviations: CrI, credible interval; HR, hazard ratio.

B.2.10.5.2 Progression-free survival

The fixed-effects model deemed the most suitable, based on the assessment of DIC (9.99 [fixed-effects model] versus 9.97 [random-effects model]), and considering the network containing single studies for each connection.

The results of the NMA for PFS are provided in Figure 17, with avelumab + axitinib as the reference treatment. All treatments are shown to lead to a reduction in the hazard of disease progression or death compared with sunitinib in fixed-effects model. Avelumab + axitinib is generally comparable with all other treatments, but is associated with an increase in the hazard of progression or death compared with cabozantinib, nivolumab + cabozantinib and pembrolizumab + lenvatinib. Compared to nivolumab + ipilimumab, avelumab + axitinib is associated with a lower hazard of progression or death.

Figure 17: PFS forest plot for intermediate-/poor-risk population comparing avelumab + axitinib to all other treatments – fixed-effects model

Abbreviations: CrI, credible interval; HR, hazard ratio.

B.2.10.6 Limitations and uncertainties in the indirect and mixed treatment comparisons

As with any ITC, there are several uncertainties in the NMA conducted to inform this appraisal.

- Subgroup analyses: The comparators for the IMDC intermediate-/poor-risk population required use of an ITC to inform the cost-effectiveness analysis, and so subgroup analyses were required to inform the NMA for this comparison. Consequently, the NMA results are expected to be subject to increased levels of uncertainty as the RCTs included in the NMA were not powered to detect differences in IMDC risk sub-groups, compared to analyses that make use of data from ITT analyses (which while more certain, are not specific to the population of relevance for decision-making).

- Heterogeneity of studies: A key consideration for the intermediate-/poor-risk subgroup is the inherent heterogeneity within a subgroup of patients that accounts for the majority of people with aRCC, though data were not available for all studies within the network for more granular populations (e.g., results in poor-risk or intermediate-risk populations reported separately). It is known that different studies will have a different mix of people with poor versus intermediate-risk, and this is expected to influence the assessment of treatment effects for the combined subgroup, though little can be done to address this with formal analysis due to reporting limitations of published studies. Another limitation of the ITC was the assumption that study design and patient populations were similar across the studies (and in the intermediate-/poor-risk subgroup). Although potential differences were investigated, data were not available for all of the studies (particularly for the intermediate-/poor-risk subgroup), so there is some uncertainty as to the heterogeneity of the studies. From the available data, however, there was evidence to indicate that the studies were generally similar, both in terms of design and patient baseline characteristics.

- Uncertainty around PH assumption: Investigation into the evidence available indicates that while uncertain, the PH assumption is likely reasonable for the purpose of generating estimates of comparative efficacy for decision-making within the economic model. While more complex ITC methods were considered, these were deemed unlikely to yield markedly different conclusions compared with the PH NMA presented here, are associated with additional complexity and in turn may contribute to further uncertainty. In the recent appraisal of pembrolizumab + lenvatinib (TA858), the Committee ultimately preferred results from the PH ITC, and that results from a more flexible ITC were *"highly uncertain"*.[14]

- Uncertainty of random effects models: For completeness, both fixed-effects and random-effects models were undertaken, though point estimates were similar. However, due to the non-informative prior distribution used for the between-study heterogeneity, the credible intervals in the random-effects model are substantially wider than the fixed-effects model. The wide credible intervals are expected to be caused by a combination of the relatively low number of studies in the network and the low number of studies informing each treatment comparison.

Overall, the results of the ITC suggest that certain immunotherapy-containing regimens demonstrate numerically better (though not statistically significantly different) results compared to avelumab + axitinib. However, it is not possible to determine which of the immunotherapy combinations is the most suitable treatment for a patient with intermediate-/poor-risk aRCC in all cases. The results of the ITC do not take into consideration individual patient characteristics which may determine the most suitable treatment of choice in real-world clinical practice, factoring in patient frailty, existing comorbidities, and risks of toxicity. Therefore, the results of the ITC should be interpreted with caution, despite the methodology representing the standard approach for estimating relative treatment effects for time-to-event outcomes in populations with advanced cancer.

B.2.11 Adverse reactions

Safety data from JAVELIN Renal 101 are reported for the safety analysis set for the full population from the FA, regardless of IMDC (Heng) prognostic criteria; this provides outcomes from the largest number of patients.

B.2.11.1 TEAEs

The avelumab + axitinib and sunitinib arms had similar incidences of TEAEs, including treatment-related TEAEs. There was a larger proportion of patients who experienced a serious TEAE in the avelumab + axitinib arm (53.2% versus 37.8% in the sunitinib arm).[99] Due to avelumab's mechanism of action and the intravenous route of administration, a larger proportion of patients experienced immune-related adverse events (irAEs) in the avelumab + axitinib arm (50.2% versus 4.6% in the sunitinib arm) and infusion-related reactions (IRRs) were reported only in the avelumab + axitinib arm.[99] An overall summary of adverse events is presented in Table 31.

Table 31: Summary of adverse events during the on-treatment period | Safety analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants	Avelumab + axitinib (n=434)	Sunitinib (n=439)
TEAEs	434 (100.0)	436 (99.3)
Grade ≥3 TEAEs	365 (84.1)	346 (78.8)
Treatment-related TEAEs	420 (96.8)	425 (96.8)
Grade ≥3 treatment-related TEAEs	290 (66.8)	270 (61.5)
Serious TEAEs	231 (53.2)	166 (37.8)
Serious treatment-related TEAEs	97 (22.4)	68 (15.5)
TEAEs leading to dose reduction of avelumab	[redacted]	[redacted]
TEAEs leading to dose reduction of axitinib	[redacted]	[redacted]
TEAEs leading to dose reduction of sunitinib	[redacted]	[redacted]
TEAEs leading to dose interruption of avelumab	[redacted]	[redacted]
TEAEs leading to dose interruption of axitinib	[redacted]	[redacted]
TEAEs leading to dose interruption of sunitinib	[redacted]	[redacted]
TEAEs leading to discontinuation of avelumab	[redacted]	[redacted]

TEAEs leading to discontinuation of axitinib	[redacted]	[redacted]
TEAEs leading to discontinuation of sunitinib	[redacted]	[redacted]
TEAEs leading to discontinuation of any study drug	149 (34.3)	77 (17.5)
TEAEs leading to discontinuation of all study drugs	57 (13.1)	77 (17.5)
Treatment-related TEAEs leading to discontinuation of avelumab	[redacted]	[redacted]
Treatment-related TEAEs leading to discontinuation of axitinib	[redacted]	[redacted]
Treatment-related TEAEs leading to discontinuation of sunitinib	[redacted]	[redacted]
Treatment-related TEAEs leading to discontinuation of any study drug	110 (25.3)	41 (9.3)
Treatment-related TEAEs leading to discontinuation of all study drugs	21 (4.8)	41 (9.3)
TEAEs leading to death	29 (6.7)	24 (5.5)
Treatment-related TEAEs leading to death	6 (1.4)	1 (0.2)
Immune-related adverse events	218 (50.2)	20 (4.6)
Infusion-related reactions	127 (29.3)	0

Abbreviations: DCO, data cutoff; NA, not applicable; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.1.1 Most common TEAEs

The most common all-causality TEAEs (any grade in ≥10% of participants or Grade ≥3 in ≥5% participants in any treatment arms) are summarised in Table 32. In the avelumab + axitinib arm, the most common TEAEs (reported by >40% of patients) were diarrhoea, hypertension, fatigue, and nausea; in the sunitinib arm, the most common TEAEs were diarrhoea, fatigue, and nausea.[99]

The system organ classes (SOCs) for TEAEs that differed most (≥10% difference) between the treatment arms and occurred more frequently in the avelumab + axitinib arm than in the sunitinib arm were: *respiratory, thoracic and mediastinal disorders* (73.3% and 56.5% of patients, respectively); *musculoskeletal and connective tissue disorders* (65.2% and 52.2%, respectively); *vascular disorders* (64.3% and 45.8%, respectively); *infections and infestations* (55.3% and 43.1%, respectively); *endocrine disorders* (38.9% and 23.7%, respectively); *injury, poisoning and procedural complications* (32.9% and 16.2%, respectively), and *cardiac disorders* (22.8% and 11.4%, respectively).[99] In the SOC of *blood and lymphatic system disorders*, a smaller proportion of patients reported TEAEs in the avelumab + axitinib arm than in the sunitinib arm (17.5% and 47.6%, respectively).[99]

Table 32: Summary of most common TEAEs (any grade in ≥10% of participants or Grade ≥3 in ≥5% participants in any treatment arms) by maximum CTCAE grade during the on-treatment period | Safety analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants with events	Avelumab + axitinib (n=434)		Sunitinib (n=439)	
	All grades	Grade ≥3	All grades	Grade ≥3
Participants with events				
Diarrhoea				
Hypertension				
Fatigue				
Nausea				
Palmar-plantar erythrodysaesthesia syndrome				
Arthralgia				
Dysphonia				
Cough				
Decreased appetite				
Hypothyroidism				
Headache				
Back pain				
Stomatitis				
Weight decreased				
Dyspnoea				
Vomiting				
Constipation				
Pruritus				
Alanine aminotransferase increased				
Abdominal pain				
Pain in extremity				
Asthenia				
Aspartate aminotransferase increased				
Pyrexia				
Chills				
Rash				
Dizziness				
Mucosal inflammation				
Blood creatinine increased				
Dry skin				

Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertriglyceridaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Taste disorder	[redacted]	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.1.2 Most common treatment-related TEAEs

The most common treatment-related TEAEs (any grade in ≥10% of participants or Grade ≥3 in ≥5% participants in any treatment arms) are summarised in Table 33.

While no new safety concerns were identified for avelumab + axitinib beyond those already described for each individual agent, the following AEs were reported at higher frequencies with the combination than observed with either single agent alone:[99]

- Diarrhoea, a known TEAE for both avelumab and axitinib, was reported at a higher frequency for avelumab + axitinib treatment ([redacted]%) than each agent as monotherapy ([redacted]% and [redacted]% for avelumab and axitinib, respectively).[99,123]
- Hypertension, a known ADR for axitinib, was reported at a higher frequency for Grade ≥3 in avelumab + axitinib treatment ([redacted]%) compared with axitinib alone ([redacted]%). However, this may have been due to more stringent criteria than those used for axitinib monotherapy studies.[99,123]
- Hypothyroidism, a known ADR for both avelumab and axitinib, was reported at a higher frequency for avelumab + axitinib treatment ([redacted]%) than that of each agent as monotherapy ([redacted]% and [redacted]% for avelumab and axitinib, respectively).[99,123]
- ALT increased, a known ADR for both avelumab and axitinib, was reported at a higher frequency for avelumab + axitinib treatment ([redacted]%) than each agent as monotherapy ([redacted]% and [redacted]% for avelumab and axitinib, respectively).[99,123]

Table 33: Summary of most common treatment-related TEAEs (any grade in ≥10% of participants or Grade ≥3 in ≥5% participants in any treatment arm) by maximum CTCAE grade during the on-treatment period | Safety analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants with events	Avelumab + axitinib (n=434)		Sunitinib (n=439)	
	All grades	Grade ≥3	All grades	Grade ≥3
Participants with events	420 (96.8)	290 (66.8)	425 (96.8)	270 (61.5)
Diarrhoea	278 (64.1)	41 (9.4)	217 (49.4)	14 (3.2)
Hypertension	224 (51.6)	120 (27.6)	153 (34.9)	77 (17.5)
Fatigue	163 (37.6)	15 (3.5)	167 (38.0)	16 (3.6)
Palmar-plantar erythrodysaesthesia syndrome	158 (36.4)	28 (6.5)	162 (36.9)	19 (4.3)
Nausea	133 (30.6)	4 (0.9)	160 (36.4)	5 (1.1)
Dysphonia	130 (30.0)	2 (0.5)	13 (3.0)	0
Hypothyroidism	128 (29.5)	2 (0.5)	79 (18.0)	2 (0.5)
Stomatitis	110 (25.3)	8 (1.8)	109 (24.8)	5 (1.1)
Decreased appetite	105 (24.2)	8 (1.8)	125 (28.5)	5 (1.1)
Pruritus	78 (18.0)	0	23 (5.2)	0
Alanine aminotransferase increased	72 (16.6)	23 (5.2)	44 (10.0)	11 (2.5)
Arthralgia	72 (16.6)	3 (0.7)	27 (6.2)	0
Mucosal inflammation	67 (15.4)	6 (1.4)	63 (14.4)	5 (1.1)
Aspartate aminotransferase increased	65 (15.0)	14 (3.2)	52 (11.8)	8 (1.8)
Chills	62 (14.3)	1 (0.2)	17 (3.9)	0
Rash	60 (13.8)	5 (1.2)	45 (10.3)	2 (0.5)
Weight decreased	60 (13.8)	9 (2.1)	21 (4.8)	1 (0.2)
Dyspnoea	57 (13.1)	5 (1.2)	29 (6.6)	1 (0.2)
Infusion-related reaction	56 (12.9)	7 (1.6)	0	0
Vomiting	56 (12.9)	2 (0.5)	74 (16.9)	8 (1.8)
Headache	51 (11.8)	0	45 (10.3)	0

Dry skin	48 (11.1)	0	46 (10.5)	0
Asthenia	46 (10.6)	7 (1.6)	59 (13.4)	9 (2.1)
Dysgeusia	44 (10.1)	0	106 (24.1)	0
Dyspepsia	35 (8.1)	0	77 (17.5)	0
Lipase increased	35 (8.1)	25 (5.8)	19 (4.3)	16 (3.6)
Epistaxis	33 (7.6)	0	47 (10.7)	0
Taste disorder	23 (5.3)	0	47 (10.7)	0
Anaemia	14 (3.2)	2 (0.5)	85 (19.4)	30 (6.8)
Thrombocytopenia	14 (3.2)	1 (0.2)	81 (18.5)	27 (6.2)
Platelet count decreased	9 (2.1)	1 (0.2)	61 (13.9)	25 (5.7)
Neutropenia	6 (1.4)	1 (0.2)	86 (19.6)	38 (8.7)
Neutrophil count decreased	5 (1.2)	1 (0.2)	46 (10.5)	30 (6.8)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.2 Deaths and serious TEAEs

B.2.11.2.1 On-study deaths

As of 31 August 2023, [redacted] ([redacted]%) patients in the avelumab + axitinib arm and [redacted] ([redacted]%) patients in the sunitinib arm had died, with [redacted] ([redacted]%) patients in the avelumab + axitinib arm and [redacted] ([redacted]%) patients in the sunitinib arm having died within 30 days after last dose of study treatment.[99] The most common cause of death was disease progression for both the avelumab + axitinib arm ([redacted], [redacted]%) and the sunitinib arm ([redacted], [redacted]%). The proportion of patients with TEAEs with an onset during the on-treatment period that led to death was [redacted]% of patients in the avelumab + axitinib arm and [redacted]% of patients in the sunitinib arm (Table 34).[99] Further information on specific TEAEs leading to death is provided in Appendix F.

Table 34: Summary of TEAEs during the on-treatment period leading to death by system organ class | Safety analysis set | Final analysis (DCO 31 August 2023)

	Avelumab + axitinib (n=434)	Sunitinib (n=439)
Participants with events	[redacted] ([redacted])	[redacted] ([redacted])
General disorders and administration site conditions	[redacted] ([redacted])	[redacted] ([redacted])
Cardiac disorders	[redacted] ([redacted])	[redacted] ([redacted])
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted] ([redacted])	[redacted] ([redacted])
Respiratory, thoracic and mediastinal disorders	[redacted] ([redacted])	[redacted] ([redacted])
Gastrointestinal disorders	[redacted] ([redacted])	[redacted] ([redacted])
Metabolism and nutrition disorders	[redacted] ([redacted])	[redacted]
Nervous system disorders	[redacted] ([redacted])	[redacted] ([redacted])
Infections and infestations	[redacted]	[redacted] ([redacted])

Abbreviations: DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.2.2 Serious TEAEs

There was a larger proportion of patients with serious TEAEs reported in the avelumab + axitinib arm than in the sunitinib arm (53.2% versus 37.8%, respectively). For treatment-related serious TEAEs, the difference between treatment arms was less evident (22.4% versus 15.5%, respectively).[99] The most commonly reported serious TEAEs (any grade reported by ≥2% of patients or Grade ≥3 in ≥2% of patients) are summarised in Table 35. No single TEAE was reported as serious and treatment-related in ≥2% of patients in either treatment arm.[99]

Table 35: Summary of most common serious TEAEs (any grade in ≥2% of participants or Grade ≥3 in ≥2% participants in any treatment arm) by maximum CTCAE grade during the on-treatment period | Safety analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants with events	Avelumab + axitinib (n=434)		Sunitinib (n=439)	
	All grades	Grade ≥3	All grades	Grade ≥3
Participants with events	231 (53.2)	[redacted]	166 (37.8)	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.3 TEAEs associated with changes in treatment

B.2.11.3.1 Permanent discontinuations due to adverse events

Patients in the avelumab + axitinib arm received two drugs, which could be discontinued independently from each other, while patients in the sunitinib arm received only one drug. Consequently, there is a larger proportion of patients in the avelumab + axitinib arm with TEAEs leading to permanent discontinuation of *either* study drug compared with sunitinib (34.3% versus 17.5%).[99] However, there is a smaller proportion of patients discontinuing *all* study drugs due to TEAEs in the avelumab + axitinib arm relative to the sunitinib arm (13.1% versus 17.5%). The results for treatment-related TEAEs leading to permanent discontinuation are similar, with proportions of patients discontinuing *either* study drug of 25.3% and 9.3%, respectively, and proportions of patients discontinuing *all* study drugs of 4.8% and 9.3%, respectively.[99]

TEAEs leading to discontinuation of any study drug in >2% of patients in either treatment arm were increased alanine aminotransferase ([redacted]% in the avelumab + axitinib arm and [redacted]% in the sunitinib arm) and increased aspartate aminotransferase ([redacted]% in the avelumab + axitinib arm and [redacted] in the sunitinib arm).[99]

B.2.11.3.2 Adverse events leading to study drug dose reductions

Avelumab dose reductions were not permitted per study protocol. No participant reported TEAEs leading to reduction of avelumab dose. TEAEs leading to reduction of axitinib dose occurred in [redacted] ([redacted]%) patients in the avelumab + axitinib arm and TEAEs leading to reduction of sunitinib dose occurred in [redacted] ([redacted]%) patients.[99] TEAEs leading to dose reduction in ≥2% of patients in either treatment arm are presented in Table 36.

Table 36: Summary of TEAEs leading to reduction of axitinib or sunitinib dose in ≥2% of patients | Safety analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants	Axitinib (n=434)	Sunitinib (n=439)
Participants with events	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Abbreviations: DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.3.3 Adverse events leading to interruption of study treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF (“drug interrupted”). IRRs were excluded in the analysis of TEAEs leading to drug interruption in case they only led to an interruption of the infusion (i.e. did not lead to a dose reduction or a dose delay.

As such, TEAEs leading to interruption of study treatment were defined as TEAEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted' excluding:

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (i.e. IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay. These IRRs will be considered as IRRs leading to interruption of infusion.
- IRRs occurring on the day after infusion and subsequent dose administration had no delay.

TEAEs leading to interruption of avelumab, axitinib, or sunitinib in ≥5% of patients are presented in Table 37.

Table 37: Summary of TEAEs leading to interruption of avelumab, axitinib, or sunitinib dose in ≥5% of patients | Safety analysis set | Final analysis (DCO 31 August 2023)

Number (%) of participants	Avelumab + axitinib (n=434)		Sunitinib (n=439)
	Avelumab	Axitinib	
Participants with events	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]

Abbreviations: DCO, data cutoff; TEAE, treatment-emergent adverse event.
Source: DoF JAVELIN Renal 101 FA CSR.[99]

B.2.11.4 Adverse events of special interest

Adverse events of special interest were immune-related adverse events and infusion-related reactions.[99] Cardiac-related TEAEs are also discussed due to the cardiac safety profile of VEGF inhibitors such as axitinib and sunitinib and the known risk of myocarditis associated with avelumab and other checkpoint inhibitors.[99]

B.2.11.4.1 Immune-related adverse events

Due to avelumab's mechanism of action, irAEs were mostly observed in the avelumab + axitinib arm. In the avelumab + axitinib arm, 220 (50.7%) patients experienced irAEs of any

grade and 64 (14.7%) patients experienced Grade ≥3 events. In the sunitinib arm, 21 (4.8%) and 1 (0.2%) patients experienced irAEs of any grade and Grade ≥3 events, respectively.[99]

In the avelumab + axitinib arm, the most frequently reported irAEs (all grades) by cluster (≥5%) were "immune-related endocrinopathies: thyroid disorders" ([redacted]%), "immune-related rash" ([redacted]%), and "immune-related hepatitis" ([redacted]%). The most frequently reported Grade ≥3 irAEs by cluster (≥1%) were "immune-related hepatitis" ([redacted]%), "immune-related colitis" ([redacted]%), "immune-related rash" ([redacted]%), and "immune-related endocrinopathies: type 1 diabetes mellitus" ([redacted]%).[99]

B.2.11.4.2 Infusion-related reactions

IRRs, which were assessed only for the avelumab + axitinib arm, were experienced by 127 (29.3%) patients. Most patients experienced Grade 1 ([redacted]%) or Grade 2 ([redacted]%) IRRs. The highest grade reported was Grade 3 in [redacted] ([redacted]%) patients.[99]

B.2.11.4.3 Cardiac-related adverse events

Cardiovascular events have been reported in patients treated with VEGFR TKIs, such as axitinib and sunitinib, and myocarditis has been reported with avelumab and other immune checkpoint inhibitors.

TEAEs in the "cardiac disorders" system organ class (SOC) were reported for [redacted] ([redacted]%) patients in the avelumab + axitinib arm and [redacted] ([redacted]%) patients in the sunitinib arm, including Grade ≥3 events in [redacted] ([redacted]%) and [redacted] ([redacted]%) patients, respectively.[99] TEAEs of a cardiac nature were also reported in the "investigations" SOC, such as:[99]

- ejection fraction decreased ([redacted] [redacted]%] patients including [redacted] [redacted]%] with Grade ≥3 events in the avelumab + axitinib arm versus [redacted] [redacted]%] patients including [redacted] [redacted]%] with Grade ≥3 events in the sunitinib arm),
- troponin T increased ([redacted] [redacted]%] patients including [redacted] [redacted]%] with a Grade ≥3 event in the avelumab + axitinib arm versus [redacted] patients in the sunitinib arm), and
- myocardial necrosis marker increased ([redacted] [redacted]%] patient with a Grade ≥3 event in the avelumab + axitinib arm versus [redacted] patients in the sunitinib arm).

B.2.12 Ongoing studies

B.2.12.1 AVION study

AVION (NCT04941768) is a real-world evaluation of the efficacy and safety of avelumab + axitinib in patients with aRCC, which is ongoing in Belgium, Germany, Greece and the Russian Federation.[124] The main purpose of this prospective, observational study is to expand knowledge on the effectiveness, safety and tolerability of avelumab + axitinib as a first-line therapy in patients with aRCC under routine conditions of daily clinical practice.[124]

Study participants (N=108) are receiving 800 mg of avelumab intravenously every 2 weeks in combination with 5 mg of axitinib orally twice per day, in accordance with the terms of marketing authorisation and as per current clinical practice and will be observed for 24 months. Estimated study completion is May 2025.[124]

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the evidence base

The JAVELIN Renal 101 trial provides comparative evidence for the efficacy and safety of avelumab + axitinib compared with sunitinib over a median follow-up of more than 6 years, with 886 patients randomised to treatment.[99]

B.2.13.1.1 Confirmation of avelumab + axitinib's efficacy from JAVELIN Renal 101 and real-world studies

Favourable-risk subgroup

In patients with IMDC favourable-risk (n=190), avelumab + axitinib was associated with a 25% reduction in risk of progression or death by investigator (HR=0.75; 95% CI: 0.53, 1.07; log rank, primary, stratified p-value=0.1109).[100] The PFS results from the IMDC favourable-risk subgroup at FA are consistent with the statistically significant improvement in PFS demonstrated with avelumab + axitinib compared with sunitinib in the previous analyses in the overall population of JAVELIN Renal 101.[99,100]

Avelumab + axitinib also demonstrated improved response rates compared with sunitinib; the objective response rate for avelumab + axitinib was 29.7% higher than sunitinib for patients with favourable-risk disease (ORR, 75.5% in the avelumab + axitinib arm, compared with 45.8% in the sunitinib arm).[100] Responses had an earlier onset (median TTR of [redacted] months and [redacted] months in the avelumab + axitinib and sunitinib arms, respectively). The proportion of patients with a CR was also higher in the avelumab + axitinib arm than in the sunitinib arm (9.6% and 5.2%, respectively).[100]

This PFS and ORR benefit translated to a numerical trend towards prolonged OS in the avelumab + axitinib arm at FA compared with the sunitinib arm, with clear separation of survival curves that continued to the end of follow-up.[100] The risk of death was numerically lower with avelumab + axitinib compared with sunitinib (HR=0.73 [95% CI: 0.48, 1.10]; log rank, primary, stratified p=0.1290), resulting in a 13.9-month increase in median OS with avelumab + axitinib.[98,100] The median OS achieved by patients treated with avelumab + axitinib was 79.4 months (59.4, NE),[98,100] although the CIs are wide because the trial was not designed or powered to show statistical significance between the treatment arms within IMDC risk groups.

Avelumab + axitinib is the only IO+TKI combination in aRCC that has reduced the risk of death by 27% versus sunitinib monotherapy in the subgroup of favourable-risk patients (trial not powered to show statistical significance for this subgroup).[107] This combination may offer a synergistic effect due to the immunomodulatory properties of VEGF pathway inhibitors and the vascular remodelling effects induced by IO.[46] Furthermore, axitinib's short half-life and high selectivity as a VEGF inhibitor make it a compelling combination partner, particularly in managing adverse events and treating highly angiogenic disease, respectively.[44]

The treatment benefit for patients with favourable-risk observed in JAVELIN Renal 101 was also observed for patients treated in routine clinical practice in the UK, and provides validation of the effectiveness of avelumab + axitinib in real-world clinical practice. In an analysis of data from the CDF cohort of the SACT dataset, median OS for favourable-risk patients who received avelumab + axitinib as part of the MAA was [redacted] (with [redacted] follow-up) which aligns with median OS being reached at 79.4 months in the JAVELIN Renal 101 trial.[21,98] Similarly, OS, PFS, ORR and best responses at 36 months

from a UK-based study of adults who initiated treatment with avelumab + axitinib for aRCC via the EAMS are in line with findings from the JAVELIN Renal 101 clinical study and other real-world studies, with no newly emerging AEs.[93,94] PFS rate was also comparable from a multicentre respective review of patients with metastatic RCC conducted across 17 centres in the UK.[37]

According to the UK ROC RWE dataset, for patients starting on TKI therapy in first-line, nivolumab (57.5%) was the most common second-line therapy.[26,37] However, a proportion (44.2%) of favourable-risk patients did not receive immunotherapy at any stage in their treatment.[26] Additionally, access to an IO-TKI as a first-line therapy may lead to improved disease control, demonstrated via numerically higher ORR and PFS in JAVELIN Renal 101 (vs sunitinib monotherapy) and numerically improved OS in the favourable-risk group. Hence, patients with favourable-risk aRCC have a high unmet medical need for an efficacious and safe first-line IO+TKI combination treatment regimen. Overall, evidence from JAVELIN Renal 101 and UK RWE, show that avelumab + axitinib can fulfil this unmet need for patients with favourable-risk aRCC.

Intermediate-/poor-risk subgroup

For patients with IMDC intermediate-/poor-risk (n=691), avelumab + axitinib was associated with a 36% reduction in risk of progression or death by investigator (HR=0.64; 95% CI: 0.54, 0.76; log rank, primary, stratified p<0.0001) compared with sunitinib.[100] The PFS results from the IMDC risk subgroups at FA are consistent with the statistically significant improvement in PFS demonstrated with avelumab + axitinib compared with sunitinib at previous analyses of the overall population of JAVELIN Renal 101, although it should be noted that PFS is by BICR assessment in IA1 and IA2, and by investigator assessment in IA3 and the FA.[99,100]

In addition to the PFS benefit, the objective response for avelumab + axitinib was 27.5% higher than with sunitinib, (the ORR was 55.7% in the avelumab + axitinib arm, compared with 28.2% in the sunitinib arm).[100] The magnitude of benefit in response rates for avelumab + axitinib was also consistent with that observed for patients with favourable prognostic risk. Median TTR was [redacted] months in both the avelumab + axitinib and sunitinib arms. The proportion of patients with a CR was also higher in the avelumab + axitinib arm than in the sunitinib arm (4.7% and 3.2%, respectively).[100]

Similar to the OS outcomes for the favourable-risk subgroup at the final analysis, the PFS and ORR benefits translated to a numerical trend towards prolonged OS in the avelumab + axitinib arm compared with the sunitinib arm, with a clear separation of survival curves that continued to the end of follow-up.[100] While the long-term difference in risk of death between the two treatment arms was not statistically significant (HR=0.90 [95% CI: 0.75, 1.08] log rank, primary, stratified p=0.2471), OS analyses nevertheless favoured avelumab + axitinib, with an 8.3-month increase in median OS compared with the sunitinib arm.[100] The median OS achieved by patients treated with avelumab + axitinib was 37.8 months (31.2, 42.6).[98,100]

In an analysis of data from the CDF cohort of the SACT dataset, median OS was [redacted] months for intermediate-risk patients who received avelumab + axitinib as part of the MAA and [redacted] months for poor-risk patients.[21] This is lower than the median OS seen in the JAVELIN Renal 101 trial (37.8 months in intermediate-/poor-risk patients) but expected as patients in clinical trials tend to have better outcomes due to the controlled environment of an RCT compared to RWE.[98] Additionally, there were more patients with ECOG 1 or 2 in the CDF cohort compared with JAVELIN ([redacted]% in the CDF cohort of the SACT dataset compared with 35.5% in JAVELIN), indicating poorer prognosis.[21,98]

Taken together with the long-term efficacy benefits of prolonged PFS and 30% higher ORR demonstrated in JAVELIN Renal 101 versus sunitinib, the data demonstrate that avelumab + axitinib could provide an additional choice, with manageable tolerability, for patients and physicians when selecting appropriate therapy for intermediate-/poor-risk aRCC.

Subsequent treatments from JAVELIN Renal 101

In the IMDC favourable-risk subgroup, fewer patients in the avelumab + axitinib arm received subsequent PD-1 or PD-L1 treatment (29.8% of patients) than in the sunitinib arm (64.6%).[98] However, data from the UK ROC real-world evidence dataset show that in clinical practice patients who receive first-line IO+TKI (of whom 95.5% received avelumab + axitinib) do not receive IO in subsequent treatment lines.[37] Additionally, evidence suggests that rechallenging with an IO following progression on previous IO therapy is not expected to improve patient outcomes.[125,126] Clinical expert opinion sought by the company validated this assumption. Therefore, adjustments for second-line IO following first-line treatment with avelumab + axitinib have not been considered.

HRQoL outcomes from JAVELIN Renal 101

In both treatment arms, EQ-5D-5L index scores and FKSI-19 total scores remained relatively stable over time, whereas slight improvement was observed for the EQ-VAS.[99] PROs were similar between the treatment arms, suggesting that adding avelumab to TKI treatment had no adverse impact on HRQoL. Sunitinib QoL may be overestimated due to the timing of the PRO measurements.[127] PROs were measured every 6 weeks, which corresponds to “off treatment” weeks in the sunitinib arm, that is, at the point of lowest symptom burden in the cycle.[127] Thus, results are not necessarily representative of the average symptom burden of patients receiving sunitinib and therefore the HRQoL difference between the treatments arms may have been underestimated in the JAVELIN Renal 101 trial.[127]

Avelumab + axitinib is well tolerated with a predictable safety profile

The safety results from JAVELIN Renal 101 demonstrated that the combination of avelumab plus axitinib has an acceptable safety and tolerability profile, with no new safety signals being observed with long-term treatment.[98]

TEAEs were reported with similar incidence in each treatment arm, with 96.8% in each arm reporting treatment-related TEAEs.[99] Of the treatment-related TEAEs, 66.8% in the avelumab + axitinib arm were Grade ≥3, compared with 61.5% in the sunitinib arm.

Serious TEAEs were more frequently reported by patients in the avelumab + axitinib arm than the sunitinib arm (53.2% and 37.8%, respectively) as were serious treatment-related TEAEs (22.4% and 15.5%, respectively).

The most frequent TEAEs were broadly consistent with those from interim analyses and reported in the previous company submission, with ≥10% more patients in the avelumab + axitinib arm than the sunitinib arm reporting TEAEs in the SOCs of *respiratory, thoracic and mediastinal disorders*; *musculoskeletal and connective tissue disorders*; *vascular disorders*; *infections and infestations*; *endocrine disorders*; *injury, poisoning and procedural complications*; and *cardiac disorders*. TEAEs in the SOC of *blood and lymphatic system disorders* were reported at a lower frequency in the avelumab + axitinib arm than the sunitinib arm.[1,99]

Overall, avelumab + axitinib for the first-line treatment of aRCC was generally well tolerated, and over the long-term follow-up, adverse events were typically manageable and consistent with the known safety profiles of avelumab and axitinib familiar to clinicians in routine clinical

use of the combination therapy.[98,99] While no new safety concerns were identified for the combination of avelumab plus axitinib beyond those already described for each individual agent, diarrhoea, hypertension, hypothyroidism and ALT increase were reported at higher frequencies than observed with the single agents.[99]

Other sources confirm the safety profile observed in JAVELIN Renal 101, including safety data from the Phase 1b JAVELIN Renal 100 trial and safety data from a UK real-world study.[113,128] Furthermore, as avelumab has been approved since 2017 and axitinib has been approved since 2012, both have well-characterised safety profiles.

B.2.13.2 Strengths and limitations of the clinical evidence base

B.2.13.2.1 Strengths and limitations of the JAVELIN Renal 101 trial

JAVELIN Renal 101 provides the longest follow-up to date for an immune checkpoint inhibitor + TKI combination treatment from a Phase 3 trial in aRCC (≥68 months of follow-up).[98] Overall, the Phase 3 clinical data for avelumab + axitinib provides an appropriate evidence base for assessment of its clinical and cost-effectiveness for the treatment of aRCC.

Key strengths of the clinical evidence base are:

- JAVELIN Renal 101 is a robust, multicentre RCT that randomised 886 patients with previously untreated aRCC across all risk groups.
- The safety and efficacy of avelumab + axitinib were assessed in comparison with that of sunitinib, a current standard of care in the UK and a NICE-recommended first-line treatment option at the time of trial design. The UK landscape has evolved since the trial design but sunitinib is still recommended as a first-line treatment option therefore head-to-head trial data against a relevant comparator are available (B.1.3.5.2).
- The trial included six sites in the UK and enrolled patients representative of those who would receive avelumab + axitinib in routine clinical practice in the UK.
- JAVELIN Renal 101 assessed PFS and OS, which are widely regarded as appropriate endpoints to assess the efficacy of anti-cancer therapies.
- Consistent with the significant improvement in median PFS demonstrated at the interim and primary analyses (DCOs of 20 June 2018 and 28 January 2019, respectively), whereby the primary outcome of PFS (BICR) in patients with PD-L1-positive tumours was met, at the FA in the ITT population, avelumab + axitinib was associated with a significant improvement in PFS versus sunitinib.[99] The trial also showed a numerical benefit in PFS (by investigator assessment) compared with sunitinib in the favourable- and intermediate-/poor-risk subgroups.[100]

Key limitations of the clinical evidence base are:

- The open-label nature of the JAVELIN Renal 101 trial. Due to the different routes of administration (IV for avelumab; oral for axitinib and sunitinib), an open-label design was necessary for JAVELIN Renal 101, as is common across oncology trials. However, BICR was used to minimise bias (including expedited BICR review for investigator-assessed disease progression). All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory. After IA2, BICR was disbanded but results from the FA are consistent with the earlier BICR results. Despite use of BICR for PFS and response rate outcomes, the open-label

nature of the trial may have influenced PROs and safety analysis, as trial participants were aware of their trial drug allocation.

- Although JAVELIN Renal 101 was a high-quality trial, patients were not randomised to the trial according to IMDC (Heng) prognostic subgroups. Subgroup analyses (for PFS, OR and DoR per BICR assessment and OS based on the FAS) according to Heng prognostic criteria at baseline (favourable, intermediate, and poor) were pre-specified in the SAP, but were exploratory with no adjustment for multiplicity, and the intermediate and poor subgroups were pooled in a *post hoc* analysis.[108] Additionally, the trial was not powered to detect statistical significance in IMDC risk subgroups. PROs and Q-TWiST analyses (Appendix M.2) were not pre-specified but conducted as *post hoc* exploratory analyses.

B.2.13.2.2 Strengths and limitations of the RWE

RWE collated in UK clinical practice provides an additional source of efficacy and safety data in a defined UK population of patients with aRCC that complements the evidence provided by RCTs. RWE represents clinical practice in England and Wales. Patients in the CDF and EAMS cohorts, which are representative of UK clinical practice, have similar characteristics to the JAVELIN trial baseline population, with a similar proportion (71%, 73% and 71.5%, respectively) of male patients, and almost all patients (87.6%, 87% and 99.8%, respectively) had an ECOG PS of ≤2.[21,99]

RWE is not without limitations, such as a lack of randomisation and the potential for missing data. It is also difficult to compare and contrast results from RWE studies in the same therapy area due to the differing population sizes, methods of data collection and statistical analyses used. Nevertheless, RWE serves as a valuable complement to RCTs and helps to reduce uncertainty around clinical effectiveness, and how outcomes may translate into routine clinical practice in England and Wales. Here, it demonstrates that OS, PFS, ORR and best responses at 36 months are largely in line with findings from the JAVELIN Renal 101 clinical study and other real-world studies, with no newly emerging AEs,[93,94] as well as showing significant benefit on OS and PFS in the IMDC favourable-risk group.[37] Thus it provides further evidence for the use of avelumab + axitinib for the first-line treatment of aRCC.

B.2.13.2.3 Strengths and limitations of the ITC

To address the final scope, an ITC was required to produce comparisons of avelumab + axitinib to four key treatment options available in NHS practice: cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib, and nivolumab + cabozantinib where head-to-head trial data is not available. The ITC was conducted in accordance with guidance set out NICE Decision Support Unit (DSU) TSDs 2–4,[115–117] and took the form of a Bayesian network meta-analysis (NMA). While best practice methodological guidance was followed to undertake the ITC, it is not without limitations. Most notably, the ITC does not take into consideration the inherent heterogeneity within the intermediate-/poor-risk subgroup, which plays an important role in decision making in real-world NHS practice. Individual factors, such as comorbidities and predisposition/susceptibility to treatment-related toxicities, determine which treatment options would be considered more (or less) suitable than others. Therefore, caution is advised when interpreting the results of the ITC, as they are unlikely to represent a true reflection of the clinical outcomes associated with the use of avelumab + axitinib versus comparator treatments, where avelumab + axitinib would be considered in real-world NHS practice for some patients with intermediate-/poor-risk disease.

B.2.13.3 Summary

The Phase 3 JAVELIN Renal 101 trial provides the longest follow-up to date for IO+TKI combination treatment from a phase 3 trial in aRCC (≥68 months of follow-up), that is also generalisable to UK clinical practice.[99] The trial demonstrated the long-term efficacy and safety of first-line avelumab in combination with axitinib in aRCC. At the FA (DCO 31 August 2023), OS, PFS, ORR and DoR analyses favoured avelumab + axitinib compared with sunitinib in the subgroup of patients with IMDC favourable-risk disease.[98,100] PFS was improved in the intermediate-/poor-risk group, and OS results suggested a trend in favour of avelumab + axitinib, with separation of the KM survival curves continuing to end of follow-up.[100]

The safety profile of avelumab + axitinib as a first line treatment for patients with aRCC is well characterised. In JAVELIN Renal 101, avelumab + axitinib was generally tolerable and no new safety signals were identified.[98,99] The long-term safety profile of avelumab + axitinib in JAVELIN Renal 101 was consistent with previous analyses, the JAVELIN Renal 100 trial and real-world studies, and was consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies.[98,99]

Real-world studies further confirmed the effectiveness and safety of first-line avelumab + axitinib in routine UK clinical practice.[21,26,37,93,94]

Results of the ITC suggest that avelumab + axitinib provides similar treatment effects compared to some treatments in the IMDC intermediate-/poor-risk subgroup, with some immunotherapy-containing regimens demonstrating numerically better (though not statistically significantly different) results. However, it is not possible to determine which of the immunotherapy combinations is the most suitable treatment for a patient with poor-to-intermediate-risk aRCC in all cases.

While the licence allows use of avelumab + axitinib in aRCC irrespective of risk subgroups, it can provide an individualised treatment option for patients with IMDC favourable-and intermediate-/poor-risk groups.

Specifically, there is an unmet medical need for first-line IO+TKI combination treatment regimens that can be used consistently with clinical practice guidelines in IMDC favourable-risk patients with aRCC. As more IO-based combination therapies become available, movement towards more individualised first-line therapy will be necessary. As such, there is a need for additional safe and effective IO-based combination therapies to increase treatment options for patients with aRCC.

Avelumab + axitinib builds on the established efficacy of TKI monotherapy through the added benefit of immunotherapy, and in favourable-risk patients – who do not have any IO treatment options that are routinely commissioned in first-line and who may not receive subsequent IO treatment (as demonstrated in RWE) – it fulfils an unmet need for an IO+TKI treatment option to be accessible to patients and physicians in the treatment of favourable-risk aRCC.

B.3 Cost effectiveness

Summary of the submitted economic analysis

The base case cost-effectiveness analysis is based on people with favourable-risk aRCC

- The favourable-risk population represents the subgroup of the aRCC population with the greatest unmet need for more effective treatment options, since no IO-containing therapies are recommended in favourable-risk through routine commissioning, and current options are limited to TKI monotherapy (i.e., treatment with sunitinib, tivozanib, or pazopanib; as per the final scope).
- Cost-effectiveness results for the intermediate-/poor-risk subgroup are also presented in line with the NICE scope and compare against other available treatment options recommended in this population.
- For completeness, cost-effectiveness results for the full intention-to-treat (ITT) population are presented, as per the final NICE scope.

Summary of the submitted model

The cost-effectiveness model adopts a three-state partitioned-survival analysis (PartSA) structure

- The PartSA model structure is consistent with the approach used in the previous appraisal conducted by NICE for avelumab + axitinib in aRCC (TA645), and more recent appraisals conducted by NICE in aRCC (e.g., TA858 of lenvatinib with pembrolizumab for untreated aRCC and TA780 of nivolumab with ipilimumab for untreated aRCC).

The model is informed primarily by the pivotal JAVELIN Renal 101 study, using updated data from the Final Analysis

- Parametric survival models were fitted to extrapolate three key time-to-event endpoints captured within JAVELIN Renal 101 required to inform the model: OS, PFS, and TTD. Data from the Final Analysis of JAVELIN Renal 101 provide estimates of OS and PFS with a minimum follow-up of 68 months (5.67 years), and therefore there is considerably less uncertainty in extrapolations compared to TA645.
- Utility values were derived based on EQ-5D data collected in JAVELIN Renal 101, with sensitivity analyses explored using alternative utility values from previous NICE appraisals in aRCC (noting that there are important differences in the population considered in the base-case cost-effectiveness analysis [i.e., people with favourable-risk aRCC] and the populations considered in previous NICE appraisals [i.e., either all people with aRCC or people with intermediate-/poor-risk aRCC).
- Additional model inputs, including dosing intensity, occurrence of adverse events, and use of subsequent therapies, were also derived using data collected in JAVELIN Renal 101.

Summary of results

- Including a simple [redacted]% PAS discount for avelumab, the base-case analysis in the favourable-risk population shows that avelumab + axitinib is associated with a cost per quality-adjusted life year (QALY) gained, or incremental cost-effectiveness ratio (ICER), of £[redacted]. However, it should be noted that this ICER does not reflect the prices paid by the NHS for all relevant treatments, including most notably the cost of axitinib.
    - The anticipated emergence of generic axitinib [redacted] would substantially affect the cost-effectiveness results outputted by the model. This has been explored in a scenario analysis.
- Sensitivity analyses demonstrated that the most impactful model settings and assumptions were related to the choice of time horizon, specification of treatment acquisition costs, and extrapolations of OS.

Overall, the results of the cost-effectiveness analysis demonstrate that avelumab + axitinib provides additional benefit in terms of a LY and QALY gain for people with favourable-risk aRCC, compared with current care which comprises TKI monotherapies. Subject to further consideration of pricing arrangements for all relevant medicines, avelumab + axitinib has the potential to provide both a clinically- and cost-effective treatment options for a population of patients for whom current options are limited.

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify economic evaluations of avelumab + axitinib in untreated aRCC. Please see Appendix G for full details.

An update of the SLR carried out to inform NICE TA645 (i.e., the previous appraisal of avelumab with axitinib for aRCC) was performed.[16] In total, three searching iterations were performed: the original search (20 September 2017), update 1 (8 March 2019), and update 2 (4 June 2024). After preliminary screening of 1,212 abstracts, 1057 records were excluded, and 156 were included for secondary screening. After the secondary screening of full-text articles, 92 studies were excluded. In addition, 23 studies were identified from HTA websites and one study from conference searching; thus, this resulted in 81 unique studies identified from 87 publications.

Of note, five studies were identified that presented cost-effectiveness results for avelumab + axitinib. Of the studies identified, all were conducted in the aRCC population as a whole and thus, none specifically reflect results by IMDC risk group. Further, only one of the identified studies adopted a UK perspective (NICE TA645). The key parameters of influence across all the cost-effectiveness studies identified were related to treatment costs, utility values and estimates of OS and PFS.

Ultimately, the majority of previous studies adopted similar methods for cost-effectiveness analysis – that is, a PartSA model was used to reflect the key outcomes of PFS and OS. This is consistent with the model structure used to inform TA645, as well as more recent appraisals conducted by NICE since the publication of TA645.[16] One exception to this is the recent RCC Pathways Pilot, which involved the development of a much more complex sequencing model to evaluate the cost-effectiveness of different treatment sequences.[129] Given the scope of this appraisal is to focus on specific use of avelumab + axitinib, this alternative, complex model structure was not considered suitable for decision-making, and the structure used to inform TA645 was retained.

B.3.2 Economic analysis

B.3.2.1 Patient population

In total, the economic analysis considers three different populations of people with previously untreated aRCC:

- People with favourable-risk, defined by IMDC (“favourable-risk”).
- People with intermediate-to-poor-risk, defined by IMDC (“intermediate-/poor-risk”).
- People with poor, intermediate, or favourable-risk, defined by IMDC (“ITT”).

The base case population considered in the cost-effectiveness analysis is people with favourable-risk disease. This represents a subgroup of the ITT previously untreated aRCC population, and is the focus of the submission since (1) there is a greater unmet need for more effective treatment options for people with favourable-risk disease, compared to people with intermediate-/poor-risk disease, and (2) results from the JAVELIN Renal 101 study showed avelumab + axinitib to be clinically effective vs. sunitinib.

A subgroup analysis, of people with intermediate-/poor-risk, is considered in Section B.3.10. In TA645, the cost-effectiveness analysis focused on a population of aRCC across all risk groups (i.e., the ITT population).[16] However, following the CDF recommendation in September 2020 of avelumab + axitinib, additional treatment options have since been recommended for people with intermediate-/poor-risk disease, therefore the treatment landscape has become more fragmented into sub-groups. For completeness, it is possible to evaluate the cost-effectiveness of avelumab + axitinib in the ITT population within the submitted economic model of this CDF review. However, this population is not expected to be relevant for decision-making owing to the availability of different comparator therapies to avelumab + axitinib for people with different IMDC risk statuses. Results are provided in Appendix O.

Populations based on PD-L1 status were not explored in the cost-effectiveness modelling as clinical expert opinion indicated PD-L1 status is not considered relevant in systemic treatment decision-making for aRCC.[1]

B.3.2.2 Model structure

B.3.2.2.1 Model health states

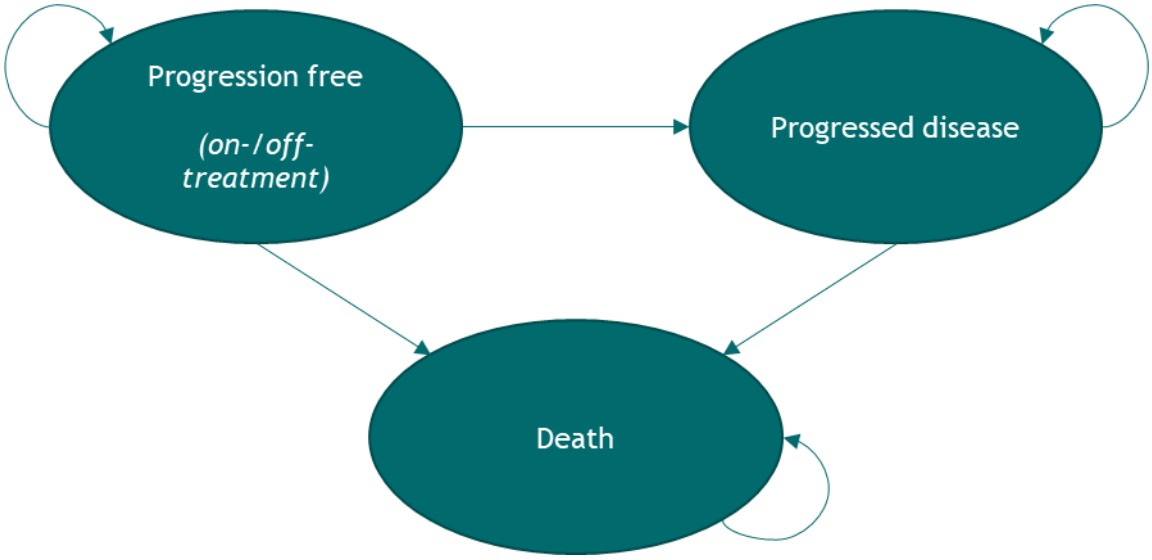
As noted in Section B.3.1, in line with the approach taken in TA645, the cost-effectiveness model was developed in Microsoft Excel® using an area-under-the-curve (PartSA) structure. The model structure consists of three overarching health states: progression-free (or pre-progression), progressed disease (or post-progression) and death. This structure was chosen for the following key reasons:

- A PartSA structure allows for an intuitive application of the outcome data captured in JAVELIN Renal 101 and accurately reflects the progressive nature of aRCC. This allows lifetime costs and health outcomes to be accurately estimated.
- Owing to the specification of survival curves to inform a PartSA structure, outputs from the ITC to compare avelumab + axitinib with the comparators can be easily leveraged to generate comparisons.
- A PartSA structure, with the specification of progression-based health states, is consistent with the previous submission and previous NICE appraisals in aRCC.[1,13–15]

The model schematic is presented in Figure 18. Patients enter the model in the progression-free health state where they receive treatment with avelumab + axitinib or a comparator. In each model cycle, patients can remain progression-free or transition to progressed disease or death. Once a patient's disease progresses, they either remain in the progressed disease health state or transition to death in each model cycle. Death is an absorbing health state.

To accurately reflect cost and health outcomes, the progression-free health state is further divided into on- and off- treatment periods, as in practice patients may discontinue therapy prior to documented disease progression. It is assumed that patients discontinue active treatment either before or upon progression (i.e., initial treatment is not permitted beyond documented disease progression).

Figure 18: Model schematic

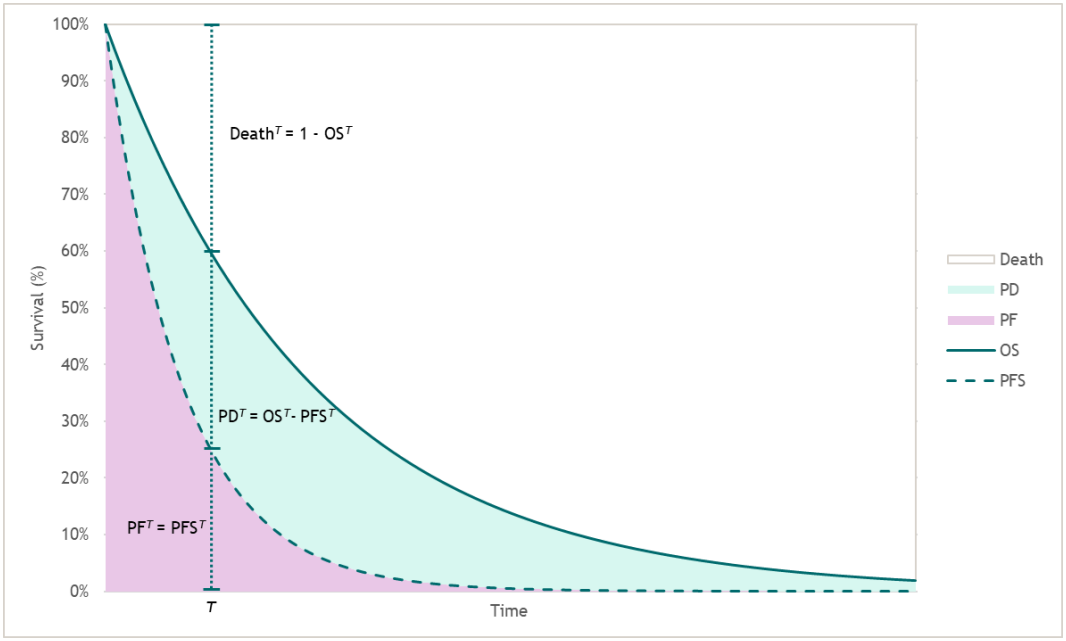


B.3.2.2.2 Health state occupancy

Health state occupancy is determined by independently modelled but non-mutually exclusive survival curves; namely, OS and PFS curves. Where available, TTD curves are used to calculate costs specific to treatment status.

Within a PartSA framework, the proportion of patients alive and free of progression at time *T* is equal to the PFS curve (PFS^T), the proportion of patients with progressed disease at time *T* is the difference between OS^T and PFS^T, and the proportion of patients in the death state is 1 minus OS^T. Figure 19 visually demonstrates how extrapolated parametric survival curves are used to derive health state occupancy within a PartSA model. Details of how the OS, PFS and TTD curves are derived are provided in Section B.3.3.

Figure 19: Health state occupancy, illustrative partitioned survival model



Abbreviations: OS, overall survival, PD, progressed disease; PF, progression free; PFS, progression-free survival.

B.3.2.2.3 Model settings

As per the NICE reference case, all health effects were measured using quality-adjusted life years (QALYs), with an annual 3.5% discount applied to both costs and QALYs.[130] The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS).

The NICE reference case stipulates that the time horizon of economic models should be long enough to reflect all important differences in costs or outcomes between technologies.[130] As such, the cost-effectiveness analysis adopts a lifetime horizon of 40 years, which was considered long enough to adequately capture the lifetime of people with aRCC with a model entry age of approximately 61 years, assuming no patients will survive beyond the age of 100 years (i.e., $100 - 61 = 39$). The average age of the cohort upon entry to the model was based on baseline median age from JAVELIN Renal 101 (see Table 40).[45]

The model uses a 1-week cycle length, which is assumed to be short enough to adequately capture meaningful changes in health status for people with aRCC being treated with avelumab + axitinib or a comparator. Due to the short cycle length, a half-cycle correction is not applied.

The most relevant comparator NICE appraisals to the favourable-risk subgroup are: NICE TA169 (sunitinib), NICE TA512 (tivozanib) and NICE TA215 (pazopanib).[4–6] However, it should be noted that the populations from the previous appraisals are not identical to the population relevant to this appraisal (ITT population versus IMDC risk sub-groups, with a focus on the favourable-risk subgroup). A summary of the main features of the economic analysis and the previous NICE appraisal are provided in Table 38.

Table 38: Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA169 (sunitinib)	TA512 (tivozanib)	TA215 (pazopanib)	Chosen values	Justification
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	In line with the NICE reference case.[130]
Model structure	Cohort level PartSA model	Cohort level PartSA model	Cohort level PartSA model	Cohort level PartSA model	Reflects the natural history of disease, allows for the incorporation of indirect treatment comparison, and is consistent with previous models.
Time horizon	10 years	10 years	10 years	Lifetime (40 years)	A time horizon of 40 years was deemed sufficiently long to capture the full extent of both costs and effects. Alternative time horizons are explored in scenario analyses.
Cycle length	4 days	1 week (7 days)	1 day	1 week (7 days)	A 7-day cycle length was considered short enough to adequately capture meaningful changes in the health status of people with aRCC.
Half-cycle correction	Unclear	No	No	No	A half-cycle correction was not considered necessary due to the short cycle length.
Discount rate	3.5% for both costs and effects	3.5% for both costs and effects	3.5% for both costs and effects	3.5% for both costs and effects	In line with the NICE reference case.[130] In the results provided, LYs are undiscounted for ease of interpretation (but can be discounted in the economic model submitted alongside this dossier).
Source of utilities	Estimated from EQ-5D-3L data from Phase 2 and 3 sunitinib trials; UK valuation tariff	EQ-5D-3L data from TIVO-1	PF: EQ-5D-3L data from pazopanib RCT; UK valuation tariff; PP: published literature	Estimated from EQ-5D-5L data collected in the JAVELIN Renal 101 study[45]	In line with the NICE reference case.[130]
Source of costs	Based on UK reference costs, literature, and expert opinion	Based on UK reference costs, literature, and expert opinion	Based on UK reference costs, literature, and expert opinion	BNF, NHS National Cost Collection, eMIT, PSSRU[131–134]	In line with the NICE reference case.[130]

Abbreviations: aRCC, advanced renal cell carcinoma; BNF, British National Formulary; eMIT, electronic market information tool; EQ-5D, Euro-QoL five-dimension; LY(s), life-year(s); NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PartSA, partitioned-survival analysis; PF, progression-free; PP, post-progression; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention investigated is a flat intravenous (IV) dose of 800mg avelumab Q2W + 5mg axitinib orally BD. The duration of therapy was based on stratified TTD data from JAVELIN Renal 101.[45] To account for the known relative dose intensity (RDI), the RDI of avelumab and axitinib from the JAVELIN Renal 101 study are included in the model base case.

B.3.2.3.2 Comparators

The final scope issued by NICE for this appraisal highlights the following potential comparators to avelumab + axitinib in first-line IMDC favourable-risk aRCC; sunitinib, tivozanib and pazopanib. In March 2024, Frazer *et al.* published data from a retrospective multi-institutional cohort of SACT patients for mRCC at 17 centres across the UK from 1 January 2018 and 30 June 2021.[37] The most prescribed first-line TKI monotherapy for people with favourable-risk aRCC was sunitinib (50.5%), followed by pazopanib (31.6%) and tivozanib (15%).

The economic evaluation includes comparisons to these treatments, dosed according to the information provided in Table 39. For consistency with avelumab + axitinib, RDI values are also included in the model base case for comparators.

Table 39: Comparator treatments and dosing details

Comparator	Dosing	Relevant population	Reference
Sunitinib	50mg orally OD for 4 consecutive weeks followed by a 2-week off-treatment period (Schedule 4/2).	1L aRCC patients	JAVELIN Renal 101[45]
Tivozanib	1.34 mg OD for 21 days followed by a 7-day rest period	1L aRCC patients	Fotivda SmPC[135]
Pazopanib	800 mg daily	1L aRCC patients	Votrient SmPC[136]

Abbreviations: 1L, first-line; aRCC, advanced renal cell carcinoma; mg, milligram; OD, once daily; NMA, network meta-analysis; SmPC, summary of product characteristics.

Cabozantinib (TKI) and the other immunotherapy combinations (nivolumab + ipilimumab, pembrolizumab + lenvatinib, and nivolumab + cabozantinib) are further recommended by NICE for use only in people with intermediate-/poor-risk aRCC (as noted in the final scope for this appraisal). A subgroup analysis for intermediate-/poor-risk population with the relevant comparators (including sunitinib, tivozanib and pazopanib) is presented in Section B.3.10. Additional details of the comparisons made in the intermediate-/poor-risk population and the cost-effective analysis for the ITT population are provided in Appendix O.

B.3.3 Clinical parameters and variables

Model efficacy estimates for avelumab + axitinib and sunitinib are presented based on the population with favourable-risk in JAVELIN Renal 101. For tivozanib and pazopanib, outcomes (i.e., OS and PFS) were assumed to be same as those for sunitinib, in keeping with the assumption made in previous appraisals (TA645, TA512) that first-line TKI monotherapies are similarly efficacious (given that there is no additional evidence comparing TKIs that has been made available since the publication of TA645).[1] Sunitinib was chosen to inform the efficacy of the TKIs owing to the availability of direct comparative evidence to avelumab + axitinib from the JAVELIN RENAL 101 trial. In 2019, Manz *et al.* [1] In 2019, Manz *et al.* published an NMA comparing different TKIs approved in the first-line setting for people

with aRCC, finding that these treatments do not differ significantly in their efficacy.[137] The assumption of a similar efficacy across all TKIs for all aRCC IMDC risk groups is also supported by clinical opinion.

For the comparators included for the intermediate-/poor-risk population (cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib, and nivolumab + cabozantinib), outcomes from the NMA were used to inform the model. Details of the NMA are provided in Section B.2.10, and additional information about the cost-effectiveness analysis for the intermediate-/poor-risk population are provided in Appendix O.

B.3.3.1 Baseline patient characteristics

Baseline patient characteristics were based on the IMDC favourable-risk population in JAVELIN Renal 101, and are presented in Table 40. Baseline patient characteristics for the intermediate-/poor-risk and ITT populations are presented in Appendix O.

Table 40: Baseline patient characteristics (favourable-risk)

Characteristic	Value	Source
Age (years)	[redacted]	Analysis of patient-level data from JAVELIN Renal 101[45]
Proportion female	[redacted]%	
Weight (kg)	[redacted]	

Abbreviations: cm, centimetre; kg, kilogram.

B.3.3.2 Overall and progression-free survival

Data from the JAVELIN Renal 101 study were used to inform OS, PFS and TTD within the economic model for avelumab + axitinib and sunitinib. The JAVELIN Renal 101 study is discussed in further detail in Section B.2.3. In the absence of direct evidence, efficacy estimates for tivozanib and pazopanib are assumed to be equivalent to sunitinib. This assumption was validated by clinical expert opinion sought by the company.

Survival modelling was required to inform the economic model to estimate costs and QALYs over a lifetime horizon. Independent parametric survival models (PSMs) were fitted to the OS, PFS, and TTD data. The most appropriate distribution was determined per guidance set out in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[138] The visual inspection of extrapolated survival, alongside Akaike and Bayesian information criteria (AIC, BIC) was used to determine the most appropriate model to characterise the Kaplan-Meier (KM) estimates of each endpoint. Validation from three clinical experts (see Section B.3.12) was sought to aid with the interpretation of OS and PFS estimates to assess the clinical plausibility of long-term outcomes and select an appropriate PSM to inform the base-case analysis. A description of the approach and rationale to inform the base case for each endpoint is discussed in turn throughout this section for the favourable-risk population.

Additional information about the cost-effectiveness analysis for the intermediate-/poor-risk and ITT populations are provided in Appendix O.

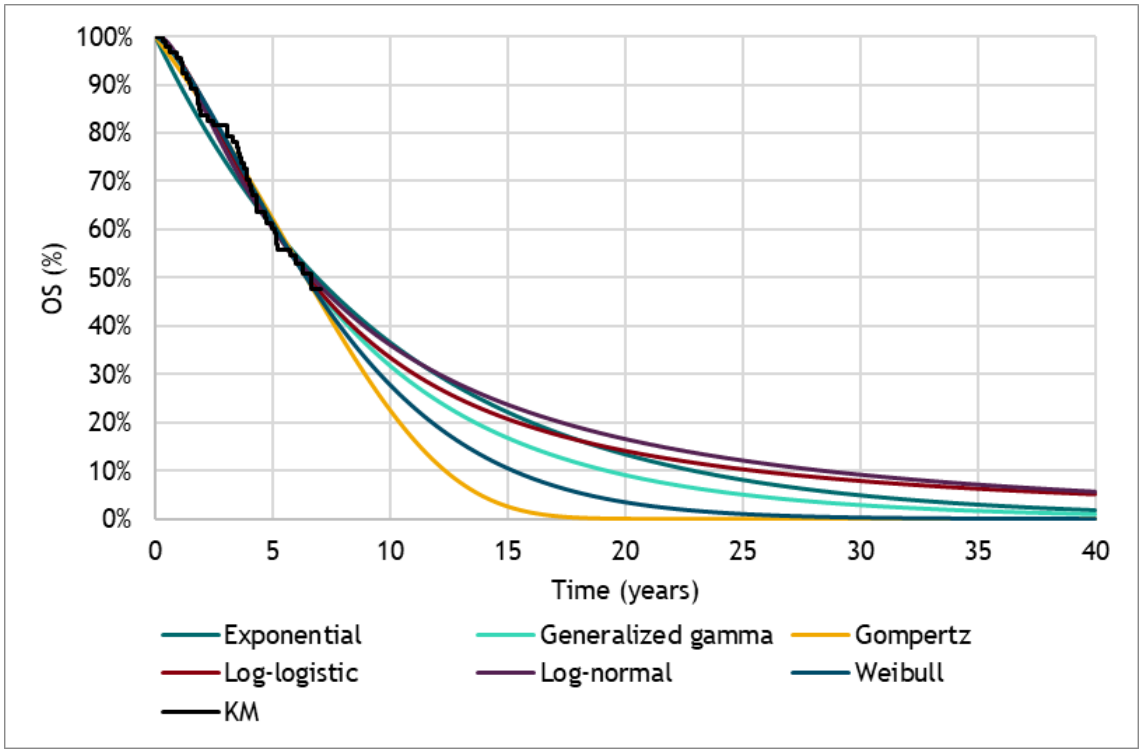
B.3.3.2.1 Overall Survival

The KM estimate of OS for avelumab + axitinib from the JAVELIN Renal 101 study for the IMDC favourable-risk population is provided in Figure 6. To ensure model validity, all curves used to produce economic and survival estimates were capped to ensure that patients' transition to death was never lower than that of the general population. In any cycle where the estimated probability of death was lower than that of the age- and sex-adjusted general population, general population was instead applied.

Avelumab + axitinib

Figure 20 presents the parametric curve fits to the observed KM. AIC and BIC scores can be used to determine the relative fit of the PSMs to the observed data. The AIC and BIC for the avelumab + axitinib OS PSMs are provided in Table 41. Based on the AIC and BIC scores, the log-logistic model provided the best fit for avelumab + axitinib, though all other PSMs had relatively similar AIC/BIC fits.

Figure 20: Parametric curve fits - avelumab + axitinib – OS (favourable-risk)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 41: Statistical goodness-of-fit scores - avelumab + axitinib – OS (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	510.82	513.36	6	4
Generalised gamma	509.36	516.99	4	6
Gompertz	509.43	514.52	5	5
Log-logistic	507.57	512.65	1	1
Log-normal	508.01	513.10	3	3
Weibull	507.71	512.80	2	2

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Each of the PSMs fit the data reasonably well in the observed period except the exponential model, which appears to underestimate OS in the initial ~5 years. After the end of follow-up, the PSMs estimate a range of long-term survival predictions. Table 42 presents the landmark OS estimates for avelumab + axitinib. Estimates remain similar between curves in the initial 5 years, with a wider spread observed at 10 years (ranging from 22.7% to 36.7% alive).

Table 42: Landmark survival estimates - avelumab + axitinib – OS (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	90.5%	81.8%	60.6%	36.7%
Generalised gamma	95.3%	86.9%	60.8%	31.9%
Gompertz	93.4%	86.2%	62.3%	22.7%
Log-logistic	95.4%	87.1%	60.7%	33.6%
Log-normal	95.4%	85.8%	60.3%	36.2%
Weibull	95.0%	87.3%	61.5%	27.9%

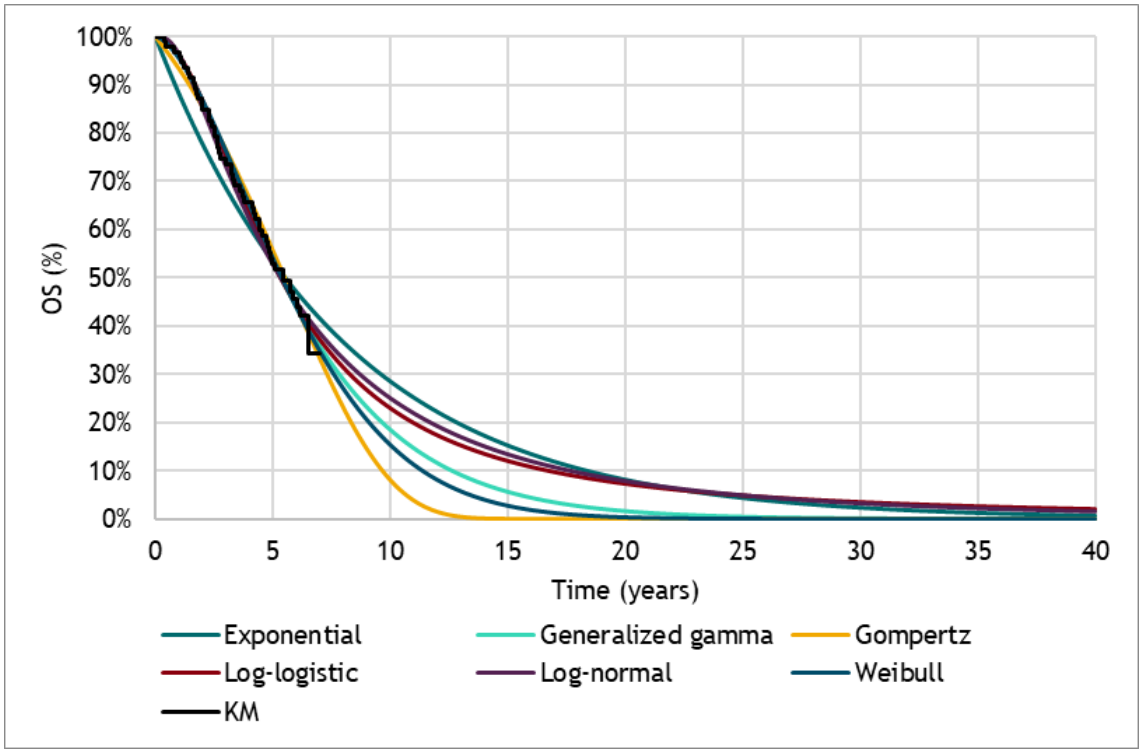
Abbreviations: OS, overall survival.

Overall, the log-normal PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, statistical goodness-of-fit and long-term survival projections which were aligned with clinical expert opinion provided to the company. Exploration of alternative curve fits is considered in scenario analysis.

Sunitinib

Figure 21 presents the parametric curve fits to the observed KM. The AIC and BIC for the sunitinib OS PSMs are provided in Table 43. Based on the AIC and BIC scores, the Weibull model provided the best fit for sunitinib, though several other PSMs had relatively similar AIC/BIC fits.

Figure 21: Parametric curve fits - sunitinib – OS (favourable-risk)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 43: Statistical goodness-of-fit scores - sunitinib – OS (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	580.32	582.88	6	6
Generalised gamma	571.59	579.28	4	5
Gompertz	572.61	577.73	5	4
Log-logistic	570.12	575.25	2	2
Log-normal	571.12	576.25	3	3
Weibull	569.82	574.95	1	1

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Each of the PSMs fit the data reasonably well in the observed period except the exponential model, which appears to underestimate OS in the initial ~5 years before overestimating the observed KM between 5 years and the end of follow up. After the end of follow-up, the PSMs estimate a range of long-term survival predictions. Table 44 presents the landmark OS estimates for sunitinib. As seen with avelumab + axitinib, estimates remain reasonably similar between the majority of curves in the initial 5 years, with a wider spread observed at 10 years (ranging from 8.2% to 28.6% alive).

Table 44: Landmark survival estimates - sunitinib – OS (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	88.2%	77.9%	53.5%	28.6%
Generalised gamma	95.9%	86.7%	53.6%	18.6%
Gompertz	93.4%	85.6%	55.8%	8.2%
Log-logistic	96.2%	86.9%	53.2%	23.1%
Log-normal	96.4%	85.4%	52.9%	25.2%
Weibull	95.5%	87.0%	54.3%	15.5%

Abbreviations: OS, overall survival.

Overall, the generalised gamma PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, statistical goodness-of-fit and long-term survival projections validated by clinical expert opinion. Exploration of alternative curve fits is considered in scenario analysis.

Tivozanib and pazopanib

OS for tivozanib and pazopanib are assumed equal to sunitinib.

B.3.3.2.2 Progression-free survival

The KM estimate of PFS for avelumab + axitinib and sunitinib from the JAVELIN Renal 101 study for the IMDC favourable-risk population is provided in Figure 7.

Avelumab + axitinib

Figure 22 presents the parametric curve fits to the observed KM. The AIC and BIC for the avelumab + axitinib PFS PSMs are provided in Table 45. Based on the AIC and BIC scores, the log-normal model provided the best fit for avelumab + axitinib, though several other PSMs had relatively similar AIC/BIC fits.

Figure 22: Parametric curve fits - avelumab + axitinib – PFS (favourable-risk)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 45: Statistical goodness-of-fit scores - avelumab + axitinib - PFS (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	[redacted]	[redacted]	4	3
Generalised gamma	[redacted]	[redacted]	3	4
Gompertz	[redacted]	[redacted]	6	6
Log-logistic	[redacted]	[redacted]	2	2
Log-normal	[redacted]	[redacted]	1	1
Weibull	[redacted]	[redacted]	5	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

All of the PSMs fit the data reasonably well in the observed period. After the end of follow-up, the PSMs estimate a small range of long-term survival predictions, with the log-logistic and log-normal models predicting the most optimistic PFS, and exponential the most pessimistic. Table 46 presents the landmark PFS estimates for avelumab + axitinib. Estimates remain similar between curves in the initial 5 years, with a slightly wider spread observed at 10 years (ranging from 1.0% to 4.9% progression-free).

Table 46: Landmark survival estimates - avelumab + axitinib - PFS (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Gompertz	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-normal	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Weibull	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Abbreviations: PFS, progression-free survival.

Overall, the log-normal PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, statistical goodness-of-fit and long-term survival projections validated by clinical expert opinion. Exploration of alternative curve fits is considered in scenario analysis.

Sunitinib

Figure 23 presents the parametric curve fits to the observed KM. The AIC and BIC for the sunitinib PFS PSMs are provided in Table 47. Based on the AIC and BIC scores, the log-normal and exponential models provide the best fit for sunitinib, though several other PSMs had relatively similar AIC/BIC fits.

Figure 23: Parametric curve fits - sunitinib – PFS (favourable-risk)

[redacted]

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 47: Statistical goodness-of-fit scores - sunitinib - PFS (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	[redacted]	[redacted]	2	1
Generalised gamma	[redacted]	[redacted]	3	6
Gompertz	[redacted]	[redacted]	6	5
Log-logistic	[redacted]	[redacted]	4	3
Log-normal	[redacted]	[redacted]	1	2
Weibull	[redacted]	[redacted]	5	4

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Each of the PSMs fit the data reasonably well to approximately 3 years, after which the log-logistic and log-normal models appears to overestimate PFS between 3 to 6 years. After the end of follow-up, the PSMs estimate a small range of long-term survival predictions.

Table 48 presents the landmark PFS estimates for sunitinib. Estimates remain reasonably similar between the majority of curves in the initial 2 years, with a wider spread observed at 5 and 10 years (ranging from 0.2% to 3.7% progression-free at 10 years). The log-logistic and log-normal models predict the most optimistic PFS, with the Weibull estimating the lowest proportion of patients' progression-free in the longer term.

Table 48: Landmark survival estimates - sunitinib - PFS (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Gompertz	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-normal	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Weibull	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Abbreviations: PFS, progression-free survival.

Overall, the generalised gamma PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, and long-term survival projections validated by clinical expert opinion. Exploration of alternative curve fits is considered in scenario analysis.

Tivozanib and pazopanib

PFS for tivozanib and pazopanib are assumed equal to sunitinib.

B.3.3.3 Time to treatment discontinuation

TTD was reported separately for avelumab and axitinib in the JAVELIN Renal 101 data; therefore, parametric model fits were conducted separately for avelumab and axitinib. TTD data for avelumab and axitinib were derived individually for each treatment, reflecting the possibility of patients discontinuing avelumab and axitinib independently. Validation from three clinical experts (see Section B.3.12) was sought to aid with the interpretation of TTD and the selection of the base case extrapolation to inform the analyses.

The KM estimates of TTD for all three drugs (i.e., avelumab, axitinib, and sunitinib) are presented in Figure 24.

Figure 24: Kaplan-Meier plot – avelumab, axitinib, and sunitinib – TTD (favourable-risk)

Abbreviations: TTD, time to treatment discontinuation.

Avelumab + axitinib

Avelumab

Figure 25 presents the PSM fits to the KM estimate. The AIC and BIC for the avelumab TTD PSMs are provided in Table 49. Based on the AIC and BIC scores, the Gompertz and exponential models provided the best fit for avelumab, though all other PSMs except the log-logistic and log-normal curves had relatively similar AIC/BIC fits.

Figure 25: Parametric curve fits – avelumab – TTD (favourable-risk)

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 49: Statistical goodness-of-fit scores - avelumab - TTD (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	[redacted]	[redacted]	2	1
Generalised gamma	[redacted]	[redacted]	4	4
Gompertz	[redacted]	[redacted]	1	2
Log-logistic	[redacted]	[redacted]	6	6
Log-normal	[redacted]	[redacted]	5	5
Weibull	[redacted]	[redacted]	3	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation.

Table 50 presents the landmark TTD estimates for avelumab. Estimates vary considerably between curves, particularly in the longer term.

Table 50: Landmark survival estimates - avelumab - TTD (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Gompertz	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-normal	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Weibull	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Abbreviations: TTD, time to treatment discontinuation.

Overall, the generalised gamma PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, and long-term survival projections validated by clinical expert opinion. Exploration of alternative curve fits is considered in scenario analysis.

Axitinib

Figure 26 presents the PSM fits to the KM estimate. The AIC and BIC for the axitinib TTD PSMs are provided in Table 51. Based on the AIC and BIC scores, the Gompertz and exponential models provided the best fit for axitinib, though all other PSMs except the log-logistic and log-normal curves had relatively similar AIC/BIC fits.

Figure 26: Parametric curve fits - axitinib – TTD (favourable-risk)

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 51: Statistical goodness-of-fit scores - axitinib - TTD (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	[redacted]	[redacted]	3	1
Generalised gamma	[redacted]	[redacted]	2	4
Gompertz	[redacted]	[redacted]	1	2
Log-logistic	[redacted]	[redacted]	5	5
Log-normal	[redacted]	[redacted]	6	6
Weibull	[redacted]	[redacted]	4	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation.

Table 52 presents the landmark TTD estimates for axitinib. Estimates vary considerably between curves, particularly in the longer term.

Table 52: Landmark survival estimates - axitinib - TTD (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Gompertz	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-normal	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Weibull	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Abbreviations: TTD, time to treatment discontinuation.

Overall, the generalised gamma PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, statistical goodness-of-fit, and long-term survival projections validated by clinical expert opinion. Exploration of alternative curve fits is considered in scenario analysis.

Sunitinib

Figure 27 presents the PSM fits to the KM estimate. The AIC and BIC for the sunitinib TTD PSMs are provided in Table 53. Based on the AIC and BIC scores, the exponential model provided the best fit for sunitinib, though several other PSMs had relatively similar AIC/BIC fits. Similar to avelumab and axitinib TTD, the log-logistic and log-normal models provide the worst statistical fit to the data.

Figure 27: Parametric curve fits - sunitinib – TTD (favourable-risk)

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 53: Statistical goodness-of-fit scores - sunitinib - TTD (favourable-risk)

Model	AIC	BIC	Rank	
			AIC	BIC
Exponential	[redacted]	[redacted]	1	1
Generalised gamma	[redacted]	[redacted]	4	4
Gompertz	[redacted]	[redacted]	2	2
Log-logistic	[redacted]	[redacted]	5	5
Log-normal	[redacted]	[redacted]	6	6
Weibull	[redacted]	[redacted]	3	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation.

Table 54 presents the landmark TTD estimates for sunitinib. Estimates remain reasonably similar between the majority of curves in the initial 2 years, with a wider spread observed at 5 and 10 years (ranging from [redacted]% to [redacted]% of patients still on treatment at 10 years).

Table 54: Landmark survival estimates - sunitinib - TTD (favourable-risk)

Model	Landmark survival estimates (years)			
	1	2	5	10
Exponential	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Generalised gamma	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Gompertz	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-logistic	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log-normal	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Weibull	[redacted]%	[redacted]%	[redacted]%	[redacted]%

Abbreviations: TTD, time to treatment discontinuation.

Overall, the generalised gamma PSM was considered appropriate to inform the base case analysis, based on visual inspection of the PSM versus the KM estimate, and long-term survival projections validated by clinical expert opinion. Exploration of alternative curve fits is considered in scenario analysis.

Tivozanib and pazopanib

Due to a lack of TTD data for tivozanib and pazopanib, TTD was assumed to be equal to the TTD of sunitinib.

B.3.3.4 Summary of base-case PSM curve fit selection for favourable-risk population

A summary of the PSMs used to inform the base case analysis for both populations is provided in Table 55.

Table 55: Summary of base case PSM curve fits (favourable-risk)

Treatment	Outcome	Choice of PSM
OS	Avelumab + axitinib	Log-normal
	Sunitinib	Generalised gamma
	Tivozanib	Assumed equal to sunitinib
	Pazopanib	Assumed equal to sunitinib
PFS	Avelumab + axitinib	Log-normal
	Sunitinib	Generalised gamma
	Tivozanib	Assumed equal to sunitinib
	Pazopanib	Assumed equal to sunitinib
TTD	Avelumab	Generalised gamma
	Axitinib	Generalised gamma
	Sunitinib	Generalised gamma
	Tivozanib	Assumed equal to sunitinib
	Pazopanib	Assumed equal to sunitinib

Abbreviations: OS, overall survival, PFS, progression-free survival; PSM, parametric survival model; TTD, time to treatment discontinuation.

The base case OS, PFS, and TTD estimates for avelumab + axitinib are presented in Figure 28; and the corresponding estimates for sunitinib, tivozanib, and pazopanib (favourable-risk comparators) are presented in Figure 29.

Figure 28: Avelumab + axitinib base case curves (favourable-risk)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.
Note: Curves are adjusted for background mortality.

Figure 29: Sunitinib, tivozanib, and pazopanib base case curves (favourable-risk)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Figure 30: All treatments, base case curves (favourable-risk)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

B.3.3.5 Adverse events

Adverse events (AEs) were included in the model to capture the costs associated with their resolution and management. Treatment-related Grade ≥3 AEs experienced by ≥5% of

patients in either arm of the JAVELIN Renal 101 study (ITT population, FA analysis datacut of 31 August 2023) were included in the model, as presented in Table 56.

Table 56: Grade ≥3 TRAEs experienced by ≥5% of patients in JAVELIN Renal 101 (ITT)

Adverse event	Avelumab + axitinib		Sunitinib	
	N	%	N	%
Alanine aminotransferase increased	23	5.30%	11	2.51%
Anaemia	2	0.46%	30	6.83%
Diarrhoea	41	9.45%	14	3.19%
Hypertension	120	27.65%	77	17.54%
Lipase increased	25	5.76%	16	3.64%
Neutropenia	1	0.23%	38	8.66%
Neutrophil count decreased	1	0.23%	30	6.83%
Hand-foot syndrome*	28	6.45%	19	4.33%
Platelet count decreased	1	0.23%	25	5.69%
Thrombocytopenia	1	0.23%	27	6.15%

Abbreviations: ITT, intention-to-treat; TRAE, treatment-related adverse events.
Note: Values taken from Clinical Study Report for Final Analysis of JAVELIN Renal 101 (Table 22).[99] *Palmar-plantar erythrodysaesthesia syndrome.

B.3.4 Measurement and valuation of health effects

To capture the impact of symptoms of aRCC on patient quality of life, HRQoL is reflected in the analysis. Utility values were applied to both alive health states in the model (progression-free, progressed disease) to capture patient HRQoL associated with treatment and disease outcomes. Trial data were preferred as a source of utility inputs given that this allowed utility and efficacy data to be derived from the same population, and in keeping with the guidance set out in NICE health technology evaluations: the manual (Section 4.3.8:*" If not available in the relevant clinical trials, EQ-5D data can be sourced from the literature"* – here, these data are available, and are therefore used to inform the economic model).

B.3.4.1 Health-related quality-of-life data from clinical trials

In the JAVELIN Renal 101 clinical trial, HRQoL outcomes were assessed using the EQ-5D five-level version (EQ-5D-5L), as well as the total score from the Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 (FKSI-19) questionnaire. In JAVELIN Renal 101, the EQ-5D-5L questionnaire was administered to patients at tumour assessment every 6 weeks. EQ-5D data obtained from IMDC favourable-risk patients are used to inform the base-case economic analysis, as detailed in the sub-sections that follow. Note that HRQoL analyses provided in Section B.2.6.4 refer to the full population in JAVELIN Renal 101, and do not provide health state utility values that could be directly applied in the model.

B.3.4.2 Mapping

EQ-5D-5L data were collected in the JAVELIN Renal 101 trial, however, NICE does not recommend using the EQ-5D-5L values set for technology appraisals**.**[130] The NICE reference case recommends mapping EQ-5D-5L data to EQ-5D-3L using the function developed by the NICE DSU (Hernández-Alava *et al.* [2017]).[139]

The following health states were considered for the health-state utility values:

- Pre-progression

- Post-progression

The mapped IMDC favourable-risk EQ-5D-3L utility values were analysed using a linear mixed-effects regression model, with patient ID included as a random-effect term and progression status included as a fixed-effect (Model 1). This model allows for the consideration of repeated EQ-5D-3L measurements at the patient level, given each individual may provide several assessments during the study follow-up period. To explore the impact of treatment status on HRQoL, a second regression model including a treatment status covariate (i.e., on/off treatment) as a fixed-effect was conducted (Model 2).

The output of the two utility regression models is presented in Table 57. Progression status was associated with a decrease in utility compared to progression-free observations ([redacted] and [redacted] for Model 1 and Model 2, respectively). The output provides evidence to support a statistically significant effect of progression status on utility (p<0.001) in both Model 1 and Model 2. Treatment status was associated with a slight decrease in utility ([redacted]), though there is no evidence to suggest this effect was statistically significant (p=0.142).

Table 57: Regression model output (favourable-risk)

Model	Parameter	Coefficient	SE	P-value	AIC	BIC
Model 1	Intercept	[redacted]	[redacted]	<0.001	[redacted]	[redacted]
	Progression status – Progressed disease	[redacted]	[redacted]	<0.001		
Model 2	Intercept	[redacted]	[redacted]	<0.001	[redacted]	[redacted]
	Progression status – Progressed disease	[redacted]	[redacted]	<0.001		
	Treatment status – On treatment	[redacted]	[redacted]	0.1424		

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; SE, standard error.

A summary of the predicted utility values (derived from the statistical regression model) by health state used in the economic model are presented in Table 58. Utilities estimated from Model 1 are used in the base case, with Model 2 utilities explored in scenario analysis.

Table 58: Predicted utility values by health state (favourable-risk)

Model	Health state	Mean	SE
Model 1	Progression-free	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]
Model 2	Progression-free - Off treatment	[redacted]	[redacted]
	Progressed disease - Off treatment	[redacted]	[redacted]
	Progression-free - On treatment	[redacted]	[redacted]
	Progressed disease - On treatment	[redacted]	[redacted]

Abbreviations: SE, standard error.

B.3.4.3 Health-related quality-of-life studies

Utility values used in previous NICE TAs in RCC are presented in Table 59. Utility values in the more recent TA858 of pembrolizumab + lenvatinib are redacted.[14] The progression-free utility value from the base case analysis of JAVELIN Renal 101 data is on the higher end of the utilities from the literature, though remains within the range of values used previously.

For progressed disease, the utility value estimated from JAVELIN Renal 101 is slightly greater than the upper estimate used in previous TAs (Model 1 in this submission: [redacted] versus 0.7600 [nivolumab, TA417]).[87]

The higher estimates observed may be attributed to a difference in populations used to estimate utility (i.e., all IMDC risk groups for previous TAs versus IMDC favourable-risk for the base case analysis in this appraisal). It should also be noted that utilities from TA432 and TA417 represent 2L+ populations, which may be anticipated to have lower utility owing to these patients having more advanced disease.[86]

Table 59: Comparator utility values from previous NICE TAs

NICE TA	Indication	Intervention	Utility value		Population	Assumptions used
			Progression-free	Progressed disease		
TA178[80]	1L aRCC	Sunitinib	Sunitinib: 0.7700 IFN: 0.7900	Sunitinib: 0.7200 IFN: 0.6900	ITT	All arms have sunitinib with the exception of the placeholders, which are assumed to have IFN utility
TA215[5]	1L aRCC	Pazopanib	0.7000	0.5900	ITT	-
TA512[6]	1L aRCC	Tivozanib	0.7260	0.6490	ITT	-
TA542[7]	1L aRCC	Cabozantinib	0.7260	0.6490	ITT	-
TA581[3]	1L aRCC	Nivolumab + Ipilimumab (Nivo + Ipi)	Nivo + Ipi: 0.7930 Sunitinib: 0.7190	Nivo + Ipi: 0.7510 Sunitinib: 0.6990	ITT	TA581: All therapies using antibodies have nivolumab + ipilimumab utility, all other have sunitinib utility
TA432[86]	2L+ aRCC	Everolimus	0.7100	0.6800	ITT	-
TA417[87]	2L+ aRCC	Nivolumab	Nivolumab: 0.8000 Everolimus: 0.7600 BSC, axitinib: 0.6900	Nivolumab: 0.7600 Everolimus: 0.7000 BSC, axitinib: 0.6100	ITT	TA417: All therapies using antibodies have nivolumab utility, all other have everolimus
Average across all appraisals			0.7440	0.6816		-
Average % utility decrement			NA	8.85%		-

Abbreviations: 1L, first-line; 2L+, second- or later-line; aRCC, advanced renal cell carcinoma; BSC, best supportive care; IFN, interferon; ipi, ipilimumab; ITT, intention-to-treat; N/A = not applicable; NICE = National Institute for Health and Care Excellence; PFS = progression-free survival; TA = technology appraisal.

B.3.4.4 Adverse reactions

Health state utility values were calculated from PLD independent of whether patients experienced a TRAE. It was therefore assumed that the derived utility values reflect any disutility from AEs, as applying disutilities related to AEs would double count the QoL impact of treatment already captured within the health state utility values for PFS and PPS. Therefore, no specific AE-related disutility values were incorporated into the model, aligned with the approach in TA645.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Analysis of the EQ-5D data collected in JAVELIN Renal 101 were used to inform the utility values for the progression-free and progressed disease health states (as described in Sections B.3.4.1 and B.3.4.2). Alternative values including a term for treatment status and values sourced from the literature and previous NICE technology appraisals were explored in scenario analyses.

An adjustment for age-related utility decrements was included in the model to account for the natural age-related decline in quality of life. This adjustment was applied by estimating general population utility values at each age using the Ara & Brazier (2010) algorithm, to determine a utility multiplier linked to the starting age of the modelled cohort.[140] The formula used to estimate general population utility (which then informs the multiplier) is shown below:

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

A summary of utility inputs for the cost-effectiveness model is presented in Table 60.

Table 60: Summary of utility values for cost-effectiveness analysis (favourable-risk)

State	Utility value: mean (SE)	95% CI*	Reference in submission	Justification
Progression-free	[redacted]	[redacted]	Section B.3.4.2, Page 125	EQ-5D-5L data mapped to EQ-5D-3L as derived from the relevant population
Post-progression	[redacted]	[redacted]	Section B.3.4.2, Page 125	

Abbreviations**:** CI, confidence interval; EQ-5D, Euro-QoL five-dimension; SE, standard error.
Note: *95% confidence interval is shown here for illustrative purposes. In the economic model, the utility values are sampled based on a variance-covariance matrix.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Acquisition costs associated with the intervention and comparators are presented in Table 61. List prices were sourced from the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT).[131,132]

Avelumab has an existing simple patient access scheme (PAS) discount of [redacted]%. Due to the confidential nature of PAS discounts, the net prices of axitinib and tivozanib are not known and are therefore not included in the base case analysis. The discounted price for pazopanib reflects a published discount of 12.5%. Since TA645, the patent for sunitinib expired which means generic alternatives to Sutent® (Pfizer) are now available, and so these costs were taken from eMIT. The generic price of sunitinib is applied in the base case analysis.

The base-case analysis uses the list price of axitinib, though it should be noted [redacted].[141] Thereafter, it is expected that potential emergence of generic formulations of axitinib will be made available in NHS practice, which is expected to have a marked effect on the total acquisition cost to the NHS of the avelumab + axitinib combination. Therefore, we have included a scenario analysis which assesses a proxy price for axitinib generic formulations to demonstrate the potential impact on cost-effectiveness. To do this, the pre-built discount functionality of the submitted economic model is used, to adjust the price of axitinib in the economic model. Based on sunitinib, the difference between a branded pack of Sutent® and the generic alternative cost from eMIT (pack size 28x 50mg) reflects an effective percentage reduction of 88.89%. Therefore, scenarios were considered assuming an estimated price of axitinib generic formulations between 50% and 90% (in 10% increments) of the current branded list price (Section B.4.10 Subgroup analysis).

Please see Appendix O.6.1 for the drug acquisition costs associated with the intermediate-/poor-risk subgroup.

Table 61: Unit drug costs

Treatment	Units (mg)	Pack size	Pack cost (£)	Source
Avelumab list price	200mg	1	£768.00	BNF (2024)[131]
Avelumab PAS price	200mg	1	£[redacted]	The company
Axitinib	1mg	56	£703.40	BNF (2024)[131]
	3mg	56	£2,110.20	
	5mg	56	£3,517.00	
	7mg	56	£4,923.80	
Sunitinib	12.5mg	28	£93.05	eMIT (Jan 2023 – Dec 2023)[132]
	25mg	28	£100.10	
	50mg	28	£348.78	
Tivozanib	0.89mg	21	£2,052.00	BNF (2024)[131]
	1.34mg	21	£2,052.00	
Pazopanib	200mg	30	£560.50	BNF (2024)[131]
	400mg	30	£1,121.00	

Abbreviations**:** BNF, British National Formulary; eMIT, electronic market information tool; mg, milligrams; PAS, Patient Access Scheme.

B.3.5.1.2 Premedication costs

Patients receive premedication with an antihistamine and paracetamol prior to the first four infusions of avelumab as per the avelumab SmPC.[39] The cost breakdown of premedication costs associated with avelumab are sourced from eMIT and shown in Table 62.[132]

Table 62: Premedication costs (avelumab)

Premedication	Cost per dose
Paracetamol	£0.07
Chlorphenamine	£0.72
Total	**£0.79**

Dosing

The dosing schedule for all treatments was taken from the relevant SmPC. Avelumab is dosed at 800mg every 2 weeks with axitinib dosed at 5mg, twice daily. Sunitinib is dosed at 50mg once daily for 4 weeks, followed by a 2-week rest period, tivozanib at 1.34mg once daily for 3 weeks, followed by a 1-week rest period, and pazopanib at 800mg once daily.

As avelumab is dosed at 800mg, comprising 4 x 200mg vials, no wastage is incurred. For axitinib and the comparators, wastage was calculated each cycle, using drug regimen and TTD to calculate whether a new drug pack was required.

RDI

Relative dose intensity (RDI) is included in the model for avelumab, axitinib and the comparators to account for missed doses, dose delays, interruptions, and modifications. Table 63 presents the RDI values incorporated in the economic model.

Table 63: Relative dose intensity estimates

Regimen	Treatment	RDI	Source
Avelumab + axitinib	Avelumab	91.7%	JAVELIN Renal 101 (ITT population)[45]
	Axitinib	83.7%	
Sunitinib	Sunitinib	81.9%	
Tivozanib	Tivozanib	94.0%	Table 21 of the NICE RCC Pathways Pilot [ID6186][129]
Pazopanib	Pazopanib	86.0%	

Abbreviations: ITT, intention-to-treat; RDI, relative dose intensity.

B.3.5.1.3 Administration costs

Administration costs associated with the avelumab + axitinib are shown in Table 64. Avelumab was assumed to be administered by a simple intravenous procedure in a hospital setting at each administration. All TKIs included in the model are administered orally, thus no administration cost was applied for simplicity. The administration costs for the intermediate-/poor-risk subgroup are provided in Appendix O.

Table 64: Intravenous administration cost (avelumab)

Administration type	Applies to	Cost	Source
Intravenous (Simple)	Avelumab	£217.00	NHS National Costs Collection 2022/23 -Deliver Simple Parenteral Chemotherapy at First Attendance. Code SB12Z Outpatient[134]

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit

B.3.5.2 Health-state unit costs and resource use

Table 65 presents the resource use frequencies associated with the progression-free and progressed disease health states. Resource use comprised general practitioner (GP) visit, CT scan, blood test, community nurse visit, and pain medication. The resources and weekly frequency of resource use were sourced from TA581 (nivolumab + ipilimumab), consistent with the approach used in TA645.[1,3]

Table 65: Healthcare resource use estimates

Resource	Frequency (per week)		Source
	Progression-free	Post-progression	
GP visit	0.25	0.25	Consistent with TA645, with original values from TA581[1,3]
CT scan	0.08	0.00	
Blood test	0.25	0.00	
Community nurse visit	0.00	0.38	
Pain medication	0.00	7.00	

Abbreviations**:** CT, computerized tomography; GP, general practitioner.

Table 66 presents unit costs for healthcare resource use items, which were sourced from the NHS National Cost Collection, PSSRU and eMIT.[133,134] The resulting healthcare resource use cost per 7-day model cycle were £28.44 and £40.83 in the progression-free and progressed disease health states, respectively.

Table 66: Healthcare resource use unit costs

Resource	Unit cost	Source
GP visit	£49.00	PSSRU (2023)[133]
CT scan	£193.00	NHS National Cost Collection (2022/23)[134]
Blood test	£3.00	NHS National Cost Collection (2022/23)[134]
Community nurse visit	£52.00	PSSRU (2023)[133]
Pain medication	£1.26	eMIT (2023), DDG040, Morphine sulphate[132]

Abbreviations**:** CT, computerized tomography; eMIT, electronic market information tool; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

The unit costs associated with managing the grade ≥3 AEs were sourced from the NHS National Cost Collection.[134] The costs associated with each AE included in the model are shown in Table 67. The cost of AE resolution was assumed equal across all AEs for simplicity.

Table 67: Adverse event unit costs

Adverse event	Cost	Source
Alanine aminotransferase increased	£801.11	Non-elective short stay unit cost across all currency codes, NHS National Cost Collection 2021/22[134]
Anaemia	£801.11	
Diarrhoea	£801.11	
Hypertension	£801.11	
Lipase increased	£801.11	
Neutropenia	£801.11	

Neutrophil count decreased	£801.11	
Hand-foot syndrome	£801.11	
Platelet count decreased	£801.11	
Thrombocytopenia	£801.11	

Abbreviations: NHS, National Health Service.

The unit costs for each AE were multiplied by the respective frequency of the AE for each treatment and applied as a one-off upfront cost to each treatment arm included in the model. AE frequencies for avelumab + axitinib and sunitinib are provided in Section B.3.3.5. The total cost of AE resolution by treatment arm are presented in Table 68.

Table 68: Total cost of adverse events

Treatment	Total adverse event costs
Avelumab + axitinib	£448.55
Sunitinib, tivozanib, and pazopanib	£523.73

B.3.5.4 Subsequent therapies

Subsequent treatments were included in the model as an average cost per patient, applied as a one-off cost to patients upon leaving the progression-free health state.

The base case analysis setting for the distribution of subsequent treatments for the avelumab + axitinib and sunitinib arms reflects the distribution of subsequent treatments (at any line) received in JAVELIN Renal 101, with one adjustment made to account for the lack of subsequent use of nivolumab in NHS practice following treatment with avelumab + axitinib. The subsequent treatment distribution following tivozanib and pazopanib are assumed equal to sunitinib.

Data for recorded subsequent therapy use in JAVELIN Renal 101 were used to determine estimated proportions for the model. Data were extracted for the favourable-risk subgroup specifically, based on the following treatment options that are likely to be considered in UK NHS practice: cabozantinib, everolimus, axitinib, sunitinib, nivolumab, lenvatinib + everolimus, and pazopanib. Treatments that were an exact match were categorised accordingly. Similar treatments, based on mechanism of action, were grouped together (for example, immunotherapies which are not available in NHS practice were grouped with nivolumab, which is available). For treatments that were not possible to categorise (e.g., “other antineoplastic agents”), these were removed from the sample, and the final proportions were re-scaled (i.e., a weighted average of the other options was assumed to apply for any ‘other’ treatments recorded).

In NHS practice, it is anticipated that patients treated with frontline avelumab + axitinib would not receive nivolumab in a subsequent setting. Clinical expert feedback to the company confirmed that subsequent use of an immunotherapy (e.g., nivolumab) following progression on an immunotherapy combination in the frontline setting is not expected to provide additional benefit,[125] and instead of subsequent immunotherapy, a different treatment option would be considered. Additionally, evidence suggests that rechallenging with an IO following progression on previous IO therapy is not expected to improve patient outcomes.[125,126] Further, subsequent use of nivolumab is not licensed in RCC for people who are immunotherapy treatment experienced.[142] Therefore, the proportion of people taking nivolumab as a subsequent therapy was removed for the avelumab + axitinib arm, and the proportion was re-allocated to the other treatments. As subsequent nivolumab use is not anticipated to provide any additional benefit to people who have previously been treated with

immunotherapy, no adjustment to the avelumab + axitinib efficacy was deemed to be required. Table 69 presents the estimated proportions for subsequent therapies that were included in the base-case analysis. Alternative proportions (presented in Appendix P) are explored in sensitivity analysis.

Table 69: Subsequent therapy distribution (any subsequent line) in base-case analysis (favourable-risk) – adjusted JAVELIN Renal 101 data

Subsequent therapy	Estimated proportion of patients	
	Avelumab + Axitinib	Sunitinib
Cabozantinib	59.45%	30.56%
Everolimus	24.10%	12.01%
Axitinib	22.50%	13.10%
Sunitinib	20.89%	15.28%
Nivolumab**	-	86.23%
Lenvatinib + everolimus*	19.28%	14.19%
Pazopanib	8.03%	10.92%

Note:* Lenvatinib is only recommended by NICE for RCC in combination with everolimus. Because everolimus was received by more patients then lenvatinib, it was assumed that all patients who received lenvatinib received it in combination with everolimus and these patients were removed from the everolimus monotherapy group. **Subsequent nivolumab use in the avelumab + axitinib arm was redistributed to other subsequent treatments as first-line immunotherapy would not be followed by subsequent immunotherapy in clinical practice, validated by clinical expert opinion.

The unit costs for subsequent treatments that were not included as first-line comparators (Table 61) are presented in Table 70. Due to the confidential nature of PAS discounts, net prices for cabozantinib, lenvatinib, and nivolumab are not known, and therefore not included in the analysis.

Table 70: Subsequent treatment unit costs

Treatment	Units	Pack size	Pack cost	Source
Cabozantinib	20 mg	30	£5,143.00	BNF (2024)
	40 mg	30	£5,143.00	
	60 mg	30	£5,143.00	
	20 mg	84	£4,800.00	
Everolimus	2.5 mg	30	£362.55	eMIT (2023)
	5 mg	30	£429.75	
	10 mg	30	£488.32	
Lenvatinib	4 mg	30	£1,437	BNF (2024)
	10 mg	30	£1,437	
Nivolumab	40 mg	1	£439.00	BNF (2024)
	100 mg	1	£1,097.00	
	120 mg	1	£1,317.00	
	240 mg	1	£2,633.00	

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; mg, milligram; NHS, National Health Service.

The dosing regimens and TTD for the subsequent therapies in a second-line (and beyond) aRCC setting were sourced from the literature to calculate an overall cost for a single full course of each subsequent therapy. Costs for a simple intravenous administration were included where applicable. Table 71 presents the dosing schedules and administration routes associated with each subsequent treatment.

Table 71: Subsequent treatment dosing

Subsequent therapy	Drug	Dose per admin	Admin route	Frequency of admin (days)	Units per dose	Mean TTD (days)	Total cost per treatment courser	References
Cabozantinib	Cabozantinib	60 mg	Oral	1.00	60.00	231.70	£39,721	TA542 Committee papers: Table 58[7]
Everolimus	Everolimus	10 mg	Oral	1.00	10.00	167.30	£2,723	TA542 Committee papers: Table 58[7]
Axitinib	Axitinib	5 mg	Oral	1.00	5.00	220.50	£13,848	TA542 Committee papers: Table 58[7]
Sunitinib	Sunitinib	50 mg	Oral	0.67	50.00	172.90	£1,436	TA542 Committee papers: Table 58[7]
Nivolumab	Nivolumab	3 mg/kg	Intravenous	0.07	240.00	294.00	£59,850	TA542 Committee papers: Table 58[7]
Lenvatinib + everolimus	Lenvatinib	18 mg	Oral	1.00	18.00	243.50	£45,477	TA498 Committee papers: Table 40[84]
	Everolimus	5 mg	Oral	1.00	5.00			
Pazopanib	Pazopanib	800 mg	Oral	1.00	800.00	348.60	£22,796	TA542 Committee papers: Table 58[7]

Abbreviations: kg, kilogram; mg, milligram; TTD, time to treatment discontinuation.

The total subsequent treatment cost for each second-line (and beyond) regimen was weighted by the proportion of patients who experienced a PFS event and the estimated proportions receiving each subsequent therapy by first-line treatment arm (Table 69). The total one-off subsequent treatment costs associated with avelumab + axitinib and the comparators are shown in Table 72.

Table 72: Total subsequent treatment costs, by treatment arm (favourable-risk)

Subsequent therapy	Calculated cost
Avelumab + axitinib	£38,287
Sunitinib, tivozanib, and pazopanib	£74,883

B.3.5.5 End of life care costs

Health and social care costs for end-of-life care are captured in the model, taken from a modelling study published by Round *et al.* (2015).[143] Each cost in Table 73 is representative of the mean estimated cost per patient. Both categories capture the direct and indirect impact (from the initiation of strong opioids to death) associated with terminal care costs in England and Wales. Both costs have been inflated to reflect 2022/23 costs using the NHS PSSRU cost inflation index, resulting in a total end-of-life cost of £7,482.71 per patient.[144]

Table 73: End of life care costs

Category	Original cost	Inflated cost	Source
Health care	£4,254.00	£5,232.85	Round *et al*. (2015)[143]
Social care	£1,829.00	£2,249.86	
Total:			£7,482.71

B.3.6 Severity

The QALY shortfall was calculated using the R-Shiny tool by Schneider *et al.* (2021).[145] To estimate the QALY shortfall, baseline characteristics were extracted from the economic model (see Table 40) and used to generate expected lifetime QALYs for an equivalent population without the disease. Using these data, the expected total QALYs for the general population were 12.29, compared to the estimated total QALYs for people living with favourable-risk aRCC managed with current treatment were 4.25. These correspond to absolute and proportional QALY shortfalls of 8.04 and 65.41%, respectively. Therefore, within the context of this appraisal, no severity modifier was applicable for the favourable-risk population. Severity modifier calculations for the intermediate-/poor-risk and ITT populations are presented in Appendix O.

B.3.7 Summary of base-case analysis inputs and assumptions

Table 74 presents a summary of base-case model settings and assumptions for the favourable-risk population. Differences in base case assumptions between the favourable-risk and intermediate-/poor-risk and ITT populations are presented in Appendix O.

Table 74: Summary of key model settings and assumptions (favourable-risk)

Assumption	Description	Justification
Model settings		
Time horizon	40 years constitutes a lifetime horizon.	>99% of the modelled cohort have entered the death state by 40 years, across treatment arms.
Cycle length	A weekly cycle length with no half-cycle correction.	This relatively short cycle length is considered appropriate due to the poor prognosis of patients with IMDC favourable-risk aRCC. Due to the short cycle length, half-cycle correction is not required.
Patient characteristics	Based on the baseline patient characteristics from JAVELIN Renal 101.[45]	Baseline patient characteristics for the relevant population from JAVELIN Renal 101 was assumed to be generalisable to the UK population.
Efficacy		
Avelumab + axitinib (OS, PFS)	JAVELIN Renal 101 data, extrapolated with: • OS – Log-normal • PFS – Log-normal	Based on clinical plausibility of the long-term extrapolations and visual fit. Validated by clinical expert opinion. Alternative parametric models are tested in scenario analysis.
Sunitinib (OS, PFS)	JAVELIN Renal 101 data, extrapolated with: • OS – Generalised gamma • PFS – Generalised gamma	Based on clinical plausibility of the long-term extrapolations and visual fit. Validated by clinical expert opinion. Alternative parametric models are tested in scenario analysis.
Tivozanib, pazopanib	Assumed equal to sunitinib.	Based on a lack of data to inform efficacy and clinical plausibility of similarity comparator efficacy. Validated by clinical expert opinion
Time to treatment discontinuation		
Avelumab TTD	JAVELIN Renal 101 data, extrapolated with a generalised gamma model	Based on clinical plausibility of the long-term extrapolations and visual fit. Validated by clinical expert opinion. Alternative parametric models are tested in scenario analysis.
Axitinib TTD	JAVELIN Renal 101 data, extrapolated with a generalised gamma model	Based on clinical plausibility of the long-term extrapolations and visual fit. Validated by clinical expert opinion. Alternative parametric models are tested in scenario analysis.
Sunitinib TTD	JAVELIN Renal 101 data, extrapolated with a generalised gamma model	Based on clinical plausibility of the long-term extrapolations and visual fit. Validated by clinical expert opinion. Alternative parametric models are tested in scenario analysis.
Tivozanib, pazopanib	Assumed equal to sunitinib.	Based on precedent from previous appraisals and supportive literature.
Costs		
Subsequent treatments	Subsequent treatment data was obtained from JAVELIN Renal 101 data, adjusted for available treatments and plausible sequences.	Subsequent treatments received in JAVELIN Renal 101 were considered generalisable to the treatments expected to be received by patients in UK practice, after adjusting for unavailable treatments and removal of subsequent use of nivolumab following avelumab + axitinib. This was validated by clinical expert opinion.
Utilities		

Utilities	Utility values were estimated from EQ-5D-5L data from the JAVELIN Renal 101 trial (using the UK tariff), mapped onto the EQ-5D-3L	In line with the NICE reference case. Utilities sourced from the literature are explored in scenario analyses.
Adverse events		
Incidence	The incidence of treatment-related, grade ≥3 AEs, affecting ≥5% of patients for any relevant comparator, were modelled (irrespective of the incidence being <2% for other comparators).	Grade ≥3 AEs are expected to have the greatest impact on patients.
Disutilities	AE disutilities are excluded.	AE disutilities are excluded as disutility is thought to be captured within the health state utility estimates.

Abbreviations: AE, adverse event; aRCC, advanced renal cell carcinoma; EQ-5D, Euro-QoL five-dimension; IMDC, International Metastatic RCC Database Consortium; NICE, National Institute for Health and Care Excellence; OS, overall survival, PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.8 Base-case results

Base case deterministic results of the IMDC favourable-risk subgroup including the avelumab PAS price are presented in Table 75 with net-health benefit (NHB) results provided in Table 76 (at willingness-to-pay [WTP] thresholds of £20,000 and £30,000 per QALY gained). Pairwise results are provided, given that all three comparator treatments are assumed to have the same efficacy (i.e., the same QALYs and LYs).

The base case results demonstrate that avelumab + axitinib is associated with deterministic ICERs of £[redacted] versus sunitinib, £[redacted] versus tivozanib, and £[redacted] versus pazopanib. The net health benefit (NHB) is negative for avelumab + axitinib versus sunitinib and tivozanib at willingness-to-pay (WTP) thresholds of £20,000 and £30,000. Compared to pazopanib, the NHB is negative for avelumab + axitinib at a WTP of £20,000, and positive at a WTP of £30,000.

Table 75: Base case results (deterministic) – avelumab PAS price (favourable-risk)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
Versus sunitinib								
Sunitinib	£92,886	6.45	[redacted]					
Avelumab + axitinib	£[redacted]	10.14	[redacted]	£[redacted]	3.70	1.53	£[redacted]	[redacted]
Versus tivozanib								
Tivozanib	£135,875	6.45	[redacted]					
Avelumab + axitinib	£[redacted]	10.14	[redacted]	£[redacted]	3.70	1.53	£[redacted]	[redacted]
Versus pazopanib								
Pazopanib	£164,977	6.45	[redacted]					
Avelumab + axitinib	£[redacted]	10.14	[redacted]	£[redacted]	3.70	1.53	£[redacted]	£[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.
Note: *No severity modifier is applied to the discounted incremental QALYs.

Table 76: Net health benefit (deterministic) – avelumab PAS price (favourable-risk)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs*	NHB at £20,000	NHB at £30,000
Versus sunitinib						
Sunitinib	£92,886	[redacted]	-	-	-	-
Avelumab + axitinib	£[redacted]	[redacted]	£[redacted]	1.53	[redacted]	[redacted]
Versus tivozanib						
Tivozanib	£135,875	[redacted]	-	-	-	-
Avelumab + axitinib	£[redacted]	[redacted]	£[redacted]	1.53	[redacted]	[redacted]
Versus pazopanib						
Pazopanib	£164,977	[redacted]	-	-	-	-
Avelumab + axitinib	£[redacted]	[redacted]	£[redacted]	1.53	[redacted]	[redacted]

Abbreviations: NHB, net health benefit; QALYs, quality-adjusted life years.
Note: *No severity modifier is applied to the discounted incremental QALYs.

B.3.9 Exploring uncertainty

B.3.9.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA). In PSA, all parameters are simultaneously varied from an assigned probability distribution. PSA inputs were randomly drawn, and results recorded across 5,000 iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing uncertainty (assessed by visual inspection of convergence plots in the submitted cost-effectiveness model).

Mean probabilistic results are presented in Table 77. When interpreting these results, it should be noted that some probabilistic draws of the generalised gamma model for the sunitinib arm (used to model OS) result in unrealistic extrapolations, and therefore the mean LYG is higher than what is seen for the deterministic analysis. In addition, it should be noted that the model was set up to consider pairwise comparisons (for ease of review, in consideration of the different combinations of populations and comparators required by the NICE scope), and so the total costs and QALYs for the avelumab + axitinib arm vary slightly across the results presented.[16]

Table 77: Base case results (probabilistic) – avelumab PAS price (favourable-risk)

Technologies	Total			Incremental				
	Costs	LYG	QALYs	Costs	LYG	QALYs*	ICER	NMB†
Versus sunitinib								
Sunitinib	£93,021	6.90	[redacted]	-	-	-	-	-
Ave+axi	£[redacted]	10.14	[redacted]	£[redacted]	3.23	1.35	£[redacted]	[redacted]
Versus tivozanib								
Tivozanib	£137,918	6.91	[redacted]	-	-	-	-	-
Ave+axi	£[redacted]	10.12	[redacted]	£[redacted]	3.21	1.34	£[redacted]	[redacted]
Versus pazopanib								
Pazopanib	£168,095	6.91	[redacted]	-	-	-	-	-
Ave+axi	£[redacted]	10.14	[redacted]	£[redacted]	3.22	1.35	£[redacted]	£[redacted]

Abbreviations: Ave+axi, avelumab + axitinib; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.
Note: *No severity modifier is applied to the discounted incremental QALYs; †(£30,000/QALY).

Figure 31, Figure 32 and Figure 33 presents the cost-effectiveness acceptability curves for avelumab + axitinib versus sunitinib, tivozanib and pazopanib, respectively.

Figure 31: Cost-effectiveness acceptability curve – versus sunitinib (favourable-risk)

Abbreviations: WTP, willingness-to-pay.

Figure 32: Cost-effectiveness acceptability curve – versus tivozanib (favourable-risk)

Abbreviations: WTP, willingness-to-pay.

Figure 33: Cost-effectiveness acceptability curve – versus pazopanib (favourable-risk)

Abbreviations: WTP, willingness-to-pay.

Figure 34: Incremental cost-effectiveness plane – versus sunitinib (favourable-risk)

Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay; PSA, probabilistic sensitivity analysis.

Figure 35: Incremental cost-effectiveness plane – versus tivozanib (favourable-risk)

Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay; PSA, probabilistic sensitivity analysis.

Figure 36: Incremental cost-effectiveness plane – versus pazopanib (favourable-risk)

Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay; PSA, probabilistic sensitivity analysis.

B.3.9.2 Deterministic sensitivity analysis

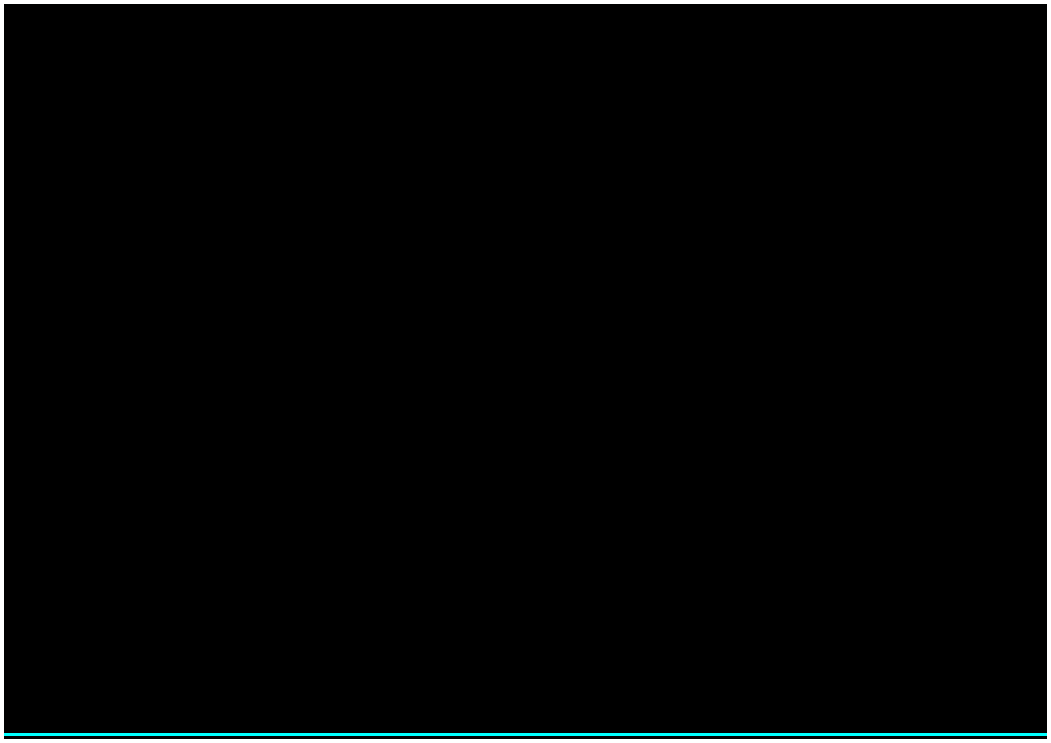
One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameter uncertainty on cost-effectiveness results, holding all else constant. In turn, inputs

were set to their respective lower and upper limits, while all other parameters were maintained at their base case setting. If the variance of a parameter was not available, a simplifying assumption was made assuming that the standard error was 10% of the mean values. Correlated inputs with joint uncertainty, such as parametric survival model coefficients which are varied in PSA using a multivariate normal distribution, were not included in the OWSA.

Figure 37, Figure 38, and Figure 39 present the tornado plots showing the 10 parameters with the largest impact on the incremental net-monetary benefit (INMB) for avelumab + axitinib versus sunitinib, tivozanib and pazopanib, respectively, at a WTP threshold of £30,000.

The OWSA demonstrates that model findings are robust to reasonable variation in parameters, with axitinib RDI having the largest impact on the results.

Figure 37: Tornado plot of OWSA results (ICER) - versus sunitinib (favourable-risk)



Abbreviations: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; HCRU, healthcare resource use.
Note: Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

Figure 38: Tornado plot of OWSA results (ICER) - versus tivozanib (favourable-risk)

Abbreviations: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; HCRU, healthcare resource use.
Note: Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

Figure 39: Tornado plot of OWSA results (ICER) - versus pazopanib (favourable-risk)

Abbreviations: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; HCRU, healthcare resource use.
Note: Correlated inputs with joint uncertainty (such as parametric survival model coefficients) are not included in the OWSA.

B.3.9.3 Scenario analysis

Scenario analyses were performed to test key structural and methodological assumptions within the model. As the base case probabilistic results and deterministic results were close, scenario analyses were conducted deterministically. Results of the scenario analyses versus each comparator are presented in Table 78.

For brevity, only the two most clinically plausible alternative model extrapolations for OS, PFS and TTD for the intervention and comparator are included below. Additional scenario analyses including all possible curve fits can be generated using the submitted model file.

As described in Section B.3.5.1.1, axitinib pricing scenarios are included to reflect the anticipated emergence of generic formulations ([redacted]).[141] Based on the price reduction between branded and generic sunitinib of 88.89%, the branded list price for axitinib was reduced by 50-80% (in 10% increments) in a scenario analysis to reflect potential plausible prices of axitinib generic formulations.

Table 78: Scenario analysis results (favourable-risk)

Topic	Base case	Scenario	ICER (avelumab + axitinib) versus.		
			Sunitinib	Tivozanib	Pazopanib
Time horizon	40 years	20 years	£	£	£
		30 years	£	£	£
Discount rates for costs and QALYs	3.5%	1.5%	£	£	£
		6.0%	£	£	£
Avelumab + axitinib OS	Log-normal	1 Generalised gamma	£	£	£
		2 Log-logistic	£	£	£
Sunitinib OS	Generalised gamma	1 Log-logistic	£	£	£
		2 Weibull	£	£	£
Avelumab + axitinib PFS	Log-normal	1 Generalised gamma	£	£	£
		2 Log-logistic	£	£	£
Sunitinib PFS	Generalised gamma	1 Exponential	£	£	£
		2 Log-normal	£	£	£
Avelumab TTD	Generalised gamma	1 Gompertz	£	£	£
		2 Weibull	£	£	£
Axitinib TTD	Generalised gamma	1 Gompertz	£	£	£
		2 Weibull	£	£	£
Sunitinib TTD	Generalised gamma	1 Exponential	£	£	£
		2 Gompertz	£	£	£
Price of axitinib	BNF	50% reduction	£	£	
		60% reduction	£	£	
		70% reduction	£	£	
		80% reduction	£		
		90% reduction	£		
RDI	Include	Exclude	£	£	£
Utility model	Model 1	Model 2	£	£	£
Utility source	JAVELIN Renal 101 EQ-5D analysis	TA178	£	£	£
		TA215	£	£	£
		TA512	£	£	£
		TA542	£	£	£
		TA581	£	£	£
		TA432	£	£	£
		TA417	£	£	£
		Average across all appraisals	£	£	£

Age-adjusted utilities	Enabled	Disabled	£[redacted]	£[redacted]	£[redacted]
Subsequent therapy	JR101 - FV risk FA, re-scale nivo	TA645	£[redacted]	£[redacted]	£[redacted]
		100% nivo or cabo	£[redacted]	£[redacted]	£[redacted]
		JR101 - FV risk FA	£[redacted]	£[redacted]	£[redacted]
		UK ROC study	£[redacted]	£[redacted]	£[redacted]

Abbreviations: EQ-5D, Euro-QoL five-dimension; FA, final analysis; FV, favourable; ICER, incremental cost-effectiveness ratio; JR101, JAVELIN Renal 101; OS, overall survival; PFS, progression-free survival; PSM, parametric survival model; QALY, quality-adjusted life year; RDI, relative dose intensity; TTD, time to treatment discontinuation; BNF, British National Formulary; TA, technology appraisal.

B.3.10 Subgroup analysis

In addition to the results for the favourable-risk subgroup, results were also obtained for the subgroup of people with intermediate-/poor-risk aRCC. For this subgroup, comparisons are available against seven different comparators (see Table 1). Details of model settings, including curve selections, are provided in Appendix O. For brevity, the results presented in Document B comprise the base-case pairwise analyses for each of the seven comparators. Full results can be obtained via the submitted economic model file.

The results for avelumab + axitinib versus other IO combinations for the intermediate-/poor-risk subgroup rely entirely on the ITC, described in Section B.2.10. These results cannot, and thus do not, take into consideration the inherent heterogeneity within this subgroup. This heterogeneity plays an important role in decision making in real-world NHS practice, where individual factors, such as comorbidities and predisposition/susceptibility to treatment-related toxicities, determine which IO combinations would be more (or less) suitable than others. Therefore, caution is advised when interpreting these results, as they are unlikely to represent a true reflection of the costs and benefits associated with the use of avelumab + axitinib versus comparator treatments, where this regimen would be considered.

Table 79: Subgroup analysis results (deterministic) – avelumab PAS price (intermediate-/poor-risk)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
Versus sunitinib								
Sunitinib	£71,387	5.05	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	£[redacted]	0.76	0.39	£[redacted]	[redacted]
Versus tivozanib								
Tivozanib	£98,716	5.05	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	£[redacted]	0.76	0.39	£[redacted]	[redacted]
Versus pazopanib								
Pazopanib	£117,039	5.05	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	£[redacted]	0.76	0.39	£[redacted]	[redacted]
Versus cabozantinib								
Cabozantinib	£127,565	6.49	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	£[redacted]	-0.68	-0.33	[redacted]	[redacted]
Versus nivolumab plus ipilimumab								
Nivolumab plus ipilimumab	£116,683	7.67	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	£[redacted]	-1.86	-0.80	[redacted]	[redacted]
Versus lenvatinib with pembrolizumab								
Lenvatinib with pembrolizumab	£195,225	7.09	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	[redacted]	-1.28	-0.60	£[redacted]	£[redacted]
Versus cabozantinib with nivolumab								
Cabozantinib with nivolumab	£150,520	8.17	[redacted]					
Avelumab + axitinib	£[redacted]	5.81	[redacted]	£[redacted]	-2.36	-1.03	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.
Note: *No severity modifier is applied to the discounted incremental QALYs.

B.3.11 Benefits not captured in the QALY calculation

Under the current treatment pathway in intermediate-/poor-risk aRCC, people potentially face the harmful side effects associated with other IO combinations, which may require management with immunosuppressants such as systemic corticosteroids. However, these people would still ideally be treated with an IO combination owing to its superiority in terms of clinical outcomes compared with TKI monotherapy. For people with intermediate-/poor-risk aRCC, avelumab + axitinib provides an alternative to existing reimbursed IO combinations, which has a manageable safety profile, and is more effective than TKI monotherapy.

The clinical evidence available to inform comparisons of IO combinations and TKI monotherapies do not capture the importance of accounting for patient heterogeneity in determining the most appropriate course of treatment. For some people with intermediate-/poor-risk aRCC, currently available IO combinations may not be deemed suitable, yet avelumab + axitinib may still be considered owing to its tolerability. This is aligned with clinical expert opinion provided to the company.

B.3.12 Validation

Prior to submission, the cost-effectiveness model (Microsoft Excel® workbook) was quality assured as part of the internal processes of the external analysts who built the model. As part of this quality-control process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process. The review comprised of a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing (e.g., how do results change if the time horizon is set to be as short or as long as possible?)
- Logical relationship testing (e.g., if intervention drug costs are increased, do total costs in the intervention arm increase, and is the impact on the ICER in line with expectations?)
- Consistency checks (e.g., is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?)

In addition to validation of the cost-effectiveness model, clinical expert opinion was sought from three RCC medical oncology specialists based in England and Wales, who currently treat patients with aRCC in NHS practice. The clinical experts were asked questions related to the treatment pathway for aRCC and the plausibility of survival estimates in order to inform the cost-effectiveness model.

B.3.13 Interpretation and conclusions of economic evidence

For this appraisal, a cost-effectiveness analysis was conducted from the perspective of the NHS and PSS. Since the publication of guidance from TA645, the treatment landscape for untreated advanced RCC has evolved markedly, including the availability of immunotherapy combination for people with IMDC-defined intermediate-/poor-risk RCC, leading to a treatment landscape fragmented into IMDC sub-groups. The base-case analysis considers the subgroup of people with IMDC-defined favourable-risk RCC, for whom current treatment options are limited to single-agent TKI monotherapy (such as sunitinib). There remains a

substantial unmet need for access to a first-line IO-containing therapy in the favourable-risk population (see Section B.1.3.8) and therefore the base case cost-effectiveness analysis is aligned with where the clinical community expects this treatment option would offer the greatest value to patients. Subgroup analyses are provided for people with IMDC-defined intermediate-/poor-risk RCC to compare against existing IO-containing treatment regimens in this group. For completeness, the economic analysis for the full ITT population from the JAVELIN Renal 101 study is also provided in line with the NICE scope.

The model is informed primarily by data collected as part of JAVELIN Renal 101. A three-state PartSA, or 'area-under-the-curve', model was used, which applies the same model structure as per the previous assessment of avelumab + axitinib in TA645, and is aligned with other previous NICE TAs for aRCC. The submitted model allows for consideration of a broad range of different survival models, utility values, and specification of subsequent therapy distributions; each of which are important drivers of cost-effectiveness results. Data from the final analysis of JAVELIN Renal 101 study provide estimates of OS and PFS with a minimum follow-up of 68 months (5.67 years), and therefore there is considerably less uncertainty in extrapolations compared to those used to inform TA645. Despite this, there still remains a need to extrapolate survival estimates over a lifetime horizon for the cost-effectiveness analysis, and this was performed for all analyses presented in this submission.

In conclusion, the cost-effectiveness analysis demonstrates that, based on list prices of all included treatments with the exception of avelumab (for which the current PAS price is applied) and pazopanib (which has a non-confidential discount), avelumab + axitinib provides a substantial LY and QALY gain against NICE recommended treatments, but would not be considered cost-effective at the standard willingness-to-pay thresholds considered by NICE. However, it should be noted that the true cost-effectiveness results for avelumab + axitinib rely upon the accurate consideration of confidential discounts offered for both comparator and subsequent treatments. Furthermore, emergence of generic axitinib formulations is expected following the anticipated loss of exclusivity for branded axitinib in [redacted][141], which would further (and considerably) improve estimates of cost-effectiveness for avelumab + axitinib (please see scenario analyses for further context, Section B.3.9.3). Therefore, subject to further consideration of commercial arrangements, avelumab + axitinib has the potential to provide both a clinically- and cost-effective treatment option in base case analysis of people with favourable-risk aRCC.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab in combination with axitinib for advanced renal cell carcinoma (MA review of TA645) [ID6294]

Summary of Information for Patients (SIP)

07 November 2024

File name	Version	Contains confidential information	Date
ID6294_Avelumab-axitinib_aRCC_SIP	1.0	No	07 November 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Executive summary

This submission is assessing the combination of avelumab and axitinib for the treatment of people with advanced renal cell carcinoma (aRCC, cancer of the kidney) who have not previously received any cancer medicines (first-line treatment).

Avelumab is a type of immunotherapy medicine that stimulates the immune system to kill cancer cells. Specifically, it is a monoclonal antibody (a type of protein) that attaches to a specific target in the body called PD-L1. Avelumab is given as an infusion (a drip) into a vein (intravenously) over a period of 1 hour every two weeks. Axinitib is a type of targeted treatment called a tyrosine kinase inhibitor (TKI). It is also known as a cancer growth inhibitor. Axitinib is given as tablets, twice a day.

1b) Name of the medicine (generic and brand name):

Generic: avelumab + axitinib

Brand name: Bavencio® and Inlyta®

1c) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

aRCC is a type of kidney cancer that is inoperable and has spread outside the kidney to blood vessels and/or local lymph nodes and/or to other parts of the body (1). Following diagnosis, people are classified as having favourable-, intermediate- or poor-risk disease, according to their International Metastatic RCC Database Consortium (IMDC) risk score (see Section 2b for more details) (2,3). This risk score helps doctors to decide the most appropriate initial treatment.

The population that avelumab + axitinib could be used for is people with aRCC who have not previously received any cancer medicines, irrespective of their IMDC risk score (4).

In September 2020, the National Institute for Health and Care Excellence (NICE) recommended avelumab + axitinib for use within the Cancer Drugs Fund (CDF) as an option for adults with untreated aRCC (5). Following the first appraisal in 2020 (TA645), NICE asked the company to collect more data on avelumab + axitinib until there was enough evidence available to address uncertainties about the long-term clinical benefit of

the treatment. This current appraisal is a review of new evidence, which comes from the final analysis of the key clinical study for avelumab + axitinib, and also from people with previously untreated aRCC who have received avelumab + axitinib in normal clinical practice, outside of clinical studies in the UK (real-world evidence). In line with the way that clinicians characterise people with aRCC, evidence is presented for people classified as having favourable-risk disease and those classified as having intermediate-/poor-risk disease.

1d) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Avelumab + axitinib currently has a marketing authorisation in Great Britain for the first-line treatment of adults with advanced RCC which was issued by The European Commission on 24 October 2019 (6).

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Merck Serono UK has existing collaborative relationships with Action Kidney Cancer and Kidney Cancer UK, including financial support.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of people and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained

Advanced renal cell carcinoma

Kidney cancer is the sixth most common cancer in the UK, accounting for 4% of all cancer cases (7). RCC is the most common kidney cancer, accounting for approximately 85–90% of all kidney cancers (8–10). There are different types of RCC, but they all arise from the lining of tubes inside the kidney (8). Of the five major subtypes of RCC, clear-cell RCC (ccRCC) is the most common, accounting for 75–88% of cases (11,12).

RCC severity is described by the disease stage, which depends on how advanced the kidney cancer is, and is based on local tumour growth (T), lymph node involvement (N) and the presence or absence of distant spread (metastases; M) (13). In Stages I and II of RCC, the cancer is confined within the kidney; in Stage III, the cancer has spread outside the kidney to blood vessels and/or local lymph nodes, and in Stage IV, it has spread to other parts of the body (13). Clinicians further classify people with aRCC (Stage III/IV RCC) into those having favourable-risk, intermediate-risk or poor-risk disease, based on various factors, to help them decide appropriate initial treatment options (see Section 2b for more information) (2,5,14). The treatment options for intermediate-/poor-risk aRCC are the same as recommended by NICE for use in routine clinical care.

Kidney cancer often has no symptoms until the advanced stage (9), and even then, classic symptoms/signs such as pain in the flank, visible blood in the urine and a mass that can be felt in the abdomen, are rare (6–10% of cases) (13,15). When present, most symptoms are general and include loss of appetite, tiredness, nausea (feeling sick) with

increasing loss of appetite, back pain/pressure, unexplained fever or weight loss, and low red blood cell count (anaemia) or other abnormal blood test results (13,15,16). Symptoms of spread to other organs may include bone pain and persistent cough (13).

While the causes of RCC are not completely understood, risk factors include increasing age, male gender, obesity, high blood pressure and smoking (8,17,18).

Number of people with favourable-risk and intermediate-/poor-risk aRCC

RCC accounts for approximately 85–90% of kidney cancer cases (8–10), and approximately 16.1% of these have favourable-risk disease and 80.8% intermediate-/poor-risk disease at diagnosis (19). In England and Wales in 2020, there were 588 people with favourable-risk aRCC and 2,951 people with intermediate-/poor-risk aRCC (7,8,19,20).

Impact of aRCC on people

aRCC is an incurable disease with a lack of curative treatments; there are an estimated 3,859 deaths per year in England due to all types of kidney cancer (21). The symptoms of aRCC and poor outlook mean that people with the disease often have a poor quality of life and emotional problems (22–25). Symptoms increase as the disease progresses and people receive an increasing number of different types of treatment, with associated side effects (23,26).

People with favourable-risk aRCC in England and Wales have limited first-line treatment options, and complete responses (no sign of cancer after treatment) to first-line TKI monotherapy are uncommon, with the cancer eventually progressing in most people (27–30).

Available first-line immunotherapy-based treatments for people with intermediate-/poor-risk aRCC are associated with immune-related side effects that can impact multiple organs and may require management with medicines such as steroids (31,32).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts people. Are there any additional diagnostic tests required with the new treatment?

Diagnosis

Most people with kidney cancer are identified incidentally, as the disease often has no symptoms (13,15,33). There is no screening programme for detecting kidney cancer in the UK (34), and there is no national UK-specific guidance relating to diagnosis, apart from the NICE guideline on suspected cancer: recognition and referral (NICE guideline NG12), last updated in October 2023 (35).

In some people, a mass may be felt in the abdomen, or there may be swollen lymph nodes in the neck, varicose veins in the scrotum or swelling of both legs. Most cases of kidney cancer are diagnosed by the use of diagnostic imaging tests, such as abdominal ultrasound, computer tomography (CT) and magnetic resonance imaging (MRI) (13,33). Chest, abdominal and pelvic CT using contrast (specialised dye injected into a person's vein to highlight structures such as blood vessels) are required to help stage the disease (see below) and a renal tumour biopsy may be used to determine the subtype of cancer (13,33). Various blood tests will also be carried out to help confirm the diagnosis and provide a risk score (see below) (13,33).

Staging and prognostic scoring

In Stages I and II, the kidney cancer is restricted to the kidney; in Stage III, the disease has spread to blood vessels and/or local lymph nodes; and in Stage IV, the disease has spread to other parts of the body (see Section 2a) (13). Staging people's kidney cancer is important because it influences treatment choices (see Section 2c): inoperable Stage III

or Stage IV, which the current submission focuses on, are referred to as 'advanced-stage' disease.

Following the tests outlined above, if a person has Stage III or IV RCC, their International Metastatic RCC Database Consortium (IMDC) risk score is usually assessed. These are criteria used to classify those people as favourable-, intermediate- and poor-risk groups to predict survival, according to various clinical factors, including time from diagnosis to treatment, performance score (a measure of how well a person is functioning) and the results of four different blood tests (2,3). The clinicians use information about a person's risk group to help them decide appropriate initial treatment options (2,5,14).

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The goal of treatment for people with previously untreated aRCC is to prevent disease progression, maintain quality of life, provide relief from cancer symptoms and extend life (36). There are no national UK-specific treatment guidelines for previously untreated aRCC, so clinical practice in England and Wales reflects key European and US treatment guidelines alongside the restrictions of recommendations from NICE technology appraisals.(10,13,33,37,38). European and US treatment guidelines recommend that people with untreated aRCC receive a combination treatment that contains immunotherapy, irrespective of risk category (i.e., in favourable-risk people as well as those with intermediate-/poor-risk) (13,33,35).

Choice of treatment is determined by IMDC risk categorisation, individual patient factors, treatment guidelines, NICE recommendations and patient and physician preference.

People with favourable-risk disease

The comparatively longer outcomes of survival and disease-free progression for favourable-risk people are only relative to intermediate-/poor-risk people but their disease remains life-limiting and incurable with current treatment. As such, extending life and minimising side effects are important treatment goals. For people with previously untreated favourable-risk aRCC, there are no immunotherapy combinations recommended for use in routine commissioning in England and Wales. The only available treatments recommended by NICE for these people are the tyrosine kinase inhibitors (TKI; a type of targeted treatment for cancer) sunitinib, pazopanib or tivozanib (39–41). Complete responses to these treatments are uncommon, with the cancer eventually progressing in most people (27–30).

Availability of an IO+TKI combination is consistent with the recommendations of international clinical practice guidelines which recommend IO-containing regimens as first-line treatment options in people with favourable-risk (13,33,35). Additionally, in Scotland, avelumab + axitinib as well as pembrolizumab + axitinib are recommended for the first-line treatment of aRCC regardless of risk group.(42,43)

The lack of IO treatment options for people with favourable-risk disease is reflected in UK clinical practice outside of clinical studies (real-world evidence), where research shows that in 2018 to 2021, 70% of UK people with favourable-risk aRCC (294 people included in the research) received initial treatment with a TKI alone (44). Of the people that received initial treatment with TKI alone, 42.5% received another TKI for their second-line treatment

(44). A proportion (44.2%) of total people with favourable-risk disease did not receive an IO at any stage of their treatment (45). This highlights that it is important for people to receive the most effective first-line (upfront) treatment.

People with intermediate-/poor-risk disease

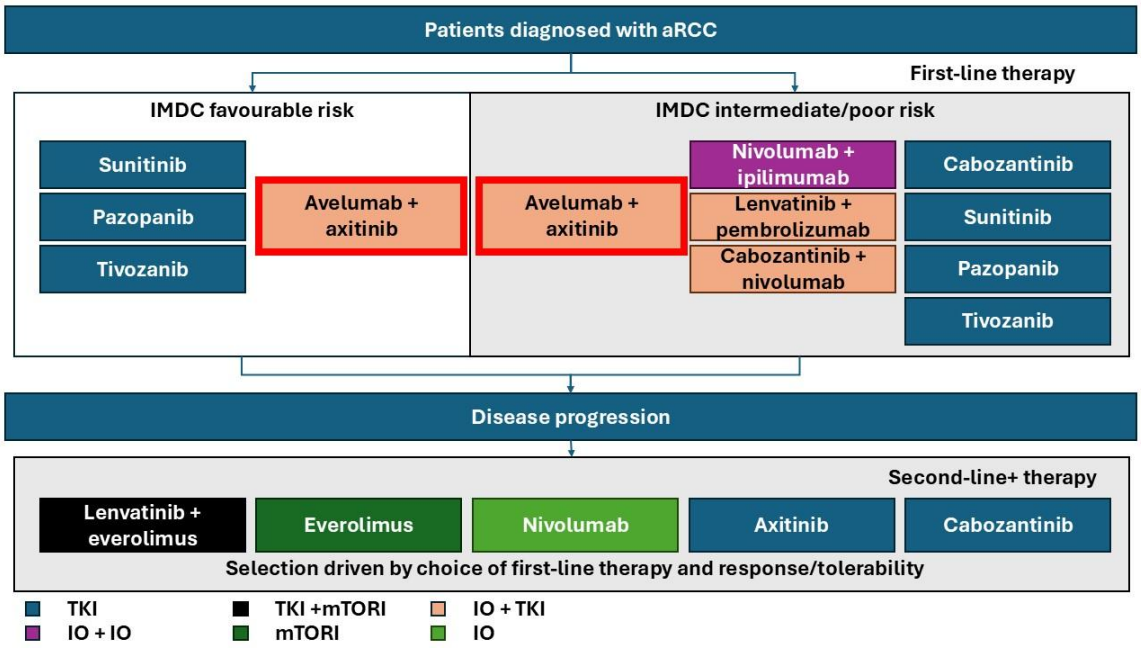
People with previously untreated intermediate-/poor-risk aRCC may receive sunitinib, pazopanib, tivozanib, cabozantinib, nivolumab + ipilimumab, lenvatinib + pembrolizumab, or cabozantinib + nivolumab (14,46–48).

Available immunotherapy-based treatments for people with intermediate-/poor-risk aRCC are associated with immune-related side effects that can impact multiple organs and may require management with medicines such as steroids (31,32).

Research from UK clinical practice outside of clinical studies (real-world evidence), shows that in 2018 to 2021, only 47.4% of people with intermediate-/poor-risk aRCC who had an initial treatment went on to receive subsequent (second-line) treatment after disease progression (44). This is typically due to a lack of fitness for treatment and highlights the importance of ensuring that people are treated with the most effective initial treatments (44,45).

If recommended by NICE, avelumab with axitinib could be used in previously untreated people with aRCC, irrespective of risk-group (Figure 1).

Figure 1: Current treatment pathway for untreated aRCC in England and Wales, and proposed positioning of avelumab + axitinib



Abbreviations: aRCC, advanced renal cell cancer; CDF, Cancer Drugs Fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; mTORI, mammalian target of rapamycin inhibitor; TKI, tyrosine kinase inhibitor.
Source: NICE (39,46–54).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when people input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to people and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Evidence from people with aRCC treated with current initial standard of care treatments

People with aRCC can experience highly burdensome symptoms (see Section 2a) and their expected survival is often very poor, with five-year survival rates in England of 75.9% for people with Stage III disease at diagnosis, and only 14.0% with Stage IV (55). Consequently, people with aRCC experience a considerable negative impact on their health-related quality of life (HRQoL), with measures such as the EuroQol 5-Dimension (EQ-5D; a questionnaire used to describe a person's health state by looking at five areas relating to health) showing that these people experience meaningfully poorer quality of life than the general population (22–25,56). The diagnosis of a cancer with poor prognosis and a lack of curative treatments can also impact the mental health of people with aRCC.

People's HRQoL continues to deteriorate as the disease progresses and they receive multiple rounds of treatment, with evidence showing that people with aRCC who experience disease progression experience worse HRQoL compared with people whose disease remains stable (23,26,57). This deterioration in HRQoL is largely driven by the symptoms of aRCC, which worsen with disease progression. A study that used the EQ-5D found that, of a group of people surveyed (who had received two or more rounds of treatment for aRCC), over half experienced substantial pain/discomfort (75%) or problems conducting their usual activities (69%) (26). As such, treatments which delay progression could in turn help to delay deterioration of people's HRQoL (58).

Caregivers also experience a substantial quality of life impact due to their loved one's aRCC. A systematic literature review (SLR) of 192 articles focused on cancer caregiving (1990–2008) found that the most common problems for caregivers included sleep disturbance, fatigue, pain, loss of physical strength, loss of appetite, and weight loss (59).

SECTION 3: The treatment

3a) How does the new treatment work?

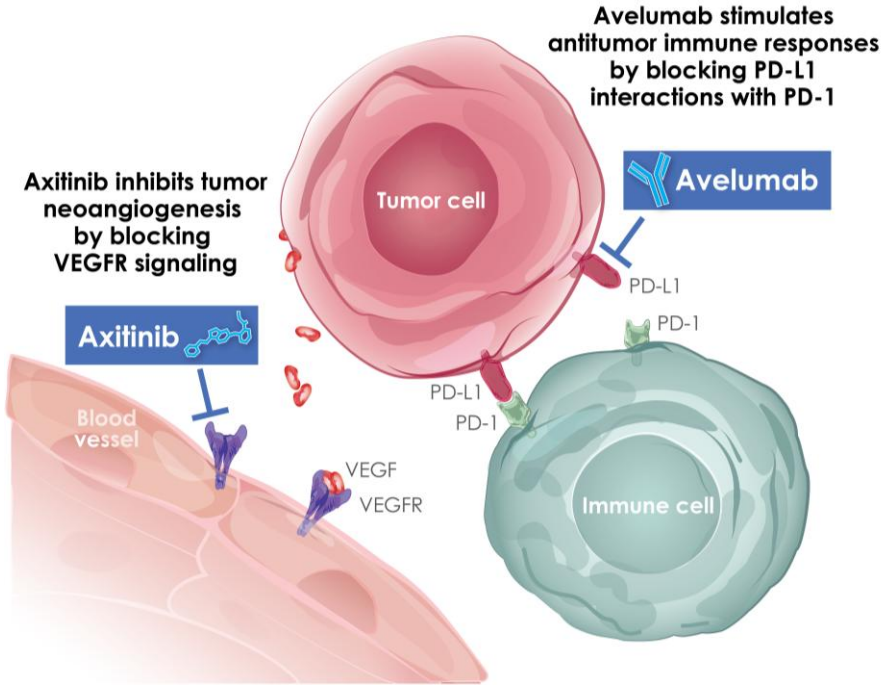
What are the important features of this treatment?
Please outline as clearly as possible important details that you consider relevant to people relating to the mechanism of action and how the medicine interacts with the body.
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to people and their communities.
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How does avelumab + axitinib work?

Avelumab is a type of immunotherapy medicine that stimulates the immune system to kill cancer cells. It is a specific monoclonal antibody (a type of protein) designed to recognise and attach to a specific protein called 'programmed death-ligand-1' (PD-L1), which is present on the surface of many cancer cells (4). PD-L1 can bind to cells of the body's immune (defence) system called T cells, preventing the T cells from attacking the cancer cells. By attaching to PD-L1, avelumab prevents the cancer cells from switching off the T cells, thereby increasing the ability of the T cells to kill the cancer cells (4).

Axitinib works by blocking enzymes known as tyrosine kinases that are found in 'vascular endothelial growth factor' (VEGF) receptors on the surface of various cells (60). VEGF receptors are involved in the growth and spread of cancer cells and in the development of new blood vessels that supply blood to the tumours to ensure their growth. By blocking these receptors, axitinib helps to reduce the growth and spread of the cancer and cut off the blood supply that keeps the cancer cells growing (61–63).

Figure 2: Avelumab + axitinib mode of action



Abbreviations: PD-L1, programmed death-ligand 1; VEGFR, vascular endothelial growth factor receptor.
Source: Motzer et al. 2018 (64).

Key features of avelumab + axitinib

Avelumab + axitinib builds on the established efficacy of a TKI monotherapy through the added benefit of an immunotherapy treatment. Together, the combination has the potential for complementary mechanisms of action, which may lead to rapid and long-lasting responses across all risk groups (65–67).

Axitinib is highly suitable for combination with an immunotherapy as it has low risk of interactions with other treatments, and its short half-life prevents substantial accumulation of the medicine in the body so that toxic side effects are generally rapidly resolved following dose interruption or reduction and allows rapid identification of which medicine may be driving toxicity (32,67). The half-life of axitinib is shorter than that of other TKI treatments in combination with immunotherapies currently available through NICE. These advantages, combined with the range of available tablet strengths, means that doctors can easily increase or decrease the dose according to an individual's tolerance (60,68). Most immune-related adverse reactions associated with avelumab are reversible and manageable (4).

As such, avelumab + axitinib provides additional choice for people and doctors in selecting appropriate initial treatment for people with aRCC.

Please refer to the Summary of Product Characteristics (SmPC) and Patient Information Leaflets for avelumab + axitinib for more details about the way these treatments work.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?
- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to people why they are used together.
If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.
If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.
How will this administration method or dosing potentially affect people and caregivers? How does this differ to existing treatments?

Avelumab is given via a 1-hour drip into a vein (intravenous infusion) every 2 weeks. The usual dose is 800 mgs (4). Axitinib is taken orally twice daily, with or without food, every day. The usual dose is 5 mg twice daily, with dose increase or reduction recommended based on individual safety and tolerability (60). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by additional treatments or dose adjustments.

Avelumab is administered through an infusion (a drip) in an outpatient setting. Treatment should be initiated and monitored by a physician with expertise in cancer care. People may need to travel to receive this treatment, similar to many other immunotherapy options for cancer. People should be pre-treated with an antihistamine and with paracetamol prior to the first four infusions of avelumab (4).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The efficacy and safety of avelumab + axitinib in people with aRCC has been shown in a Phase 3 study (the JAVELIN Renal 101 study) (69–72), as well as in real-world studies, which have included people from the UK.

The JAVELIN Renal 101 study was a multinational, multicentre study in 886 untreated adult people with confirmed aRCC (with a clear cell subtype) (69,71,72). It compared the effectiveness and safety of avelumab + axitinib with that of sunitinib, which was standard

of care in England and Wales, and a NICE-recommended initial treatment option when the study was designed (69).

The study included 32 people from the UK. People were randomly assigned to receive either avelumab 10 mg/kg as a 1-hour intravenous infusion every 2 weeks plus axitinib 5 mg taken by mouth twice daily every day, or sunitinib 50 mg taken by mouth once daily for 4 consecutive weeks followed by a 2-week off treatment period. Treatment with the study medicines continued until confirmed disease progression assessed by an independent reviewer, unacceptable side effects, or the person didn't want to continue or stopped attending study visits. At final analysis of the study results, the overall median follow-up was 6 years, which represents the longest follow-up for an immunotherapy and TKI combination treatment in aRCC from Phase 3 clinical studies reported to date (69).

There were 442 people in the avelumab + axitinib group (94 with favourable-risk disease and 343 with intermediate-/poor-risk disease) and 444 people in the sunitinib group (96 with favourable-risk disease and 348 with intermediate-/poor-risk disease) (69). Five people in the avelumab + axitinib group did not have a risk group recorded at the start of the study (69).

Key inclusion criteria included age at least 18 years (at least 20 years in Japan) and confirmed aRCC with a clear cell subtype, (69). Key exclusion criteria included prior cancer treatments, major surgery in previous 4 weeks or major radiation therapy in previous 2 weeks (69).

The main study outcomes were overall survival, progression-free survival, tumour response to treatment, patient-reported outcomes, and safety outcomes (69).

Further evidence of the effectiveness and safety of avelumab + axitinib for the initial treatment of people with aRCC comes from UK real-world data studies. These include data from:

- The Systemic Anti-Cancer Cancer Therapy (SACT) dataset, collected by NHS England as part of the managed access agreement for CDF entry for avelumab + axitinib (i.e., an arrangement made between a company and NICE to enable people to have access to an innovative treatment as a means of reducing uncertainty about the clinical benefit of a medicine when long-term evidence is not yet available, and as a potential solution to address restricted healthcare budgets) (73). This includes 1,597 people.
- An analysis by Nathan et al. (2024) using data from 130 UK people who received avelumab + axitinib via an Early Access to Medicines Scheme (74,75).
- A review of 1,319 people from 17 centres in the UK who started anti-cancer treatment for Stage IV RCC between 01 January 2018 and 30 June 2021 (McGrane et al. (2024) (44). Most of the people in the group treated with an initial immunotherapy + TKI (85.3% of 197) received avelumab + axitinib.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to people than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In line with the way that clinicians characterise people with aRCC, evidence is presented below for people classified as having favourable-risk disease and those classified as having intermediate-/poor-risk disease. Results are different between these two groups as people' disease differs resulting in a generally different prognosis between the two groups.

In the full study population in the JAVELIN Renal 101 study the overall survival outcomes of the analyses favoured avelumab + axitinib over sunitinib, but did not show a statistical difference between the two groups (71,72).

People with favourable-risk aRCC (190 people out of 886 people overall)

Overall survival

(For further information, see company submission, Document B, Section B.2.6.1.1)

People treated with avelumab + axitinib resulted in a 27% lower risk of dying compared to people treated with sunitinib after an average of 68 months of follow-up (70). Median overall survival (the length of time from the start of treatment that half of the people are still alive) was 14 months longer in the avelumab + axitinib group (79.4 months) than the sunitinib group (65.5 months). The difference in treatment effect started at approximately 30 months, and continued to the end of follow-up (70). There is an unmet need to improve survival for people with favourable-risk aRCC.

Progression-free survival (PFS)

(For further information, see company submission, Document B, Section B.2.6.1.2)

Avelumab + axitinib showed improvements in how long people lived before their disease worsened compared with sunitinib (70). After 69 months of follow-up, avelumab + axitinib was associated with a notable improvement in PFS compared with sunitinib. Median PFS (the length of time from the start of treatment that half of the people experienced disease progression or death) was 20.7 months in the avelumab + axitinib arm and 13.8 months in the sunitinib arm; therefore, people receiving avelumab + axitinib had a 25% reduction in the risk of their cancer getting worse (disease progression) or death. The event-free rate (lack of disease progression or death) was higher for avelumab + axitinib than with sunitinib from 12 months through to 72 months (70).

Objective response

(For further information, see company submission, Document B, Section B.2.6.1.3)

The proportion of people who had a treatment response (objective response rate; meaning that their cancer became undetectable [complete response] or target tumours shrank more than a specified threshold during treatment [partial response]), was almost 30% higher for avelumab + axitinib (75.5%) than for sunitinib (45.8%), and the proportion of people with a complete response was higher in the avelumab + axitinib group (9.6%) compared with the sunitinib group (5.2%) (70). This is important because complete responses to single-treatment TKIs remain uncommon in these people and the disease of almost all people will eventually progress (27,28). The proportion of people with favourable risk aRCC with partial response was higher in the avelumab + axitinib group (66.0%) compared with the sunitinib group (40.6%). More people in the avelumab + axitinib group reached disease control (the effectiveness of a treatment in reducing the tumour volume [complete or partial response] or halting progression [stable disease]) compared with those in the sunitinib group (70).

Time to response and duration of response

(For further information, see company submission, Document B, Section B.2.6.1.4)

In the 71 people with a confirmed complete or partial response to avelumab + axitinib, the median time to response was marginally shorter than that of sunitinib and the median duration of response was longer compared with those in the sunitinib group (70).

People with intermediate-/poor-risk aRCC (691 people out of 886 people overall)

Overall survival

(For further information, see company submission, Document B, Section B.2.6.2.1)

People treated with avelumab + axitinib resulted in a 10% lower risk of dying compared to people treated with sunitinib after an average of 68 months of follow-up. Median overall survival was 8.3 months longer in the avelumab + axitinib group (37.8 months) than the sunitinib group (29.5 months) (70). The difference in treatment effect started early in treatment, and continued to the end of follow-up (70).

Progression-free survival (PFS)

(For further information, see company submission, Document B, Section B.2.6.2.2)

Similarly in the people with intermediate-/poor-risk aRCC, avelumab + axitinib showed improvements in how long people lived before their disease worsened compared with sunitinib (70). After 69 months of follow-up, avelumab + axitinib was associated with a notable improvement in PFS compared with sunitinib. Median PFS was 11.1 months in the avelumab + axitinib arm and 8.1 months in the sunitinib arm; therefore, people receiving avelumab + axitinib had a 36% reduction in the risk of their cancer getting worse (disease progression) or death. The event-free rate (lack of disease progression or death) was higher for avelumab + axitinib than with sunitinib from 12 months through to 72 months (70).

Objective response

(For further information, see company submission, Document B, Section B.2.6.2.3)

The proportion of people who had a treatment response (objective response rate; meaning that their cancer became undetectable [complete response] or target tumours shrank more than a specified threshold during treatment [partial response]), was almost double for avelumab + axitinib than for sunitinib, with a 27.5% difference in rates (55.7% and 28.2%, respectively) the proportion of people with a complete response (cancer became undetectable) was higher in the avelumab + axitinib group (4.7%) compared with the sunitinib group (3.2%) The proportion with partial response was more than double that for sunitinib. More people in the avelumab + axitinib group reached disease control (the effectiveness of a treatment in reducing the tumour volume [complete or partial response] or halting progression [stable disease]) (83.4%) compared with those in the sunitinib group (73.6%) (70).

Time to response and duration of response

(For further information, see company submission, Document B, Section B.2.6.2.4)

In the 191 people with a confirmed complete or partial response to avelumab + axitinib, the median time to response was similar to that of sunitinib and the median duration of response was 19.4 months (versus 9.8 months in the sunitinib group) (70).

UK real-world studies show that the outcomes observed in the JAVELIN Renal 101 study translate into real-world treatment benefits for a broad population of UK people with aRCC, including in people with favourable-risk aRCC (44,73–75).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of people and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?
Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).** Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

People's quality of life was measured in JAVELIN RENAL 101 using the following published and validated patient-reported questionnaires, where higher scores signify better quality of life than lower scores:

- The EuroQol 5-Dimension 5-Level (EQ-5D-5L), a questionnaire used to describe a person's health state by looking at five areas relating to health: how easily you move around, take care of yourself, handle daily activities, deal with pain or discomfort, and manage feelings of anxiety or depression. It helps to assess how the treatment influences different parts of people's daily lives (76)
- The Functional Assessment of Cancer Therapy – Kidney Symptom Index-19 (FKSI-19), used to measure symptoms and quality of life in people with advanced kidney cancer (77)

EQ-5D-5L and FKSI-19 were assessed on the first day of treatment Cycle 1, and then at the beginning of each treatment cycle (every six weeks), as well as at the end of treatment or withdrawal from the study (78). During the follow-up period, after the end of treatment, assessments were collected at the same time as tumour assessments.

In both treatment groups, EQ-5D-5L scores and FKSI-19 total scores remained relatively stable over time (69). Patient-reported outcomes were similar between the avelumab + axitinib and the sunitinib groups, suggesting that adding avelumab to TKI treatment had no adverse impact on people's quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer. Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Because avelumab has been approved since 2017 and axitinib has been approved since 2012, both have well-characterised safety profiles. Safety results from JAVELIN Renal 101 have shown that the combination of avelumab and axitinib has an acceptable tolerability profile with no new safety signals (information on a new or known medical occurrence) observed with long-term treatment (71,72). Other sources confirm the safety profile observed in JAVELIN Renal 101, including safety data from the Phase 1b JAVELIN Renal 100 study and safety data from a UK real-world study (75,79).

A similar proportion of people in each treatment group (almost 100%) reported adverse events (untoward medical occurrences not necessarily caused by the treatment) and reported side effects that the JAVELIN Renal 101 investigators considered to be related to the treatment being received in each case (96.8% of people in each treatment group) (69).

In people treated with avelumab + axitinib, the most common types of adverse event (reported by more than 40% of people) were diarrhoea, hypertension (high blood pressure), fatigue (tiredness), and nausea (feeling sick). In the sunitinib group, the most common events were diarrhoea, fatigue, and nausea (5,69).

Because avelumab + axitinib is a combination of two medicines, clinicians can discontinue one of them to manage adverse events, which is not the case for sunitinib. In total, 25.3%

of people treated with avelumab + axitinib discontinued one of these two medicines, and 4.8% of people discontinued both medicines, due to adverse events. In the sunitinib group, 9.3% of people discontinued sunitinib treatment (69). Likewise, the dose could be interrupted for adverse event management, which occurred in 65.2% of people for avelumab, 75.6% for axitinib, and 62.6% of people treated with sunitinib (69). The dose of axitinib or sunitinib could also be reduced to manage adverse events, but this was not allowed for avelumab; in total, 24.7% of people in the avelumab + axitinib group reduced their dose of axitinib, compared with 28.9% of people treated with sunitinib (69).

The summary of product characteristics (SmPC) for avelumab states that warnings and precautions for use include infusion-related reactions and immune-related side effects and sets out guidance to clinicians for managing these (4).

If low-severity (classed as Grade 1 or 2) infusion-related reactions occur, clinicians should slow or pause infusions. Pre-treatment with paracetamol and antihistamines can be considered for subsequent infusions. For more severe (Grade 3 or 4) events, the clinician will discontinue the person from avelumab treatment (4). In JAVELIN Renal 101, seven people (1.6%) reported infusion-related adverse events that were severe enough for discontinuation as per the SmPC (all were Grade 3) (69).

Most immune-related side effects are considered to be reversible and can be managed by temporary or permanent discontinuation of avelumab, with guidance in the SmPC specific to the types of event. Treating the person with medicines such as corticosteroids may help lessen symptoms (4).

An exploratory risk versus benefit analysis was carried out using data from the JAVELIN Renal 101 study. In this analysis, researchers looked at the effects of avelumab + axitinib and sunitinib treatment on a person's quality of life (a measure of well-being) and they also looked at how long people lived without cancer symptoms or severe side effects to assess the 'quality' of survival the treatments (80). Results showed that people lived longer without cancer symptoms or severe side effects with avelumab + axitinib compared with sunitinib treatment. These findings provide more support for using avelumab + axitinib as a treatment for people with advanced renal cell cancer (80).

3h) Summary of key benefits of treatment for people

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for people, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Improvement in progression-free survival and overall survival

The Phase 3 JAVELIN Renal 101 study provides the longest follow-up to date for an immunotherapy +TKI combination treatment from a Phase 3 study in aRCC (≥68 months of follow-up). The study included some people from the UK and overall, the study involved people with characteristics similar to those seen in UK clinical practice. The study demonstrated the long-term efficacy (progression-free survival only) and manageable toxicity profile of first-line avelumab in combination with axitinib compared with sunitinib in aRCC. OS, PFS and ORR outcomes favoured avelumab + axitinib compared with sunitinib in the subgroup of people with IMDC favourable-risk disease. In the intermediate-/poor-risk group PFS was favourable to avelumab + axitinib, and OS results suggested a trend in favour of avelumab + axitinib compared with sunitinib, with differences between the treatments in terms of survival continuing to end of follow-up.

As shown in the Phase 3 JAVELIN Renal 101 study, avelumab + axitinib has a well-characterised safety and tolerability profile (see below), with a low rate of discontinuations due to side effects. There are a range of available tablet strengths for axitinib, which provide clinicians with dosing flexibility, allowing them to increase or decrease the dose according to an individual's tolerance.

Benefits for favourable-risk people

Although these people are classified as having favourable-risk disease, they still have incurable advanced cancer. No immunotherapy treatment combinations are currently recommended for use in people with previously untreated IMDC favourable-risk aRCC in routine commissioning in England and Wales (unlike Scotland), and many people receive a TKI alone. There is an unmet medical need for a reimbursed immunotherapy +TKI combination treatment that can be used so that treatment aligns with European and US clinical practice guidelines for this group of people. There is also an unmet need for people with aRCC favourable-risk disease to be given the opportunity to be treated initially with an immunotherapy-based regimen. Avelumab + axitinib provides an additional option for people and doctors in the treatment of aRCC. It builds on the established efficacy of TKI treatment alone through the added benefit of immunotherapy.

Benefits for intermediate-/poor-risk people

For people with intermediate-/poor-risk disease, avelumab +axitinib could provide an additional immunotherapy + TKI combination with a manageable tolerability profile. Unlike other immunotherapy + TKI combinations used for the treatment of intermediate-/poor-risk aRCC, axitinib has a short half-life; this can help with quick determination of which medicine is causing an adverse event, so that dose interruption or reduction can rapidly resolve side effects. As above, the ease of axitinib dose adjustment without compromising safety, combined with the range of available tablet strengths, provides clinicians with dosing flexibility, allowing them to increase or decrease the dose according to an individual's tolerance. As such, avelumab + axitinib provides additional choice for people and physicians.

3i) Summary of key disadvantages of treatment for people

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for people, caregivers and their communities when compared with current treatments. Which disadvantages are most important to people and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Avelumab is administered through an infusion (a drip) into a vein (intravenously) every two weeks in an outpatient setting. Treatment should be initiated and monitored by a physician with expertise in cancer care and people may need to travel to receive this treatment. In common with most cancer therapies, treatment with avelumab + axitinib is associated with side effects (Section 3g). The two types of special warnings listed in the warnings and precautions section of avelumab's SmPC are immune-related adverse reactions and infusion-related reactions, which occurred more frequently in the avelumab + axitinib group than the sunitinib group in the JAVELIN Renal 101 study. The avelumab SmPC provides guidelines to clinicians for managing these events if they occur, such as temporary or permanent discontinuation of avelumab and administration of antihistamines or corticosteroids, depending on the type and severity of the event (4).

3j) Value and economic considerations

Introduction for people:
Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating people and how people' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.
In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by people; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for people or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model

As part of the submission to NICE, the manufacturer built a cost-effectiveness model to assess whether the benefits of treating people with avelumab and axitinib outweighed the associated costs to the NHS in comparison to other available treatments. The economic model reflected the treatment benefits and costs in three main health states: progression-free (or pre-progression), progressed disease (or post-progression) and death.

As part of the submission to NICE, the company generated a cost-effectiveness model to assess whether the benefits of treating people with avelumab and axitinib outweighed the associated costs to the NHS in comparison to other available treatments.

The main population considered in this analysis were people with previously untreated aRCC with IMDC favourable-risk disease, as this group has the highest unmet need for an immunotherapy-based therapy.

Compared to available treatments, the economic model showed that avelumab + axitinib could increase the amount of time people with favourable-risk aRCC spent in the progression-free health state, and therefore extends their life by delaying disease progression.

The model also showed that avelumab + axitinib improved QoL of people with favourable-risk aRCC due to prolonged time in the progression-free state where symptoms are anticipated to be less severe compared to the symptoms experienced in the progressed disease health state.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Benefits not captured in the QALY

The existing immunotherapy combinations for people with intermediate-/poor-risk aRCC are associated with potentially harmful side effects. However, people would ideally still be treated with an IO combination as IO-based therapies are associated with better clinical outcomes compared to TKI monotherapy. Therefore, for people with intermediate-/poor-risk aRCC, avelumab + axitinib is an alternative immunotherapy combination option that has manageable tolerability and is more effective than TKI monotherapy.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? 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

It is important that all people regardless of their IMDC risk group have access to the most effective initial therapies. The comparatively longer survival outcomes for favourable-risk people are only relative to intermediate-/poor-risk people but the disease of people in the favourable-risk group remains life-limiting and incurable with current treatment. There are currently no immunotherapy containing regimens recommended by NICE for use in people with favourable-risk disease (outside of the CDF); however, IO+TKI combinations are recommended in people with intermediate-/poor-risk disease. International guidelines recommend IO-containing regimens as first-line treatment options in favourable-risk and intermediate-/poor-risk people (13,33,35). Additionally, in Scotland, the SMC recommends avelumab + axitinib as well as pembrolizumab + axitinib for the first-line treatment of aRCC, regardless of risk group.(42,43) It is important for people to receive the most effective first-line (upfront) treatment therefore all people, but especially people with favourable risk disease where there is an unmet need, should have access to an IO-containing regimen at first-line treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that people would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that people can access.

Information related to aRCC:

- Cancer research UK
- Macmillan cancer support
- NHS
- Kidney Cancer UK

Key treatment guidelines (Europe and US)

- European Association of Urology (EAU) guidelines on renal cell carcinoma 2024
- European Society for Medical Oncology (ESMO) guidelines on renal cell carcinoma diagnosis, treatment and follow-up 2024
- National Comprehensive Cancer Network (NCCN) guidelines on kidney cancer 2025
- American Society of Clinical Oncology (ASCO) guideline on management of metastatic renal clear cell cancer 2022
- American Society of Clinical Oncology (ASCO) guideline on management of metastatic renal clear cell cancer (Rapid Recommendation Update) 2023

NICE appraisals in first-line (previously untreated) aRCC:

- Avelumab with axitinib (TA645)
- Sunitinib (TA169)
- Pazopanib (TA215)
- Tivozanib (TA512)
- Cabozantinib (TA542)
- Nivolumab with ipilimumab (TA780)
- Lenvatinib with pembrolizumab (TA858)
- Cabozantinib with nivolumab (TA964)

Key published JAVELIN RENAL 101 clinical study data:

- Avelumab + Axitinib vs sunitinib in people with advanced renal cell carcinoma: final overall survival analysis from the JAVELIN Renal 101 Phase 3 trial (ASCO conference abstract 2024)

Avelumab + axitinib

- Avelumab summary of product characteristics
- Axitinib summary of product characteristics

Further information:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Advanced renal carcinoma (aRCC) – advanced cancer of the kidney which has spread outside of the kidney to blood vessels and/or local lymph nodes (Stage III) and is inoperable, or to other parts of the body (Stage IV/metastatic).

Adverse event – an untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine.

Cancer Drugs Fund (CDF) – a source of funding for cancer medicines in England that provides early access to promising new treatments, via an arrangement between NICE and the medicine manufacturer, while further evidence is collected to address clinical uncertainty.

Clinical trial – a type of research that studies new tests and treatments and evaluates their effects on human health outcomes.

Complete response (CR) – no sign of cancer after treatment.

EuroQol 5-Dimension (EQ-5D) – a questionnaire used to describe a person's health state by looking at five areas relating to health: how easily you move around, take care of yourself, handle daily activities, deal with pain or discomfort, and manage feelings of anxiety or depression. It helps to assess how the treatment influences different parts of people' daily lives.

First-line treatment – standard and preferred initial/first treatment given when a disease or illness is first diagnosed.

Functional Assessment of Cancer Therapy – Kidney Symptom Index-19 (FKSI-19) – a specific scale used to measure symptoms and quality of life in people with advanced kidney cancer.

Health-related quality of life (HRQoL) –an individual's or a group's perceived physical and mental health over time.

ICER – incremental cost-effectiveness ratio. Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition.

Immunotherapy – targeted cancer medicines that stimulate the immune system to kill cancer cells.

Intravenous – administration of medications directly via a person's vein.

Licensed medicine – a medicine that has been assessed for efficacy, safety, and quality, has been manufactured to appropriate quality standards, and, when placed on the market, is accompanied by appropriate product information and labelling, that is, it has been authorised for marketing.

Marketing authorisation – permission to sell a medicine after the evidence around it (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS.

Monoclonal antibody – medicines designed to attach to specific targets on cancer cells, where they make use of the body's immune system to destroy the cancer cells.

Neoangiogenesis – is the development of new blood vessels to supply cancerous tumours and ensure their growth.

Open-label trial – a trial where people and physicians have knowledge of the assigned treatment.

Overall response rate (ORR) – a clinical study outcome measuring the percentage of people who have either no sign of cancer, shrinkage of the tumour or a decrease in the extent of the cancer, after treatment.

Overall survival (OS) – a clinical study outcome measuring how long people live after receiving a treatment. Median overall survival is the length of time from the start of treatment that half of the people are still alive.

PD-1 inhibitor immunotherapy – a type of immunotherapy treatment that acts against a checkpoint protein called PD-1 or its partner protein PD-L1. Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor allows the T cells to kill tumour cells.

Patient-reported outcome (PRO) – a clinical study outcome reported directly from the patient of how well they are doing.

Phase 3 – a clinical study that investigates how safe and efficacious a medicine is. The medicine will previously have been tested in Phase 1–2 studies, which test whether the medicine is safe enough to use in humans and has an effect on the disease.

Phase 1b – Phase 1 studies usually test new medicines for the first time in a small group of people to evaluate a safe dosage range and identify side effects.

Progression-free survival (PFS) – a clinical study outcome that reports how long people live without their disease getting worse.

QALY – quality-adjusted life year. A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines.

Randomised trial – a study in which a number of similar people are randomly assigned to two (or more) groups to test a specific medicine or other intervention (e.g., a group being given the medicine or a group being given a comparator).

Real-world evidence (RWE) – data relating to patient health or treatments collected outside of highly controlled clinical trials. It can come from many different sources including patient health records, administrative records, patient registries, surveys, observational studies and digital health technologies.

Safety signal – information on a new or known adverse event that may be caused by a medicine and requires further investigation.

Second-line treatment – treatment for a disease or condition after the initial treatment (first-line treatment) has failed, stopped working, or has side effects that aren't tolerated.

Standard of care – treatment that medical experts consider to be most appropriate for a specific disease.

Systematic literature review (SLR) – a type of review that uses repeatable methods to find, select, and synthesise all available evidence. It answers a clearly formulated research question and explicitly states the methods used to arrive at the answer.

Tyrosine kinase inhibitor (TKI) – a type of targeted treatment for cancer that blocks enzymes known as tyrosine kinases that are found in ‘vascular endothelial growth factor’ (VEGF) receptors on the surface of cancer cells. VEGF receptors are involved in the growth and spread of cancer cells and in the development of blood vessels that supply the tumours. By blocking these receptors, TKIs help to reduce the growth and spread of the cancer and cut off the blood supply that keeps the cancer cells growing.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Clarification questions

16 December 2024

File name	Version	Contains confidential information	Date
ID6294_Avelumab-axitinib_aRCC_Company-response-to-clarifications_[Redacted]	1.0	No	16 December 2024

Section A: Clarification on effectiveness data

The JAVELIN Renal 101 trial

A1. Priority question: If possible, please provide versions of CS Figure 7 and CS Figure 9 which also show the PFS assessments by blinded independent central review (BICR). If this is not possible for the favourable and intermediate/poor IMDC prognostic risk groups, please provide a figure showing BICR PFS for the period this was assessed and investigator PFS for the full trial period on the same plot for the total trial population.

As discussed in Section B.2.6.1.2 of the CS, PFS was assessed by BICR for the preplanned interim and primary analyses for PFS only (IA1 [DCO 20 June 2018] and IA2 [DCO 28 January 2019]). BICR activities subsequently ended and PFS was assessed by the investigator for the later analyses (IA3 and for the FA presented in the CS). Therefore, PFS by BICR is not available for the FA presented in the CS, either for the overall ITT population or for patients with favourable-risk or intermediate-/poor-risk disease.

The JAVELIN Renal 101 study met its primary endpoint at IA1 (DCO 20 June 2018) of PFS as assessed by BICR in patients with PD-L1 positive tumours.[1]

The company consider it is not appropriate to plot PFS by BICR and PFS by investigator assessment on the same graph given these represent different assessments of PFS. Figure 1 shows the Kaplan-Meier plot of PFS by BICR for the overall ITT population for IA2 (DCO 28 January 2019) and Figure 2 shows the Kaplan-Meier Plot of PFS based on Investigator assessment for the same population at final analysis (DCO 31 August 2023). The PFS by BIRC for the overall ITT population for IA2 can be also found in Figure 5 of the IA2 CSR.[2]

Figure 1: Kaplan-Meier Plot of PFS based on BICR assessment (RECIST v1.1) (FAS) | IA2 (DCO 28 January 2019)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; FAS, full analysis set; HR, hazard ratio.
Source: DoF IA2 for overall survival.[2]

Figure 2: Kaplan-Meier Plot of PFS based on Investigator assessment (RECIST v1.1) (FAS) | Final analysis (DCO 31 August 2023)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; FAS, full analysis set; HR, hazard ratio.
Source: DoF Final analysis;[3] DOF draft manuscript.[4]

A2. CS Table 6 and CS Table 7 refer to the outcome for '*Time to deterioration in the FKSI-DRS'*, however the results are not reported in CS section B.26 nor have we identified them in the CSR. Please provide the results or signpost to where they are in the submission.

Time to deterioration in FKSI-DRS was assessed and presented only at IA1 (DCO 20 June 2018).[1] This endpoint was mistakenly left in this table from the previous submission, as data for this outcome are not available in the final analysis.

At this endpoint at IA1, the observed HR for time to deterioration was 1.266 (95% CI: 1.044, 1.536) for patients irrespective of PD-L1 tumour expression, but it was thought that sunitinib quality of life outcomes may have been overestimated due to the timing of the PRO measurements since these analyses measure how quickly the patients deteriorate and are sensitive to the schedule of the assessment relative to the dosing period for sunitinib.[1]

The final analysis CSR presents FKSI-DRS scores by visit for the FAS[3] which are included in the CS (Section B.2.6.4.2).

A3. **CS Table 11. We note that the number of participants who discontinued due to death differs for avelumab and axitinib (n=25 and n=28 respectively). Is this because some participants were only in receipt of either avelumab or axitinib at the time of death? If not, please explain why these numbers differ.**

Avelumab + axitinib is a combination treatment; but patients may discontinue one component while continuing the other. During the JAVELIN Renal 101 study, patients were monitored closely for toxicity, and in the event of significant toxicity, dosing of one or both drugs could be modified.[5] In accordance with the study protocol, avelumab doses could be omitted or permanently discontinued; and axitinib and sunitinib doses could be delayed, reduced or permanently discontinued.[5]

As shown in the footnotes at the bottom of CS Table 11, in the avelumab + axitinib arm, 7 (1.6%) patients discontinued avelumab without discontinuing axitinib, and 4 (0.9%) patients discontinued axitinib without discontinuing avelumab.[3] This accounts for the difference in deaths reported in the avelumab and axitinib groups. A further 411 (93%) patients discontinued both treatments and the remaining patients are ongoing treatment (Table 1).

Table 1: End of treatment disposition for patients in the avelumab plus axitinib treatment group (ITT population)

	Avelumab	Axitinib	
		Discontinued, n (%)	Ongoing, n (%)	Total, n (%)
Avelumab + axitinib	Discontinued, n (%)	411 (93.0)	7 (1.6)	418 (94.6)
	Ongoing, n (%)	4 (0.9)	20 (4.5)	24 (5.4)
	Total, n (%)	415 (93.9)	27 (6.1)	442 (100.0)

The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment group. Status of discontinued or ongoing is based on End of Treatment Disposition CRF page.
Abbreviations: DCO, data cutoff; FAS, full analysis set.
Source: DoF Final analysis.[3]

A4. CS Table 11. If possible, please provide versions of CS Table 11 for the favourable and intermediate/poor IMDC prognostic risk subgroups.

In the CS, safety data from JAVELIN Renal 101 are reported for the safety analysis set for the full population from the FA, regardless of IMDC (Heng) prognostic criteria as this provides outcomes from the largest number of patients. Furthermore, the study was not designed to show safety data for the prognostic criteria subgroups. Therefore, equivalent versions of Table 11 in the CS (Summary of patient disposition at final analysis [DCO 31 August 2023]) for favourable- and intermediate-/poor-risk groups are not available.

A5. **CS section B.2.11.1.2 reports that some AEs were at higher frequencies with the combination than observed with either single agent alone. Please would you indicate where we can find the adverse event data for each agent as monotherapy (e.g. for diarrhoea, where in the CSR or elsewhere is it reported that [redacted] and [redacted] of avelumab monotherapy and axitinib monotherapy patients respectively experienced this event?).**

These data are reported in Table 14 of the Summary of clinical safety document which is included in the reference pack.[6] These safety analyses are from 489 treatment-naïve patients with aRCC who received at least one dose of study drug when treated with avelumab 10 mg/kg IV Q2W in combination with axitinib 5 mg PO BID and 439 patients who received sunitinib 50 mg PO once daily (QD) on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off).[6] This is a different dataset from

that reported in the CSR, but these data were included in the CS for full transparency.

Real-world evidence

A6. Please would the company confirm if the EAG's understanding is correct that the only UK sources of real-world evidence without overlap (or potential overlap) are the SACT-EAMS cohort ([redacted] unique patients) and the SACT-CDF cohort ([redacted] unique patients) i.e. there were no patients who contributed data to both the SACT-EAMS cohort and the SACT-CDF cohort after exclusions. Some or all of the patients whose data contributes to the analyses in Nathan et al. and McGrane et al. may also be included in the SACT database.

Yes, the EAG's understanding is correct.

According to the final NICE SACT report, there was a de-duplication process between the CDF and EAMS cohorts as follows:[7]

- There were [redacted] applications for CDF funding for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma between 31 July 2020 and 29 February 2024 in the NHS England Blueteq database. Following de-duplication this relates to [redacted] unique patients.
- A further [redacted] applications were identified in the Blueteq database as receiving avelumab with axitinib to treat advanced or metastatic renal cell carcinoma as part of an Early Access to Medicines Scheme (EAMS) that ran from August 2019 to July 2020; this relates to [redacted] unique patients. The eligibility of these patients at treatment start was the same as the CDF cohort which is why they were included in the analyses.

Following exclusions, [redacted] unique CDF patients and [redacted] unique EAMS patients were included in the final cohorts.[7]

In the two peer-reviewed publications,[8, 9] patients overlap with the CDF and EAMS cohorts above. The McGrane et al. retrospective review included patients with a clinical, radiological or pathological diagnosis of metastatic renal cancer (mRCC) who commenced systemic anti-cancer therapy (SACT) for mRCC between 01

January 2018 and 30 June 2021.[8] The analysis by Nathan et al. included patients with an aRCC diagnosis, age ≥18 years, and avelumab + axitinib initiation on or after August 2019 via EAMS.[9]

A7. CS B.2.8.2.1. What were the reasons for excluding patients from the SACT-CDF and SACT-EAMS cohorts?

According to the SACT report, reasons for excluding patients included the following:

- Duplicate applications
- Died before treatment (confirmed by the trusts)
- Did not receive treatment (confirmed by the trusts)
- Not in SACT.

Please refer to Figure 1 (on page 12) and Figure 2 (on page 17) of the final NICE SACT report.[7]

A8. Appendix D.6 directs the reader to the RWE SLR report for further information and full results. Please provide this reference (or indicate which reference in the reference pack it is).

This was not included in the submitted reference pack as part of the CS on 07 November 2024. However, it has now been submitted along with these responses (DOF_Avelumab plus axitinib in 1L RCC RWE SLR Report_24Oct2024). In addition, an abstract describing the RWE SLR (by Kearney et al.)[10] which has been accepted for publication at ASCO-GU 2025 is also included with these responses.

Indirect and mixed treatment comparisons

A9. Priority question: If there is a separate report with full details for the NMAs and any feasibility assessment conducted please provide this (or indicate which reference in the reference pack it is). If there is not a specific report please provide:

- **a table of the PFS and OS data used in the NMAs for the intermediate/poor risk subgroup**
- **a summary of baseline characteristics for the participants from the studies included in the NMAs for the intermediate/poor risk subgroup**

- **Critical appraisal/risk of bias assessments for the comparator RCTs in the NMA**

The following table displays the input data used in the OS and PFS NMAs for the intermediate-/poor-risk subgroup.

Table 2: Input data used in the OS and PFS NMAs for the intermediate-/poor-risk subgroup

Outcome	Trial Name	Treatment Comparison	Ln(HR)	SE[Ln(HR)]	HR 95% CI
OS	JAVELIN Renal 101	Avelumab + Axitinib vs Sunitinib	-0.124	0.091	0.88 (0.74, 1.06)
	CheckMate 214	Nivolumab 3 + Ipilimumab 1 vs Sunitinib	-0.371	0.081	0.69 (0.59, 0.81)
	CABOSUN	Cabozantinib vs Sunitinib	-0.223	0.211	0.80 (0.53, 1.21)
	CLEAR	Pembrolizumab + Lenvatinib vs Sunitinib	-0.301	0.133	0.74 (0.57, 0.96)
	CheckMate 9ER	Nivolumab + Cabozantinib vs Sunitinib	-0.431	0.124	0.65 (0.51, 0.83)
PFS	JAVELIN Renal 101	Avelumab + Axitinib vs Sunitinib	-0.439	0.087	0.64 (0.54, 0.76)
	CheckMate 214	Nivolumab 3 + Ipilimumab 1 vs Sunitinib	-0.315	0.091	0.73 (0.61, 0.87)
	CABOSUN	Cabozantinib vs Sunitinib	-0.734	0.222	0.48 (0.31, 0.74)
	CLEAR	Pembrolizumab + Lenvatinib vs Sunitinib	-0.844	0.123	0.43 (0.34, 0.55)
	CheckMate 9ER	Nivolumab + Cabozantinib vs Sunitinib	-0.580	0.103	0.56 (0.46, 0.69)

Abbreviations: CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

The following table shows the baseline characteristics (where available) for the studies included in the Intermediate-/poor-risk network of studies. Note, no baseline characteristics data was available for the CLEAR study.

Table 3: Baseline characteristics for the studies included in the intermediate/poor network of studies

		JAVELIN RENAL 101		CheckMate 214		CABOSUN		CheckMate 9ER	
Demographic	**Summary**	**Ave + Axi**	**Sunitinib**	**Nivo 3 + Ipi 1**	**Sunitinib**	**Cabo**	**Sunitinib**	**Nivo + Cabo**	**Sunitinib**
N		343	348	425	422	79	78	249	256
Age (years)	<65	[redacted]	[redacted]						
	Mean year (SD)	[redacted]	[redacted]						
	Median (Min, max)	[redacted]	[redacted]	62 (26–85)	61 (21–85)	63 (56–69)	64 (57–71)	62 (29–90)	61 (28–86)
Gender (%)	Male	[redacted]	[redacted]	74	71	84	73	77.5	71.5
Pooled region (%)	Europe	37.03	43.39	35	35			47.8	48.4
	N America	34.99	34.2	26	26				
	ROW*	11.95	8.91	39	39			52.2	51.6
	Asia	16.03	13.51						
Race (%)	Asian	18.37	14.94			4	3		
	Black	2.62	2.59						
	White	73.18	74.14			89	96		
ECOG (%)	0	[redacted]	[redacted]			46	46		
	1	[redacted]	[redacted]			42	41		
	2	[redacted]	[redacted]			13	13		
Prior nephrectomy (%)		[redacted]	[redacted]	80	76	72	77	67.9	71.5
MSKCC (%)	Favourable	1.75	2.01						
	Intermediate	81.92	84.77						
	Poor	15.16	12.36						
	Intermediate	78.72	79.6	79	79	81	81	75.1	71.9

		JAVELIN RENAL 101		CheckMate 214		CABOSUN		CheckMate 9ER	
Demographic	**Summary**	**Ave + Axi**	**Sunitinib**	**Nivo 3 + Ipi 1**	**Sunitinib**	**Cabo**	**Sunitinib**	**Nivo + Cabo**	**Sunitinib**
IMDC, a.k.a. Heng, (%)	Poor	21.28	20.4	21	21	19	19	24.1	26.2
PD-L1 (%)	Positive	[redacted]	[redacted]	26	29			28.1	28.1
	Negative	[redacted]	[redacted]	74	71			69.5	70.3
	Unknown	[redacted]	[redacted]	0	0			2.4	1.6
Target sites	Mean (SD)	[redacted]	[redacted]						
Non-target sites	Mean (SD)	[redacted]	[redacted]						

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death-ligand 1; ROW, rest of world; SD, standard deviation.

As the SLR has been updated five times since 2018, the quality assessment/risk of bias tools used to assess the studies were different and the summaries are provided in the tables below.

Table 4: Study quality assessment using the NICE checklist

Study name (Trial name)	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	ITT analysis
Choueiri 2018 (CABOSUN)	LR	HR	LR	HR	LR	LR	LR
Motzer 2018 (CheckMate 214)	LR	HR	LR	HR	LR	LR	LR
Motzer 2019 (JAVELIN Renal 101)	LR	LR	LR	HR	LR	LR	LR

Notes: Randomisation: was randomisation carried out appropriately? Concealment grade: was the concealment of treatment allocation adequate? Blinding: were the care providers, participants, and outcome assessors blind to treatment allocation? Baseline comparability: were the groups similar at the outset of the study in terms of prognostic factors? Follow-up: were there any unexpected imbalances in dropouts between groups? Selective reporting and other sources of bias: is there any evidence to suggest that the authors measured more outcomes than they reported? State any important concerns about bias not addressed in the other domains in the tool. If particular

questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry. Analysis: did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Abbreviations: HR, high risk; ITT, intention-to-treat; LR, low risk.

Table 5: Study quality assessment using the ROB 2.0 checklist

Study name (Trial name)	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
Motzer 2021 (CLEAR)	Y	Y	Y	N	Y
Choueiri 2021 (CheckMate 9ER)	Y	Y	Y	N	Y

Systematic review methods

A10. **Please report how many reviewers carried out critical appraisal of studies for the main clinical effectiveness systematic literature review (SLR) and the real-world evidence SLR and, if more than one reviewer, whether the reviewers worked independently.**

Critical appraisal of all the included studies identified in the systematic literature review for both clinical and RWE evidence was conducted in parallel to the data extraction and quality checks procedures i.e. all extracted data (hence, the critical appraisal checklist items) was verified and checked from the source publication by another independent reviewer. For both the clinical and RWE SLRs, primary (Level 1) and secondary (Level 2) screening was performed by two independent reviewers and any uncertainty regarding the inclusion of studies was checked by a third reviewer (see Section 3 of the Clinical SLR report for further details [DOF_Clinical SLR update for avelumab_axitinib in 1L aRCC_03Sep2024]) and Section 4 of the RWE SLR report for further details [DOF_Avelumab plus axitinib in 1L RCC RWE SLR Report_24Oct2024]).

Section B: Clarification on cost-effectiveness data

Time horizon

B1. Priority question: What is the rationale for using a much longer time horizon (40 years) than in previous appraisals for aRCC (10 years)?

By considering a time horizon of 40 years in this submission, the lifetime of the population is captured to inform the model. Mean ages of all IMDC risk populations in the model are around 60 years, thus a 40-year time horizon adequately captures survival up to 100 years of age. If a 10-year lifetime horizon was considered in the model (as that considered in other TKI therapies, i.e., sunitinib, pazopanib and tivozanib for the first-line treatment of advanced renal cell carcinoma), 36.03% of patients in the avelumab + axitinib arm and 18.46% of patients in the sunitinib arm would still be alive. In the avelumab + axitinib arm, the overall survival (OS) does not reach 0 until approximately 38 years, therefore a 40-year time horizon allows all health benefits associated with avelumab + axitinib treatment to be observed. The

40-year time horizon is also aligned with the assumption made in the original submission (TA645), and other recent appraisals of IO-based therapies in RCC (TA964, TA858, TA780 and TA650). Please also note that the favourable risk population has a better overall prognosis versus populations that were the focus of previous NICE appraisals, which considered a combined risk population, or a subgroup of people with intermediate/poor-risk.

Clinical parameters and variables

B2. Priority question: Hazard function plots for the survival curves in the intermediate/poor-risk subgroup are provided in CS Appendix N Figures 1–4. Please provide equivalent hazard function plots for overall survival (OS), progression free survival (PFS) and time to treatment discontinuation (TTD) for both arms of the JAVELIN 101 trial (avelumab + axitinib and sunitinib) for the favourable risk population.

a) **Is there evidence to support or reject an assumption of proportional hazards for OS and PFS in the favourable risk population from the JAVELIN 101 trial?**

b) **Please provide a justification for the choice of parametric survival curve for each outcome and arm based on the hazard function.**

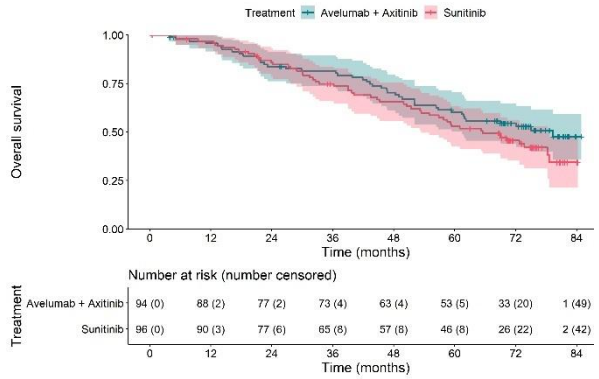
Please see the requested hazard plots for the outcomes of OS and PFS for the favourable risk subgroup in JAVELIN Renal 101 in

Figure 3 and

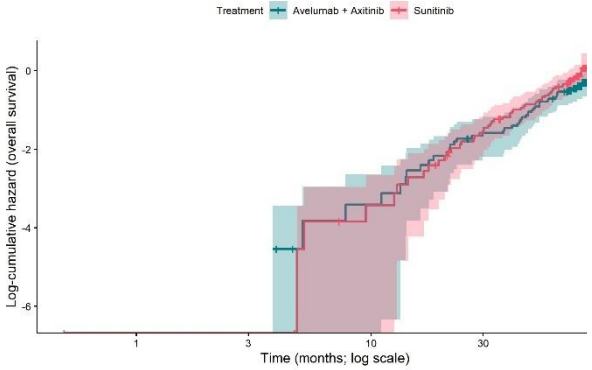
Figure 4, respectively. For the outcome of TTD, only log-cumulative hazard plots have been produced, owing to there being three different estimates produces (i.e., estimates for avelumab, axitinib, and sunitinib – see Figure 5).

Figure 3: Exploratory analyses for JAVELIN Renal 101 (FA) – Overall survival (favourable risk)

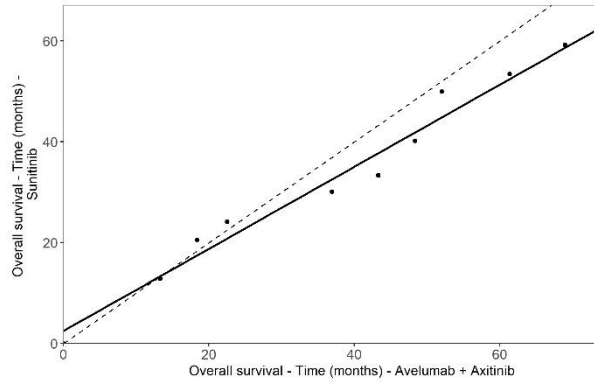
A) Kaplan-Meier plot



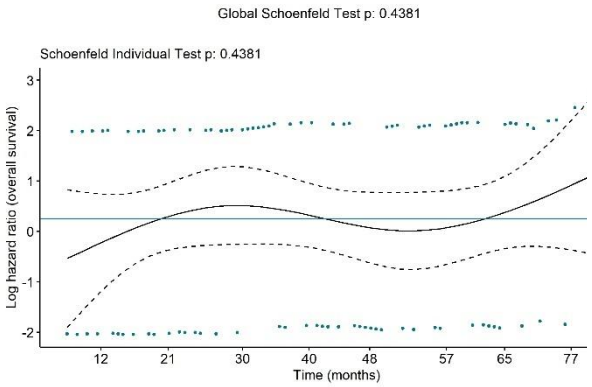
B) Log-cumulative hazard plot



C) Quantile-quantile plot

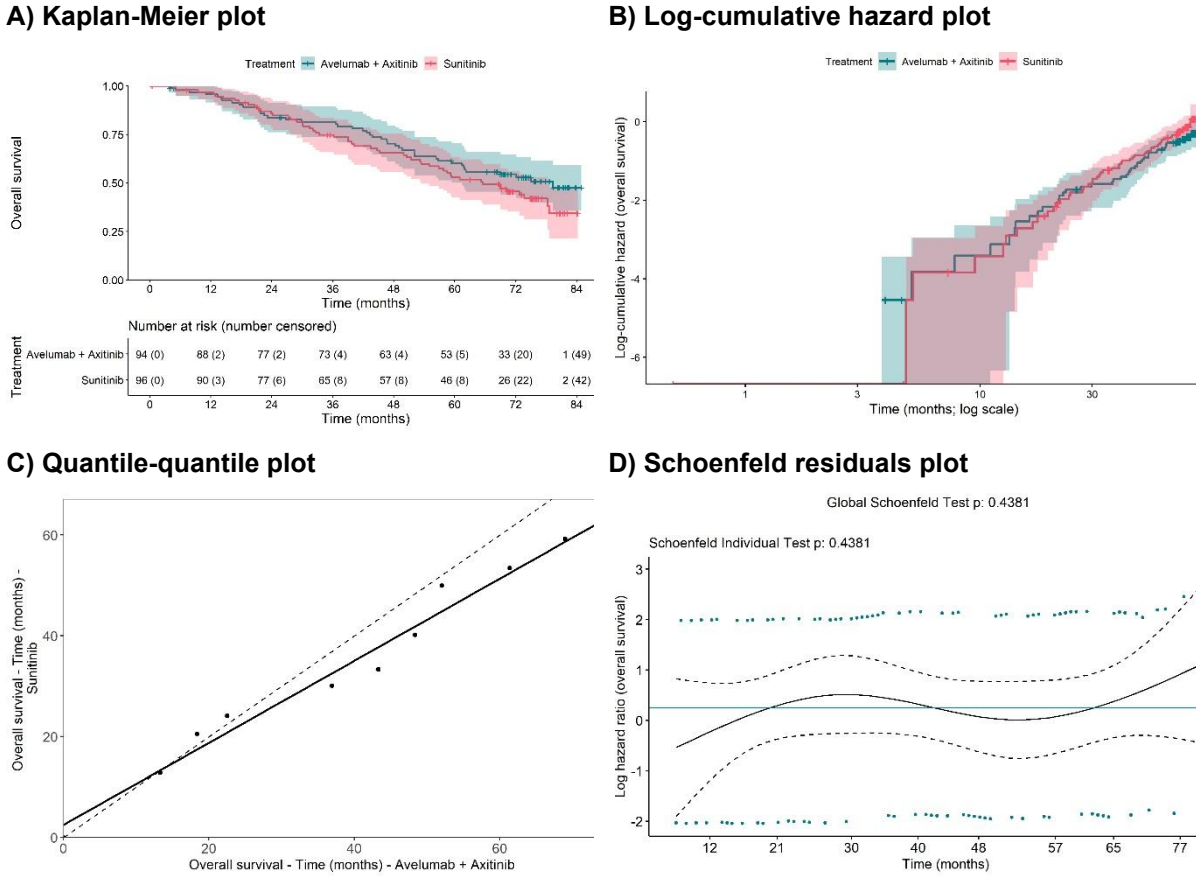


D) Schoenfeld residuals plot



Abbreviations: FA, final analysis.

Figure 4: Exploratory analyses for JAVELIN Renal 101 (FA) | Progression-free survival (favourable risk)



Abbreviations: FA, final analysis.

Figure 5: JAVELIN Renal 101 (FA) – Time on treatment log-cumulative hazard plot

The evidence available from JAVELIN Renal 101 for the favourable risk subgroup does not clearly support the proportional hazards assumption, as may be inferred from the plots provided (most notably, the log-cumulative hazard plots). Consequently, independent models were chosen to be fitted to each treatment arm, across all three outcome measures. The choice of parametric model for each endpoint was determined based on a combination of visual inspection of the model versus the Kaplan-Meier estimate, statistical goodness-of-fit and long-term survival projections which were aligned with clinical expert opinion provided to the company from three clinicians with experience treating patients with avelumab + axitinib.

B3. The Kaplan-Meier data provided in the KM data sheet of the model (KM data!BK46:CM233) have different time points to those reported in the source (DOF additional analyses, tables 3.1a and 31.d in subgrp-heng.html, and tables 5.1a and 5.1d in subgrp-heng-OS.html). For example, for OS in the model the timepoints are 0 months, 3.81 months, 5.09 months etc, while the source provides data for 4 months, 8 months, 12 months, etc. (at 4-month intervals). We also note that the timepoints in the model differ between OS, PFS, and TTD. Please could the company confirm that this discrepancy is due to the model data being derived from individual patient level data, or alternatively provide a source with the matching KM data.

This is correct, the Kaplan-Meier estimates included in the model were derived from the individual patient level data.

B4. Please provide a justification as to why some treatment-related adverse events of grade ≥3 experienced by more than 5% of patients that are reported in the JAVELIN Renal 101 trial are missing from CS Table 56. For example, fatigue, nausea, decreased appetite, stomatitis, mucosal inflammation, aspartate aminotransferase increased, and vomiting.

The model includes all treatment-related adverse events (TRAEs) of grade ≥3 experienced by more than 5% of patients that are reported in Table 22 of the JAVELIN Renal 101 FA CSR.[3] CSR Table 22 reports both TRAEs of grade ≥3 experienced by more than 5% of patients and, TRAEs of any grade that were reported in either more than 10% of patients. The grade ≥3 TRAEs listed in the

question were not reported for more than 5% of patients in either arm (please see Table 6).

Table 6: Grade ≥3 TRAEs experienced by ≥5% of patients in JAVELIN Renal 101 (ITT)

Adverse event	Avelumab + axitinib	Sunitinib
Fatigue	3.5%	3.6%
Nausea	0.9%	1.1%
Decreased appetite	1.8%	1.1%
Stomatitis	1.8%	1.1%
Mucosal inflammation	1.4%	1.1%
Aspartate aminotransferase increased	3.2%	1.8%
Vomiting	0.5%	1.8%

Note: Values taken from Clinical Study Report for Final Analysis of JAVELIN Renal 101 (Table 22).
Abbreviations: ITT, intention-to-treat; TRAE, treatment-related adverse events.

Patient reported outcome measures: EQ-5D-5L index and FKSI-19

B5. Please state the method used to attribute index scores to the EQ-5D-5L FAS data, as reported in CS section B.2.6.4.1. In particular, please confirm whether the Hernández-Alava et al. (2017) mapping approach was used as in the analysis of EQ-5D-5L data for the economic model (CS section B.3.4.2).

Section B.2.6.4.1 of the CS presents the EQ-5D-5L utility index scores as reported in the JAVELIN Renal 101 CSR. For the cost-effectiveness model, the EQ-5D-5L responses were mapped to EQ-5D-3L utility values using the Hernández-Alava at al. mapping approach.

B6. Descriptive information and results for the EQ-5D-5L index score is reported in CS section B.2.6.4.1 for the FAS population. Please provide this information for the favourable-risk and intermediate/poor risk subgroups. For each subgroup, please provide a graph of EQ-5D-5L index scores change from baseline by visit, with numbers at risk (as in CS Figure 11).

This information is not available from the CSR as results were not reported separately by risk subgroups. Following the clarification call with the EAG, utility over time plots for the favourable-risk and intermediate-/poor-risk populations are presented (Figure 6,

Figure 7). The plots present utility values mapped from the EQ-5D-5L observations collected in the trial to EQ-5D-3L using the Hernández-Alava at al. mapping approach (i.e., those used in the cost-effectiveness modelling).

Figure 6: Utility over time by progression (favourable-risk)

Figure 7: Utility over time by progression (intermediate-/poor-risk)

Utilities

B7. Priority question: Please provide more explanation on the methods used to derive health state utility values for the economic model. CS section B.3.4.2 provides a brief description of the mixed-effects regression models used in the utility analyses. The model specifications are simple, with one or two fixed-effect variables: progression status in Model 1; and progression and treatment status in Model 2.

a) **Please describe the volume and pattern of missing EQ-5D-5L data from the JAVELIN Renal 101 trial that are used in the utility analyses for the favourable-risk, intermediate/poor-risk and ITT populations (CS Table 57 and Appendix Tables 84 and 86).?**

The overall number of EQ-5D-5L observations for each population are presented in Table 7. Also shown are the total number of observations with at least one missing dimension [redacted] of the total for all populations) and the number of dimensions missing.

Table 7: Missing EQ-5D-5L observations

Population	Total observations	Total missing ≥1 dimension n (%)	Number of missing dimensions					
			0	1	2	3	4	5
Favourable risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate-/poor-risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; n, number.

Table 8 presents the distribution of complete and missing observations recorded in the pre-progression and post-progression states, for each population. 'Complete' refers to responses being recorded for all 5 dimensions of the EQ-5D-5L per observation. 'Missing' refers to at least 1 missing dimension, such that the utility for that observation could not be calculated.

Table 8: Distribution of complete and missing EQ-5D-5L observations

	Favourable risk	Intermediate-/poor-risk	ITT
Number of patients with observations	[redacted]	[redacted]	[redacted]
Number of complete observations			
Overall	[redacted]	[redacted]	[redacted]
Pre-progression	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]
Number of missing observations (missing ≥1 dimension)			
Overall	[redacted]	[redacted]	[redacted]
Pre-progression	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat.

b) Was any attempt made to impute the missing data in the utility regressions? If yes, please describe and justify the imputation method used. If not, please explain and justify the decision not to impute missing data.

No missing data were imputed for this analysis. As there was only a small quantity of missing observations in the data [redacted] for each population as seen in Table 7), exclusion of these observations without imputation was considered reasonable.

c) **Please justify the chosen regression model specifications for Model 1 and Model 2. Would the fit of these models (e.g. AIC/BIC statistics) be improved by including other baseline co-variates? Would it have been more efficient to use a single model based on ITT data, with fixed-effect and interaction terms for risk group status?**

The regression covariates included were progression status (pre-/post-progression) only in Model 1, with progression status and treatment status (on-/off-treatment) explored in Model 2. Progression status was included in both regression models to align with the 'alive' economic model health states (pre-progression, post-progression). Treatment status was included as an exploratory analysis to determine whether being on-/off-treatment had a statistically significant impact on patient utility. Progression status was found to be statistically significant in both models ($p < 0.001$), and treatment status was not associated with a statistically significant impact on utility ($p = 0.142$), thus the cost-effectiveness model incorporates different utility values by progression status and utilises the output from Model 1.

It is possible that the fit of the models could be improved by including other baseline co-variates. However, owing to the cost-effectiveness model adopting a 3-state Part-SA cohort structure, it would not be feasible to capture baseline differences at the patient-level in the economic modelling.

Progression status was included in the utility regression model to align the efficacy inputs in the cost-effectiveness model with the approach taken to model overall and progression-free survival from the trial. As the OS, PFS and TTD data were estimated by subgroup, the same approach was applied to estimate utility values for these groups to best align analyses of data, rather than fit the regression model to the ITT data and include a covariate for risk subgroup.

Costs and resource use

B8. Priority question: The base case analysis includes an assumption that nivolumab is not used as subsequent treatment after progression on avelumab + axitinib (CS Table 69), with scenario analysis conducted assuming different proportions of subsequent treatment options (CS Appendix P Table 95). This

assumption is justified in CS section B.3.5.4 on the basis of clinical expert feedback to the company. Please provide a clearer justification for this assumption based on evidence from NICE guidance, NHS England prescribing policy and NHS practice (as documented for example in SACT data). Please also explain and justify the alternative assumptions used for scenario analysis.

Firstly, international guidelines for the management and treatment of advanced renal cell carcinoma do not recommend use of an IO therapy in patients who have received IO as first-line treatment.[11–14] Furthermore, the NHSE Blueteq Approval Criteria for nivolumab for previously treated advanced renal cell carcinoma (i.e., 2L treatment) states that the patient should be either completely treatment naïve for immune-modulatory therapies (anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD L2, anti-CD137 or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibodies) of any kind for RCC or if the patient has received prior immune-modulatory therapies in the context of adjuvant/neoadjuvant therapy, then such treatment was completed 12 or more months prior to the first relapse and the patient meets all other criteria listed (Page 141).[15]

Secondly, evidence from previous TAs additionally supports this assumption; including the following:

- TA780 (Nivolumab with ipilimumab for untreated aRCC) states that clinical experts considered that the SACT treatments best matched NHS clinical practice – and noted that after sunitinib, people will often have either nivolumab or cabozantinib; whereas after nivolumab with ipilimumab, people will have a tyrosine kinase inhibitor – usually cabozantinib, but sometimes sunitinib, tivozanib, or lenvatinib with everolimus (Section 3.2).[16] **The committee noted that the NHS would not offer immunotherapy twice**, and heard from the clinical experts that there is little evidence that a second round of immunotherapy works. The committee was concerned about using CheckMate 214 as a source of data for second-line and beyond treatments if any of these treatments not used in the NHS influenced survival outcomes. It considered that the true cost-effectiveness results may be somewhere

between those based on trial data and those based on SACT data. It also noted that removing additional costs of nivolumab monotherapy after treatment with nivolumab with ipilimumab in the CheckMate 214 trial (because **immunotherapy would likely not be offered twice**) would reduce the cost-effectiveness estimates. The committee preferred to use evidence on effectiveness and costs from the same source, and concluded that it was appropriate to use CheckMate 214 data for second-line and beyond treatments.[16]

- TA964 (Cabozantinib with nivolumab for untreated aRCC) Committee papers state that nivolumab + ipilimumab, pembrolizumab + lenvatinib, avelumab + axitinib, cabozantinib + nivolumab and **nivolumab cannot be used if an IO was used in the last 12 months in the adjuvant setting**; lenvatinib + everolimus can only be used after one prior anti-VEGF (avelumab + axitinib, axitinib, cabozantinib cabozantinib + nivolumab, pazopanib, pembrolizumab + lenvatinib, sunitinib, tivozanib), and sunitinib, tivozanib and pazopanib when 2L+ can only be used after nivolumab + ipilimumab, pembrolizumab + lenvatinib, avelumab + axitinib and cabozantinib + nivolumab (Page 527).[17]

- The NICE RCC Pathways Pilot Preliminary Assessment Report [ID6186] states that current treatment options for previously treated aRCC include **nivolumab for people who have only had one or two prior lines of therapy and have not previously had a PD-1/PD-L1 inhibitor**; TA417 (Page 527).[18]

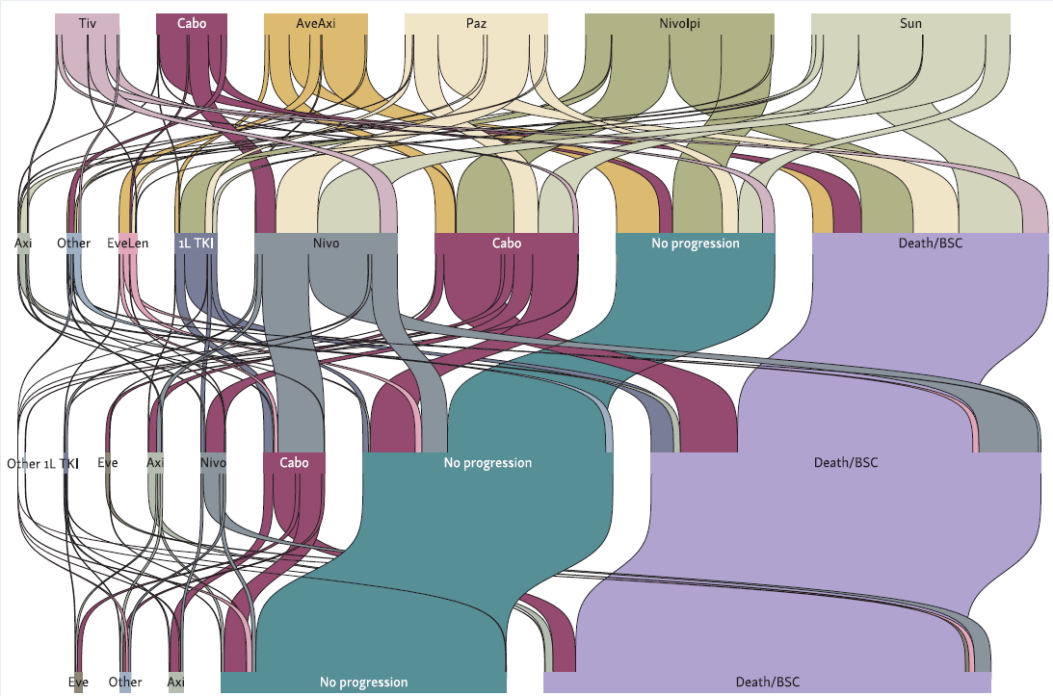
Thirdly, RWE from retrospective multi-institutional cohort of SACT patients for mRCC at 17 centres across the UK from 01 January 2018 and 30 June 2021 provides additional evidence.[19] As can be seen in Figure 8 below, patients did not receive 2nd-line nivolumab after receiving 1st-line avelumab plus axitinib.

The company do not have SACT data relating to this as it was not a part of the Data Collection Agreement (DCA) with NHSE.

Owing to the time that has elapsed since the design of the JAVELIN Renal 101 study, and potential differences in the use of subsequent therapies compared to contemporary NHS practice, a number of scenarios were explored in the model. The

different scenarios were chosen to either reflect the subsequent treatments received in JAVELIN Renal 101 (scenarios using the TA645 and JR101-FV risk FA) or closely reflect UK clinical practice (scenario using UK ROC study). Finally, a more extreme scenario assuming that 100% of patients treated with avelumab and axitinib will receive cabozatinib and 100% of patients treated with sunitinib will receive nivolumab was explored to assess the impact of alternative assumptions on cost-effectiveness results. However, the base-case analysis was considered the most plausible setting, which aligns with the use of the trial data (for consistency with the other model inputs), plus alignment with the use of subsequent immunotherapy only for patients that have not previously been treated with an anti-PD-1/PD-L1 therapy.

Figure 8: Sankey diagram showing the percentage of patients who received which treatment per line of therapy and how treatment in the previous line influenced the choice in the subsequent line



Abbreviations: AveAxi, avelumab plus axitinib; Axi, axitinib; BSC, best supportive care; Cabo, cabozantinib; Eve, everolimus; EveLen, everolimus plus lenvatinib; 1L, first line; Nivo, nivolumab; NivoIpi, nivolumab plus ipilimumab; Paz, pazopanib; Sun, sunitinib; Tiv, tivozanib; TKI, tyrosine kinase inhibitor.
Source: Frazer *et al.* (2024).[19]

B9. Please provide a justification as to why costs are assumed equal for all adverse events, and how this impacts the model results. Please also explain why a non-elective short stay cost is used for all grade ≥3 adverse events.

The cost of adverse events were assumed equal for model simplicity and owing to their minimal impact on the ICER. When adding adverse event costs to the economic model, the latest version (22/23) of the NHS National Cost Collection was retracted for unknown reasons and not available for a long period of time, meaning older costs from version 21/22 were used. The cost of a non-elective short stay was selected as a proxy cost as it was thought to adequately capture the cost of resolution for each grade ≥3 adverse event included.

A scenario has been added to the model to explore the impact of including adverse event specific costs rather than assuming equal cost across all adverse events. This scenario uses the same currency codes for adverse event costs as the prior appraisal of avelumab and axitinib (TA645), however these have been updated to the National Cost Collection 22/23.[20] The impact of including adverse event specific costs showed a minimal increase to the base case ICER ([redacted]).

B10. Priority question: The values in the model table Costs!AK162:AL185, which presents the distribution of follow-up treatments for the poor-/intermediate-risk group, are different from those reported in Table 10.5.a of the relevant source (ASCO presentation analysis). This seems to be related with the fact that only the first six drugs of Table 10.5.a were considered for the poor-risk group (Costs!AI162:AJ185) while 24 were considered for the intermediate-risk group (Costs!AG162:AH185). Please provide a rationale for this assumption.

Apologies, this was an error. The subsequent treatment distribution for the poor-risk group has been corrected in the model, which has in turn aligned the distribution of the intermediate-/poor-risk group. The impact on the ICERs for the ITT and intermediate-/poor-risk subgroup is minimal ([redacted] for ITT, and [redacted] for intermediate-/poor-risk).

Model inputs

B11. Priority question: The EAG are unable to identify the sources of several model input parameters which are reported in the CS and used in the company's model (Table 1 below). Please clarify how these values were derived from the corresponding sources, by stating where they can be found in the source and, if applicable, the calculations needed to derive the model input value. Where required, please update the economic model.

Table 9: ***EAG queries on sources of model input parameters***

Parameters	Location in company submission	Source	Describe where the input parameters are in the source (providing detail of how they were derived and any calculations needed)
Average age, proportion female and average weight (favourable risk)	CS Table 40	JAVELIN Renal 101	The mean age, proportion female and average weight for the favourable risk population were extracted from the patient-level data of the JAVELIN Renal 101 trial using a R studios script.
Average age, proportion female and average weight (intermediate/poor risk)	CS Appendix O Table 50	JAVELIN Renal 101	The baseline patient demographics for the intermediate-/poor-risk population were extracted from the patient level data of the JAVELIN Renal 101 trial using a R studios script.
Average weight (ITT population)	CS Appendix O Table 51	JAVELIN Renal 101	The mean weight for the ITT population was extracted from the patient level data of the JAVELIN Renal 101 trial using a R studios script.

All baseline characteristics were sourced from the JAVELIN Renal 101 patient-level data, using R code to extract patient demographics (mean age, female proportion and mean weight) for each IMDC risk population. This was necessary as the desired baseline demographics by IMDC subgroup were not available from any existing subgroup analyses of the JAVELIN trial data at the required reporting (e.g., mean age instead of median age). Upon reviewing these values, we realised that in the model it states the median age was extracted, this is incorrect and we can confirm these values are the mean age. Apologies for this error.

B12. Priority question: Different input values are reported in the company submission and in the company's model for several input parameters (Table 2 below). Please clarify which of the values should be considered in the company's base case. Where required, please update the economic model.

Table 10: ***EAG queries on discrepancies between reported model input parameters***

Parameters	Location in company submission	Location in company model	Source	Which value (company submission or model) should be considered in the company's base case?
IV administration costs	CS Table 64	Costs!G86 Costs!AE86	NHS National Costs Collection 2022/2023 (SB12Z)	Please consider the value in the CS as the base case input for simple IV administration (£217.00).
CT scan and blood test costs	CS Table 66	Costs!G118:G122	NHS National Costs Collection 2022/2023	The values presented in the CS should be considered in the base case (£193.00 for CT scan and £3.00 for blood test)
Nivolumab treatment dosing	CS Table 71	Costs!H183	TA542	The dose of 240 mg presented in the economic model should be used in the base case for nivolumab.
Total subsequent treatment costs – avelumab + axitinib (intermediate/poor risk)	CS Appendix O Table 91	Costs!G234	N/A	Please use the model value in the base case for the intermediate-/poor-risk subgroup (£26,910).

When constructing these parts of the economic model, the latest version (22/23) of the National Cost Collection was retracted due to unknown reasons, thus the older version was used (21/22). The economic model has now been updated to reflect the most recent version of the NHS National Cost Collection (22/23). The base case results of the updated costs are provided in Appendix A.

Regarding nivolumab treatment dosing, the model value of 240 mg should be taken as the base case as per the SmPC guidance around nivolumab dosing.[20]

Nivolumab is only dosed at 3 mg/kg in combination with ipilimumab for the first 4 doses of treatment, before nivolumab monotherapy commences at 240 mg per dose. For simplicity the model only considers the dose of 240 mg. Furthermore, the average weight of the intermediate-/poor-risk population in which this regimen is approved is [redacted] kg, meaning a minimal difference in nivolumab dose would be

observed. This means that an average intermediate-/poor-risk patient would theoretically receive [redacted] mg (assuming [redacted] kg, 3 mg/kg) of nivolumab with ipilimumab for 4 doses and then continue with 240 mg of nivolumab.

Subsequent therapy treatment costs in Appendix O of the company submission for the intermediate-/poor-risk population is incorrect as it still appears to be using the estimated proportion of patients associated with the favourable risk population. We apologise for this error, please consider the model value of £26,910 as the base case. As noted in response to B10, this has a minimal impact on results.

Section C: Textual clarification and additional points

C1. Should we treat all the data-on-file (DOF) references as commercial in confidence?

Yes, please treat all DOF references as confidential in this submission.

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Appendix A

A1. Changes to the economic base case

The revised economic model features a new sheet (‘Clarification questions’) featuring new inputs used to inform changes suggested by the EAG and switches to facilitate the use of these values in model calculations. Also this sheet aims to provide clarity and transparency regarding any changes made from the initial submission. Following the clarification questions from the EAG, the base case in the economic model has been updated to include the following:

- Adverse event specific costs are applied rather than a single value for all adverse events, with costs updated to the 22/23 National Cost Collection.
- Blood test, CT scan, simple IV and complex IV costs have all been updated from 21/22 to 22/23 National Cost Collection values.
- All poor risk subsequent therapies are considered.

A summary of these changes are provided in Table 11, with revised base case results provided in Table 12 to Table 14 respectively.

Table 11: Summary of updated costs

Parameters	Original value (NCC 21/22)	Updated value (NCC 22/23)
Simple IV	£207.59	£217.22
Complex IV	£440.71	£360.69
Blood test	£2.96	£2.75
CT scan	£165.76	£192.56

Table 12: Base case results (deterministic) – avelumab PAS price (favourable-risk)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
Versus sunitinib								
Sunitinib	£93,185	6.45	[redacted]					
Avelumab + axitinib	[redacted]	10.14	[redacted]	[redacted]	3.70	[redacted]	[redacted]	[redacted]
Versus tivozanib								
Tivozanib	£136,173	6.45	[redacted]					
Avelumab + axitinib	[redacted]	10.14	[redacted]	[redacted]	3.70	[redacted]	[redacted]	[redacted]
Versus pazopanib								
Pazopanib	£165,275	6.45	[redacted]					
Avelumab + axitinib	[redacted]	10.14	[redacted]	[redacted]	3.70	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years.
Note: *No severity modifier is applied to the discounted incremental QALYs.

Table 13: Base case results (deterministic) – avelumab PAS price (intermediate-/poor-risk)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
Versus sunitinib								
Sunitinib	£72,283	5.05	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	0.76	[redacted]	[redacted]	[redacted]
Versus tivozanib								
Tivozanib	£99,613	5.05	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	0.76	[redacted]	[redacted]	[redacted]
Versus pazopanib								
Pazopanib	£117,935	5.05	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	0.76	[redacted]	[redacted]	[redacted]
Versus cabozantinib								
Cabozantinib	£128,584	6.49	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	-0.68	[redacted]	[redacted]	[redacted]
Versus nivolumab plus ipilimumab								
Nivolumab plus ipilimumab	£117,515	7.67	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	-1.86	[redacted]	[redacted]	[redacted]
Versus lenvatinib with pembrolizumab								
Lenvatinib with pembrolizumab	£196,392	7.09	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	-1.28	[redacted]	[redacted]	[redacted]
Versus cabozantinib with nivolumab								
Cabozantinib with nivolumab	£151,668	8.17	[redacted]					
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	-2.36	[redacted]	[redacted]	[redacted]

Note: *No severity modifier is applied to the discounted incremental QALYs.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 14: Base case results (deterministic) – avelumab PAS price (ITT)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs*	ICER versus baseline (£/QALY)	Incremental NMB (£, £30,000/QALY)
Versus sunitinib								
Sunitinib	£77,045	5.59	[redacted]					
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	1.11	[redacted]	[redacted]	[redacted]
Versus tivozanib								
Tivozanib	£108,667	5.59	[redacted]					
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	1.11	[redacted]	[redacted]	[redacted]
Versus pazopanib								
Pazopanib	£129,901	5.59	[redacted]					
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	1.11	[redacted]	[redacted]	[redacted]

Note: *No severity modifier is applied to the discounted incremental QALYs.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

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 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	Action Kidney Cancer
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	Action Kidney Cancer started as a patient support group called the Kidney Cancer Support Network, founded in 2006 by cancer survivors Rose Woodward and Julia Black. The group provided practical and bespoke support to individual patients for access to life-extending cancer drugs to treat advanced/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 closed patient support 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 is now a registered charity, which enables it to better meet the growing needs of the kidney cancer community in the UK.
4b. Has the organisation received any funding from the company/companies of the treatment and/or	We received £9,210 from Merck Serono towards our multi-funded community support programme for 2024. Merck Serono were not involved in the planning, management, or implementation of the project.

comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	
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 using avelumab/axitinib for the treatment of metastatic or advanced kidney cancer through our closed patient support forum. Over 1400 patients and carers use this facility to communicate on a regular basis, and we receive in the order of 5-600 interactions and comments a day.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to	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.

your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Most patients with advanced/metastatic RCC will have surgery to remove their primary 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 should 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. 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 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 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."*
7. 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, both psychologically and physically. 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.
8. What do patients and carers think of current treatments and care available 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

Please state how they help and what the limitations are.	and treatment (shared decision-making) to get the best out of these medicines 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 sequencing 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. 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. 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. 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 NHS England, so that patients in England have the same choices as patients in other countries and to improve outcomes.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	There are several different subtypes of RCC, which do not respond well to current treatments, for example, papillary, chromophobe and collecting duct RCC. Currently, these subtypes are treated in the same manner as clear cell RCC, but their prognosis is poor. 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 is treated with currently available systemic anti-cancer treatments, which are not always successful. Effective, tolerable treatments for rare subtypes of RCC, RCC with sarcomatoid features and hereditary subtypes of RCC are unmet needs for this type of cancer.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	When avelumab plus axitinib was available under the Early Access to Medicines Scheme (EAMS), some patients had to change hospitals and oncologists to be able to access the treatment. However, once it became available through the CDF, they were able to revert to their original hospital/consultant: *"I was initially treated at Northampton having a radical nephrectomy in Dec 2018 removing kidney and local lymph nodes. CT scan in Mar 2019 showed enlarged lymph nodes in chest and lump on lung. Had 5 radiotherapy treatments in July but the following scan showed growth in right node had increased so oncologist recommended immunotherapy. Said new Axitinib and Avelumab treatment available if I would go to Royal Derby ….. Started this in Sept 2019. Stayed there for about 2 years until treatment available everywhere and then switched back to Northampton."* When treatment became available on the CDF, there were no issues accessing the treatment if it was deemed appropriate for the patient. However, some patients experienced problems with the avelumab infusion: *"My renal oncologist suggested I have Avelumab every 4 weeks and Axitinib 5mg twice a day. I was offered it after a period of watch and wait and after a change in the pace of the growth of the metastases. I have the infusions of the Avelumab at …… Leeds…... The first infusion went well but at the second infusion there was a struggle to find a vein in my hand, so I have had a portacath fitted. For the third and subsequent infusions everything has gone smoothly with the application of the infusion."*

11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The avelumab plus axitinib combination has been proven to be a clinically effective and well-tolerated treatment and was designated a breakthrough therapy and approved by the FDA for the treatment of advanced RCC IN 2019. As a breakthrough therapy, this combination treatment was fast tracked for approval in several countries and was available via the EAMS in England. The combination was one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in metastatic RCC. Patients and carers opinions of the avelumab plus axitinib combination are based on their experience of other immunotherapy/VEGFR TKI combinations in the first-line setting. This is borne out by the results from the JAVELIN Renal 101 study in which the combination of avelumab plus axitinib significantly lowered the risk of disease progression or death by 31% and nearly doubled response rates (52.5%) compared with sunitinib (27.3%) in patients with advanced RCC, regardless of whether the patients were PD-L1 positive or negative or they had low, intermediate or high risk RCC. Progression-free survival was nearly doubled with an average of 13.8 months in the combination group and 7.0 months in the sunitinib group. In addition, the safety profile of the avelumab plus axitinib combination is no worse than that for the individual drugs alone, and is, therefore, seen as being better tolerated than standard first-line VEGFR inhibitor treatments, such as sunitinib and pazopanib. This results in improved quality of life to enable patients to contribute both socially and economically to society. The following quote is taken from a patient with stage 4 clear cell RCC who was one of the first patients in the JAVELIN Renal 101 trial: *"I have been taking Avelumab and Axitinib as part of the Javelin Renal 100 trial since January 2015. Before I found out I had cancer, I was enjoying early retirement, travelling abroad and in the UK, meeting friends for pub lunches, doing some physical voluntary work, walking long distances and doing DIY jobs. The drug combination … has been good to me and I had clear scans for 2 years. The cancer has returned but even now my condition is stable, and I am still taking the drugs. I believe that the drugs have extended my life expectancy.* *"I have had a wide variety of side effects…... I have very little energy, I sleep most afternoons, I am short of breath and I am no longer able to walk long distances, the most I can manage now is a mile but often I can't even manage that. At times I had sore hands and feet which further reduced my*

	mobility. I also suffered from a very sensitive mouth for periods that meant spicy food had to stop and I had to use children's toothpaste. I have a chronic cough and my voice fades after talking for a while so even socialising is a problem. I also suffer from periods of constipation and diarrhoea. *"I had already retired so work was not a problem, but I did have to give up my voluntary work. I manage my time well; I plan ahead and try and get as much done as possible in the mornings. I have had had great support and understanding from almost everybody around me, but I am fairly self-sufficient in day-to-day things. I still do the shopping cooking etc. I just have to plan everything."* The following two quotes are taken from patients who received avelumab plus axitinib through the CDF: *"After I had been on the treatment for 11 weeks I had a CT scan. The scan showed that the treatment was working, and all the metastases had shrunk; with shrinkage ranging from 23% through 37% to 54% with some of the smaller ones in the lungs disappeared totally. I have recently had another scan, and I hopefully get similar results from that scan ……."* *"The clear advantage of the treatment is that it works (on me anyway) and is relatively mild in side effects so is quite easy to tolerate. I was able to continue playing sport and have an active life. I have had no evidence of disease for 18 months."*
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	The main disadvantages of the avelumab plus axitinib combination for advanced/metastatic RCC include: • The toxicity of the treatment where over 90% of patients in clinical trials reported a treatment-related adverse event. • The seriousness of adverse events to avelumab, 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 the treatment on the quality of life of the patients and the family and carers, for example, severe hand and foot syndrome that 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.
- Costs for additional medicines to mitigate the side effects.
- The effect of less serious side 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 can be distressing. White, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients.
- Avelumab is administered as an intravenous infusion, requiring regular trips to hospital and the use of infusion chairs. Some patients may need to travel long distances 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 avelumab plus axitinib 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.

Here are some quotes from patients who have accessed avelumab plus axitinib via the CDF:

"A negative aspect is the lack of an exit plan (death or stops working seem to be the only two). It is quite disruptive on lifestyle with biweekly blood tests and treatment, but this gets easier over time as I was allowed breaks if it clashed with holidays etc. on side effects, Diarrhoea was the worst as this became a daily challenge and aching joints (hard to say if this was age or treatment). The treatment day itself is a bit of a write off as it made me very tired but was fine the next day."

"The only disadvantages I can see are the side effects:

	• *On the day of the infusion I have had episodes of drowsiness, not every time, and whether that is due to the Avelumab or the antihistamine that I have before I am not sure.* • *I have had a sore/sensitive tongue on and off from the beginning of the treatment……* • *I have been having very regular bouts of sweating without a high temperature for which I did not know the cause. I had a break from the Axitinib due to taking antibiotics for an abscess/infection in my gums and whilst off Axitinib the sweating stopped totally and then restarted after finishing the antibiotic and taking the Axitinib again.* • *I didn't start having diarrhoea until around the 4th infusion, but it was very easily managed, it has got slightly more intense lately but still manageable.* • *I have had dry skin, on my hands, and dry, cracked and slightly peeling skin on my feet ...* • *I am currently being investigated by rheumatology as I am experiencing painful joints of my fingers, hips and knees.* *All in all, I feel that the side effects could have been much worse and that I have been lucky in my responses to the treatment."*
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	There is an unmet need for a first-line treatment that improves overall survival and allows patients to live a good quality of life without the incumbent debilitating side effects of current first-line treatments. There is also a significant unmet need for effective and safe treatments for people with hereditary kidney cancer, sarcomatoid RCC, or rare RCC subtypes, who currently have very limited treatment options.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	We have no knowledge of the tests/assessments performed for the purposes of the MAA and are, therefore unable to comment.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	We have no knowledge of the tests/assessments performed for the purposes of the MAA.

16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	We have no knowledge of the tests/assessments performed for the purposes of the MAA.
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	We have no knowledge of the outcomes data captured for the purposes of the MAA.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	No

19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	We do not have access to this information/data.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

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.

Section 7 Other issues

21. 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.

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The avelumab plus axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in advanced RCC, and has been designated a breakthrough therapy by the FDA
- The avelumab plus axitinib 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 avelumab plus axitinib 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 avelumab plus axitinib combination enhances quality of life and enables patients to contribute socially and economically to society
- The avelumab plus axitinib combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

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 20 pages.

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This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	Hazel Jackson
2. Name of organisation	Kidney cancer UK
3. Job title or position	Nurse
4a. Provide a brief description of the organisation. How many members does it have?	As the UK's leading kidney cancer charity our focus is on reducing the harm caused by kidney cancer for today's patients and their families and by reducing its prevalence and impact for future generations. To achieve this, we work closely with patients, nurses and doctors to identify patients' needs and help ensure they are being met by delivering various professional and educational programmes. We also deliver and support awareness programmes that are aimed at changing at-risk lifestyle factors and encouraging an earlier diagnosis, which makes a significant difference on survival rates We receive no government funding and as such our main sources of income are donations from the public and unrestricted corporate grants. We communicate with around 4000 patients, carers, and their families a month across our website, social media platforms, our telephone Careline and counselling service and our face to face support groups and meetings.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant	**Yes** **These funds are restricted funds for specific projects and are not general donations.** **Merck Serano £6,708.33** **Pfizer £20,125.00**

companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	
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?	I have gathered the information from our annual survey. I have talked to people at our support groups around the UK. I have also talked to people via our closed Facebook support group. If people were interested in being involved, I talked to them by phone.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life).	1. 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 2. 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, 3. scans and procedures can be emotionally draining. Knowledge that there are a variety of treatment options available to them will give them some comfort.

For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	4. 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 recent annual survey patients with kidney cancer 5. reported feeling anxious, emotionally low, abandoned after surgery and scared about their cancer 6. returning. 7. 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, depression, weight loss, anorexia, anaemia and pain which varies in severity according to the stage of their disease, which 8. 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.
7. What do carers experience when caring for someone with the condition?	Carers of patients with kidney cancer can find the situation very difficult. Their family members can have times of acute illness, daily side effects of treatment or pain and this can cause much disruption in the family. One carer said I still get anxious, depressed, scared and overwhelmed by the "what ifs" Carers can feel overprotective of their relatives and often not know what to say. A Carer said;" I think we all put on a brave face, which to the world (and each other) makes it look like we are coping"
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	The treatment and outcomes for kidney cancer are very much dependant on how early the kidney cancer has been diagnosed. Ideally if the primary tumour can be discovered in the initial stages of the disease and be removed by surgical intervention, this being a full or partially nephrectomy or alternatively cryotherapy if the patients is unfit for surgery. Many people have a good life expectancy after surgical intervention and are able to continue with their lives, whilst having surveillance. This does not always negate the sense of anxious and anticipation of reoccurrence the patients may live with. Once the kidney cancer has become metastatic, which can be within a variable amount of time (months to years) from initial diagnosis depending on the grade of the tumour then other treatment is needed. Sometimes solitary metastases can be surgically removed, or radio ablation or cryotherapy can be used.

	If the metastatic disease is more widespread systemic treatment is the next step. Although over the last few years the options of treatment for kidney cancer are expanding, the most commonly used 1st line treatments are tyrosine kinase inhibitor (sunitinib, pazopanib, tivozanib or cabozantinib) and more recently has become nivolumab and ipilimumab for the intermediate to poor risk patients. 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. The most commonly used Tyrosine kinase inhibitors (sunitinib and pazopanib) act to extend life and in some cases, they work very well and extend life for many years, although this is always with numerous side effects. The most common side effects (occurring in over 30% of all patients) are nausea and vomiting, diarrhoea, fatigue, heartburn, hypertension, anaemia, low white blood cell count and skin yellowing. One patient described the restricting side effects of sunitinib stating; my scans look good, but I am unable to get out of bed most days. I don't have a life; I would like to see my granddaughter go to school in a few months, but I am not hopeful. For others, although the extension of life maybe a matter of months these can be invaluable for individuals and their families. The newly licenced treatment of nivolumab and ipilimumab has a high rate of immune side effects, which can be very serious; such as colitis, pneumonitis, encephalitis, hepatitis, nephritis, hormone gland problems, skin problems and infusion reactions. One patient reports the perfuse diarrhoea she experienced due to immune related colitis was one of the worse experiences she had been through. It was subsequently treated and resolved with steroids after several months. Patients in the UK feel very fortunate to be able to be involved in cutting edge clinical trials that are changing the face of how kidney cancer is being treated. A patient said "The options from the NHS are being expanded all the time and the licencing of this new technology will be adding to the options available. This is good as not all treatments suit all patients; a new option could be just right for some people." Generally, patients feel hopeful that they are in this golden era of treatment for kidney cancer and it helps them to feel that whatever treatment they are on it is not the end of the road. The combination of immunotherapy and TKI could dramatic change the landscape since it is using two targeted pathways to treat the cancer and the clinical trial has shown a greater overall survival and longer period of progression free survival.

9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	Yes there is an unmet need for treatment of advanced RCC, it would most certainly improve some outcomes in patients surviving kidney cancer and to be free of cancer for the foreseeable future. We understand that most drug treatments aim to extend the lives of people with kidney cancer and viewing kidney cancer as a chronic disease that can be lived with would be a desirable outcome.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	Some started an extended access, so took a while due to being one of the first in the area to start it. Majority no issues.
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	• Mets no longer visible on scans (multiple people), worked well for them. • Been on it years, started on extended access programme. • Able to look forward to life. • Positive experience. • Some say no side effects. • Fact they are still alive, getting to spend with friends and family. • Good quality time.

	• Tumour shrunk by 90%, enabled having a nephrectomy.
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	• Side effects found had diarrhoea severe to start with. • Some blood pressure medications made it worse. • Found had to do own research about issues. • Finds staff aren't very informed about it, gave her a medication for diarrhoea that made side effects worse as slowed down axitinib in there body as well. • Fatigue, joint pain. • Experiencing side effects following a year off treatment and has been told this will be long term and may actually go on to have even more due to the immunotherapy.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	Very important, but people need help with side effects. Invaluable. Should be available to those who need it and would benefit from it.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	Not applicable.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Not applicable.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	Not applicable.

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	Not applicable.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Unknown.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Unknown.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

None

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Side effects were the main disadvantage and common theme of people not feeling supported with them
- No access issues identified
- NED or good response to treatment

Thank you for your time.

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Single Technology Appraisal

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology 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.

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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	British Uro-Oncology Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? ~~Yes or~~ No A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	BUG is a registered Charity (registration number 1116828) with the overriding aim of "The relief of sickness of persons suffering from urological cancers & the advancement of education for the benefit of the public concerning its identification, diagnosis and treatment". Set up in 2004, the running of the Charity is funded by Membership fees. Its Meetings organisation & provision, solely for Healthcare Professionals, is funded by Delegate registration fees & hands-off grants from Pharmaceutical companies. Any Pharmaceutical support is clearly stated as "having had no input into the programme, selection of speakers, or topics discussed". BUG also runs a website with educational resources and distributes an annual newsletter – both for Healthcare Professionals. BUG's provision of a networking & support forum for discussion & exchange of research & policy ideas ultimately reaps benefits for patients.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	**2023 From the manufacturer Merck** The 2023 BUG Annual Meeting received an unconditional grant and exhibition stand sponsorship to the sum of £8,000 (plus VAT) from MERCK. **2023 From comparator products** The 2023 BUG Annual Meeting received an unconditional grant and exhibition stand sponsorship to the sum of £19,800 (plus VAT) from ACCORD & NOVARTIS. And £7,000 (plus VAT) from each of BMS, EISAI, IPSEN, MSD. This funding covered the purchase of exhibition stand space and had no input into the meeting programme, selection of speakers or topics discussed. At Major Sponsor Level, Accord & Novartis along with other sponsors, supported a session on prostate cancer with an educational grant, but had no input into the programme selection of speakers or topics discussed. MERCK, ACCORD, BMS, EISAI, IPSEN, MSD &NOVARTIS were seven of 13 sponsors for the 2023 BUG Annual Meeting. **2024 From the manufacturer Merck** The 2024 BUG Annual Meeting received an unconditional grant and exhibition stand sponsorship to the sum of £19,800 (plus VAT) from MERCK. **2024 From comparator products** The 2024 BUG Annual Meeting received an unconditional grant and exhibition stand sponsorship to the sum of £19,800 (plus VAT) from NOVARTIS. Sponsorship was also from ACCORD, PFIZER (each £10,000 plus VAT); EISAI & IPSEN each £9,500 (plus VAT), MSD £9,000 (plus VAT). This funding covered the purchase of exhibition stand space but had no input into the meeting programme, selection of speakers or topics discussed. BMS £1,000 (plus VAT) company attendees only. MERCK, NOVARTIS, ACCORD, EISAI, IPSEN, MSD & PFIZER were seven of 12 sponsors for the 2024 BUG Annual Meeting.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of the treatment for these patients is to achieve higher response rates, delaying progression with longer duration of response, maintaining/improving quality of life and improving overall survival.
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.)	The trials of IO-TKI combinations have shown an overall response rate (ORR) of over 60% with the IO-TKI combinations compared with ORR of around 30% with control arm of Sunitinib. In addition to shrinkage of tumours on the scan, the rate at which symptoms are alleviated to make patients feel better and the duration of response are also important.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Axi/avelumab is the only IO based regime currently approved for use in favourable risk patients.

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

9. How is the condition currently treated in the NHS?	Patients with advanced renal cell carcinoma currently have the options of Pazopanib, Sunitinib, Tivozanib and Axitinib/ Avelumab for favourable risk group patients and Cabozantinib, Len/Pem, Cabo/Nivo, Axi/Avelumab and Ipi/Nivo for intermediate and poor risk group patients as first line options.
9a. Are any clinical guidelines used in the	ESMO guidelines and NICE TA's

treatment of the condition, and if so, which?	
9b. 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.)	Axitinib/ Pembrolizumab is an additional option available in Scotland. The choice of 1st line therapy is dependent on shared decision making keeping in perspective the disease related factors.
9c. What impact would the technology have on the current pathway of care?	The TA will allow another agent to be available to choose from for intermediate and poor risk patients and will be the only IO based therapy available for favourable risk patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The treatment is already in use routinely in the NHS through the cancer drugs fund (CDF)
10a. How does healthcare resource use differ between the technology and current care?	No difference.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It will be used in secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is needed as it is already in use.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not applicable
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	It is already in use, so no need for any extra resources.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This option will be discussed when patients are diagnosed with metastatic spread. The treatment will be stopped either on progression (on radiology) or significant toxicity
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology 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?	The QoL benefits are similar to other options available.
16a. Is the technology a 'step-change' in the management of the condition?	

16b. Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side-effect profile is similar to other treatment options of IO and TKI.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, they do
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, response rates, duration of response, and overall survival. These were measured in the JAVELIN Renal 101 trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical	No

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There has been an update on the final OS analyses presented at ASCO this year. https://www.urotoday.com/conference-highlights/asco-2024/asco-2024-kidney-cancer/152605-asco-2024-avelumab-axitinib-vs-sunitinib-in-patients-pts-with-advanced-renal-cell-carcinoma-arcc-final-overall-survival-os-analysis-from-the-javelin-renal-101-phase-3-trial.html https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.4508
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 964 [TA964], TA858, TA780, TA542, TA512, TA215 and TA169?	As above
21. How do data on real-world experience compare with the trial data?	The RWE experience from UK is comparable with the trial data. https://pmc.ncbi.nlm.nih.gov/articles/PMC11192966/ https://www.sciencedirect.com/science/article/pii/S2949820124000055

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Already used in routine care in the NHS • Only IO-TKI combination approved for use in the favourable risk group patients. • Manageable toxicity profile • RWE from UK shows comparable outcomes

Thank you for your time.

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

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma – data review

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

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NHS England

Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of avelumab with axitinib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of avelumab with axitinib in the CDF population, during the managed access period. This report presents the results of the use of avelumab with axitinib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99.6% of CDF patients and 100% of EAMS patients as well as 88% of CDF patient outcomes and 93% of EAMS patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 31 July 2020 and 29 February 2024, 1,422 CDF applications and 175 EAMS applications for avelumab with axitinib were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 1,296 unique CDF patients, and 161 unique EAMS patients, who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

1,296/1,302 (99.6%) unique patients with CDF applications and 161/161 (100%) unique patients with an EAMS application were reported in the SACT dataset and were included in the final cohort.

The median treatment duration amongst the CDF cohort was 13 months [95% CI: 11.7, 14.2] (395 days) and the median treatment duration amongst the EAMS cohort was 18 months [95% CI: 14.4, 24.3] (547 days).

The difference in treatment duration was statistically significant between the two groups.

Treatment duration was also calculated at 6, 12, 18, 24, 36 and 48 months; results showed that there was a statistically significant difference between both the CDF and EAMS cohorts at months 24 and 36.

At data cut off, 67% (N=873) of CDF patients were identified as no longer being on treatment. Of these 873 patients:

- 47% (N=414) of patients stopped treatment due to disease progression
- 17% (N=150) of patients stopped treatment due to acute toxicity
- 13% (N=111) of patients died not on treatment
- 9% (N=77) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 4% (N=36) of completed treatment as prescribed
- 4% (N=32) of patients were treated palliatively and did benefit from the treatment they received
- 2% (N=19) of patients died on treatment
- 2% (N=18) of patients chose to end their treatment
- 1% (N=13) of patients were treated palliatively and did not benefit from the treatment they received
- Less than 1% (N=3) of patients stopped treatment due to having other comorbidities

Of the 161 patients in the EAMS cohort 131 (81%) patients were identified as no longer being on treatment. Of these 131 patients:

- 46% (N=60) of patients stopped treatment due to disease progression
- 16% (N=21) of patients stopped treatment due to acute toxicity
- 9% (N=12) of patients were treated palliatively and did benefit from the treatment they received
- 8% (N=11) of patients died not on treatment

- 8% (N=10) of completed treatment as prescribed
- 5% (N=7) of patients chose to end their treatment
- 5% (N=7) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 2% (N=2) of patients were treated palliatively and did not benefit from the treatment they received
- 1% (N=1) of patients died on treatment

The median OS amongst the CDF cohort was 33.9 months [95% CI: 30.7, 36.5] (1,031 days) and the median OS amongst the EAMS cohort was 52.5 months (1,597 days).

OS was also calculated at 6, 12, 18, 24, 36 and 48 months; results showed that there was a statistically significant difference between both the CDF and EAMS cohorts at 18, 24, and 36 months.

A treatment duration and OS sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

A secondary sensitivity was carried out comparing treatment duration and overall survival by IMDC factors, information captured in Blueteq. Results showed results were statistically significantly different between the three groups.

A third sensitivity was carried out comparing treatment duration and overall survival by RCC histology, information captured in Blueteq. Results showed results were statistically significantly different between the two groups.

Conclusion

This report analysed SACT real-world data for patients treated with avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma in the CDF. It evaluated treatment duration, OS and treatment outcomes for all patients treated with avelumab with axitinib for this indication.

Introduction

Renal cell carcinoma (ICD-10: C64) accounts for 3% of all cancer diagnoses in England. In 2021, 10,193 patients were diagnosed with renal cell carcinoma (males 6,598, females 3,595)[2].

Avelumab with axitinib is recommended for use within the Cancer Drugs Fund as an option for untreated advanced renal cell carcinoma in adults. It is recommended only if the conditions in the managed access agreement for avelumab with axitinib are followed and tumours have the programmed cell death ligand-1 (PD-L1) biomarker expression on 50% or more of their tumour cells[3].

2.Background to this report

Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using Systemic Anti-Cancer Therapy (SACT) data collected by the National Disease Registration Service (NDRS).

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

NICE Appraisal Committee review of avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [TA645]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of avelumab with axitinib (Merck and Pfizer) for untreated advanced or metastatic renal cell carcinoma in adults [TA645] and published guidance for this indication in September 2020[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma through the CDF for a period of 46 months, from July 2020 to May 2024. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from an ongoing clinical trial (JAVELIN Renal 101 study[7]) evaluating avelumab with axitinib in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the JAVELIN Renal 101 study is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the JAVELIN Renal 101 study[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection.

- the immaturity of the overall survival data and the companies' approach to modelling overall survival over the long term
- the lack of data on whether the treatment is effective for non-clear cell disease
- the companies' methods for adjusting both the costs and benefits of subsequent treatments to reflect NHS practice.

NHS England have calculated overall survival. Other uncertainties will be addressed by the JAVELIN Renal 101 study.

Treatment duration was not an area of clinical uncertainty but has been included in this report.

Approach

Upon entry to the CDF, representatives from NHS England, NICE and the company (Merck and Pfizer) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA sets out the real-world data to be collected and analysed to support the NICE re-appraisal of avelumab with axitinib. It also detailed the eligibility criteria for patient access to avelumab with axitinib through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for avelumab with axitinib, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

3.Methods

CDF applications – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NDRS has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS England, through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England.

NDRS in NHS England collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Avelumab with axitinib clinical treatment criteria

- application is made for the first cycle of systemic anti-cancer therapy by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.
- prescribing clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to checkpoint inhibitor treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis.
- patient has unresectable locally advanced or metastatic renal cell adenocarcinoma (RCC).
- risk status is assessed using the international metastatic RCC database consortium (IMDC) system.
- patient is either completely treatment naïve for systemic therapy for RCC or if the patient has received prior systemic therapy in the context of adjuvant/neoadjuvant therapy, then such treatment was completed ≥12 months previously.
- patient has an ECOG performance status of 0 or 1.
- patient has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.
- patient is to be treated until loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner. If either avelumab or axitinib has to be permanently discontinued on account of toxicity, treatment with the other drug can be continued as monotherapy as long as there is no evidence of progressive disease.
- avelumab and axitinib will otherwise be prescribed and administered as outlined in the avelumab summary of product characteristics and in the axitinib summary of product characteristics (SPC).
- a formal medical review to assess the tolerability of treatment with avelumab and axitinib will be scheduled to occur at least by the start of the 3rd 4-weekly cycle of treatment and thereafter on a regular basis.
- treatment breaks of up to 12 weeks beyond the expected 4-weekly cycle length are allowed but solely to allow any toxicities to settle.
- if the disease progresses on the avelumab and axitinib combination and further systemic therapy is appropriate, the next line of treatment will be chosen from those options which are routinely commissioned to be used after VEGF- or VEGFR-targeting and immune-modulating therapies.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.
3. If two applications are submitted for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

The analysis cohort is limited to the date avelumab with axitinib entered the CDF for this indication, onwards.

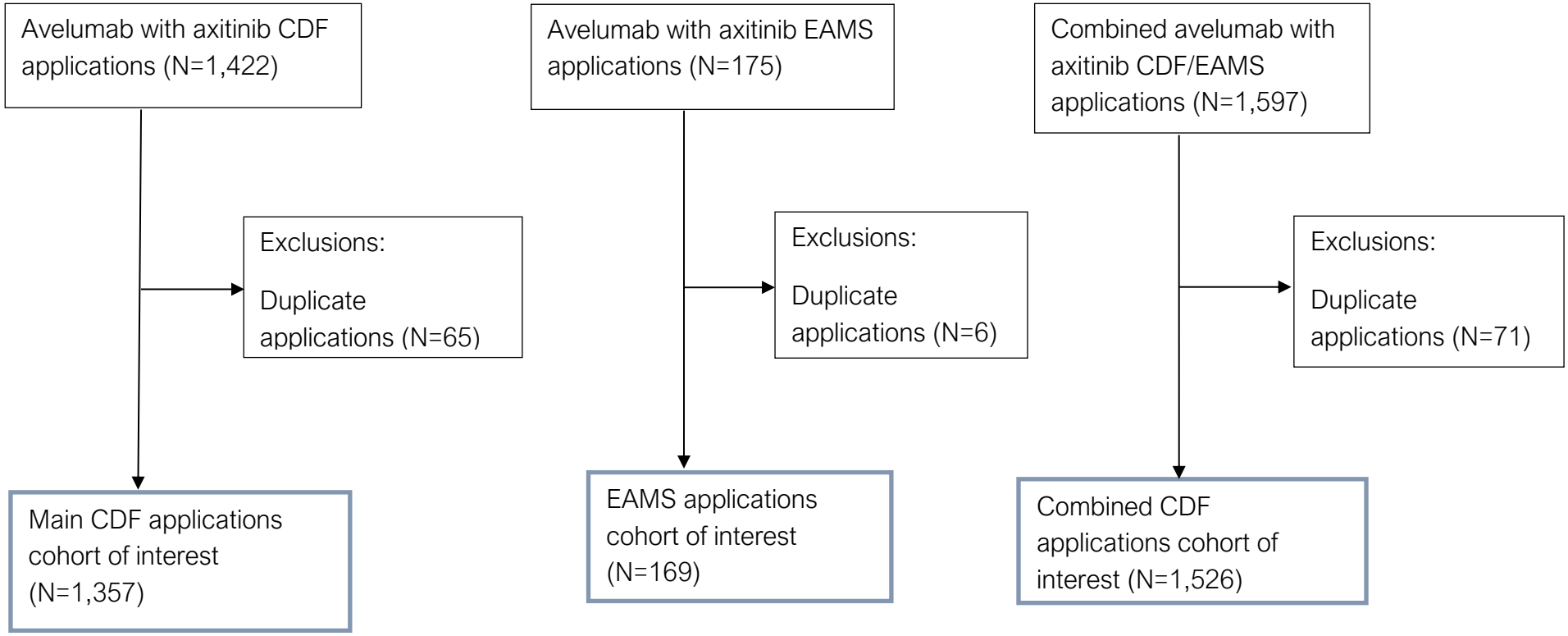
The CDF applications included in these analyses are from 31 July 2020 to 29 February 2024. A snapshot of SACT data was taken on 1 June 2024 and made available for analysis on 10 June 2024 and includes SACT activity up to 29 February 2024. Tracing the patients' vital status was carried out on 2 July 2024 using the Personal Demographics Service (PDS)[1].

There were 1,422 applications for CDF funding for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma between 31 July 2020 and 29 February 2024 in the NHS England Blueteq database. Following de-duplication this relates to 1,357 unique patients.

Early Access to Medicine (EAMS) cohort

A further 175 applications were identified in the Blueteq database as receiving avelumab with axitinib to treat advanced or metastatic renal cell carcinoma as part of an Early Access to Medicines Scheme (EAMS) that ran from August 2019 to July 2020, this relates to 169 unique patients. The eligibility of these patients at treatment start is the same as the CDF cohort which is why they have been included in these analyses.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for avelumab with axitinib for treating untreated advanced or metastatic renal cell carcinoma between 31 July 2020 and 29 February 2024 and via the Early Access to Medicines scheme



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for avelumab with axitinib in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[9] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example, a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death, and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Avelumab, used in combination with axitinib is administered intravenously. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that the prescribing of treatment has taken place on a specified date. A duration of 13-days has been added to final treatment date for all patients; this represents the duration from a patient's last avelumab cycle to their next[9].

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patient's censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #60.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Lost to follow-up:

Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

4. Results

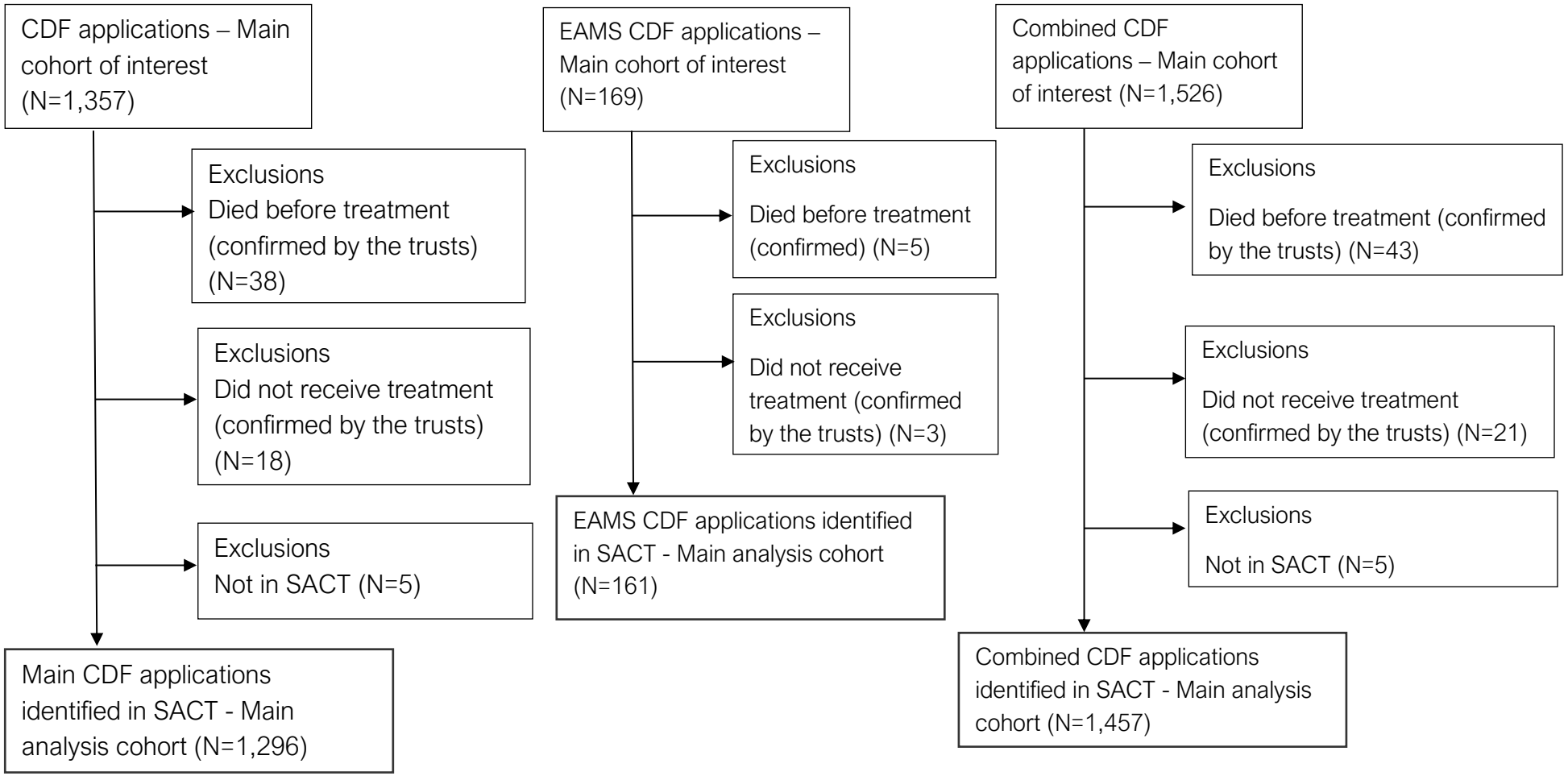
Cohort of interest

Of the 1,357 applications for CDF funding for avelumab with axitinib in untreated advanced or metastatic renal cell carcinoma, 38 patients died before treatment started, 18 patients did not receive treatment and five were missing from SACT [a] (see Figure 2).

Of the 169 patients with an EAMS application, five patients died before treatment and three patients did not receive treatment (see Figure 2).

[a] The 38 CDF patients who died before treatment, the 18 patients who did not receive treatment, the five EAMS patients who died before treatment and the three who did not receive treatment, all were confirmed by the relevant trust by the SACT data liaison team.

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma between 31 July 2020 and 29 February 2024 and via the Early Access to Medicines Scheme



A maximum of 1,301 CDF avelumab with axitinib records are expected in SACT for patients who were still alive and eligible to commence treatment (Figure 2). 99.6% (1,296/1,301) of these eligible patients have a treatment record in SACT.

For EAMS patients, a maximum of 161 avelumab with axitinib records are expected in SACT for patients who were still alive and eligible to commence treatment (Figure 2).100% (161/161) of these eligible patients have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender, and treatment dates. Performance status at the start of regimen is 88% complete for the CDF cohort and 87% complete for the EAMS cohort.

Table 1: Completeness of key SACT data items for the avelumab with axitinib cohort (CDF cohort, N=1,296), (EAMS cohort, N=161)

Variable	CDF cohort completeness (%)	EAMS cohort completeness (%)
Primary diagnosis	100%	100%
Date of birth (used to calculate age)	100%	100%
Gender	100%	100%
Start date of regimen	100%	100%
Start date of cycle	100%	100%
Administration date	100%	100%
Performance status at start of regimen	88%	87%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with avelumab with axitinib in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment.

Based on these criteria, outcomes are expected for 873 CDF patients and 131 EAMS patients. 88% (764/873) of the CDF cohort have an outcome summary recorded in the SACT dataset and 93% (122/131) of the EAMS cohort have an outcome summary recorded in the SACT dataset

Table 2: Completeness of outcome summary for patients that are expected to have ended treatment (CDF cohort, N=873), (EAMS cohort, N=131)

Variable	CDF cohort completeness (%)	EAMS cohort completeness (%)
Outcome summary of why treatment was stopped	88%	93%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq.

Table 3: Completeness of previous treatments in Blueteq – (CDF cohort, N=1,296), (EAMS cohort, N=161)

Variable	CDF cohort completeness (%)	EAMS cohort completeness (%)
Renal cell carcinoma (RCC) histology	100%	Not applicable
International metastatic RCC database consortium (IMDC) factors	100%	Not applicable
Previous systemic therapy for renal cell carcinoma (RCC)	100%	9%

Patient characteristics – CDF cohort

The median age of the 1,296 patients avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma was 67 years. The median age in males and females was 66 and 68 years respectively.

Table 4: Patient characteristics (N=1,296)

Patient characteristics[b]			
		N	%
Gender	Male	920	71%
	Female	376	29%
Age	<40	19	1%
	40 to 49	70	5%
	50 to 59	269	21%
	60 to 69	450	35%
	70 to 79	428	33%
	80+	60	5%
Performance status at the start of regimen	0	465	36%
	1	645	50%
	2	25	2%
	3	3	Less than 1%
	4	0	0%
	Missing	158	12%

[b] Figures may not sum to 100% due to rounding.

Patient characteristics – EAMS cohort

The median age of the 161 patients avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma was 65 years. The median age in males and females was 64 and 66 years respectively.

Table 5: Patient characteristics (N=161)

Patient characteristics[c]			
		N	%
Gender	Male	117	73%
	Female	44	27%
Age	<40	0	0%
	40 to 49	9	6%
	50 to 59	46	29%
	60 to 69	50	31%
	70 to 79	45	28%
	80+	11	7%
Performance status at the start of regimen	0	65	40%
	1	73	45%
	2	2	1%
	3	0	0%
	4	0	0%
	Missing	21	13%

[c] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 6 presents the clinical indicator values collected on the Blueteq form for this indication. Only available for the CDF cohort.

Table 6: Distribution of key Blueteq data items – (CDF cohort, N=1,296), (EAMS cohort, N=161)

Blueteq data items		N	%
Renal cell carcinoma (RCC) histology – only available for the CDF cohort	RCC with a clear cell component	1,091	84%
	Unclassified RCC	99	8%
	Papillary RCC	62	5%
	Chromophobe RCC	24	2%
	XP11 translocation RCC	9	1%
	Collecting duct RCC (Bellini collection duct RCC)	5	Less than 1%
	Medullary RCC	2	Less than 1%
	Mucinous tabular and spindle cell RCC	2	Less than 1%
	Multilocular cystic RCC	0	0%
	Not captured	2	Less than 1%
IMDC factors – only available for the CDF cohort	Good risk disease (IMDC score of 0)	498	38%
	Intermediate risk disease (IMDC score of 1 or 2)	589	45%
	Poor risk disease (IMDC score of 3-6)	207	16%
	Not captured	2	Less than 1%

Blueteq data items		N	%
Previous systemic therapy for RCC – **CDF cohort**	No previous adjuvant/neoadjuvant systemic therapy of any kind and treatment naïve for the locally advanced/metastatic RCC indication	1,270	98%
	Prior adjuvant/neoadjuvant therapy for RCC with agents which target VEGF, and the last dose received by the patient was >=12 months prior to this application and treatment naïve for the locally advanced/metastatic RCC indication	12	1%
	Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte associated antigen-4 (anti CTLA-4) antibodies) and last dose received by the patient was =12 months prior to this application and treatment naïve for the locally advanced/metastatic RCC indication	9	Less than 1%
	Not captured	5	Less than 1%
Previous systemic therapy for RCC – **EAMS cohort**	No previous adjuvant/neoadjuvant systemic therapy of any kind and treatment naïve for the locally advanced/metastatic RCC indication	15	9%
	Not captured	146	91%

Treatment duration

Of the 1,296 patients with a CDF application, 873 (67%) were identified as having completed treatment by 29 February 2024 (latest follow up in SACT dataset). Of the 161 patients with an EAMS application, 131 (81%) were identified as having completed treatment.

Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset, or they have not received treatment with avelumab with axitinib in at least three months (see Table 10 and Table 12).

The median follow-up time in SACT for the CDF cohort was 10.1 months (308 days). The median follow-up time in SACT for the EAMS cohort was 18 months (548 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

Trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up of 43 months for the CDF cohort. For the EAMS cohort, the maximum follow-up was 55 months.

By the end of the follow-up period, 29 February 2024, 873 patients with a CDF application and 131 patients with an EAMS application had ended treatment. 423 CDF patients and 30 EAMS patients were still receiving treatment at the end of the follow-up period (see Table 7 and Table 8).

Table 7: Breakdown by patients' treatment status – CDF cohort [d,e,f]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	535	41%
Patient died – on treatment	19	1%
Treatment stopped	319	25%
Treatment ongoing	423	33%
Total	1,296	100%

[d] Figures may not sum to 100% due to rounding.
[e] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 7 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: https://digital.nhs.uk/ndrs/data/data-sets/sact/sact-cdf-methodologies

Table 8: Breakdown by patients' treatment status – EAMS cohort [g,h,i]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	79	49%
Patient died – on treatment	1	1%
Treatment stopped	51	32%
Treatment ongoing	30	19%
Total	161	100%

Table 9 shows the 6, 12, 18, 24, 36 and 48-month treatment duration for patients receiving avelumab with axitinib in untreated advanced or metastatic renal cell carcinoma.

Table 9: Treatment duration at 6, 12, 18, 24, 36 and 48-month intervals

Time period	Treatment duration (%) CDF cohort	Treatment duration (%) EAMS cohort
6 months	71% [95% CI: 69%, 74%]	79% [95% CI: 73%, 85%]
12 months	52% [95% CI: 49%, 55%]	61% [95% CI: 54%, 69%]
18 months	40% [95% CI: 38%, 43%]	50% [95% CI: 43%, 59%]
24 months	30% [95% CI: 27%, 33%]	42% [95% CI: 35%, 51%]
36 months	17% [95% CI: 15%, 20%]	29% [95% CI: 22%, 36%]
48 months		20% [95% CI: 14%, 27%]

Results in Table 9 show treatment duration amongst the EAMS cohort is longer than the CDF cohort, this difference is statistically significant at 24 and 36 months.

[g] Figures may not sum to 100% due to rounding.
[h] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[i] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: https://digital.nhs.uk/ndrs/data/data-sets/sact/sact-cdf-methodologies

The Kaplan-Meier curve for treatment duration is shown in Figure 3. The median treatment duration for all patients in the CDF cohort was 13 months [95% CI: 11.7, 14.2] (395 days). The median treatment duration for all patients in the EAMS cohort was 18 months [95% CI: 14.4, 24.3] (547 days).

The median treatment duration between the CDF and EAMS cohorts is statistically significant.

Figure 3: Kaplan-Meier treatment duration – (CDF cohort, N=1,296), (EAMS cohort, N=161)

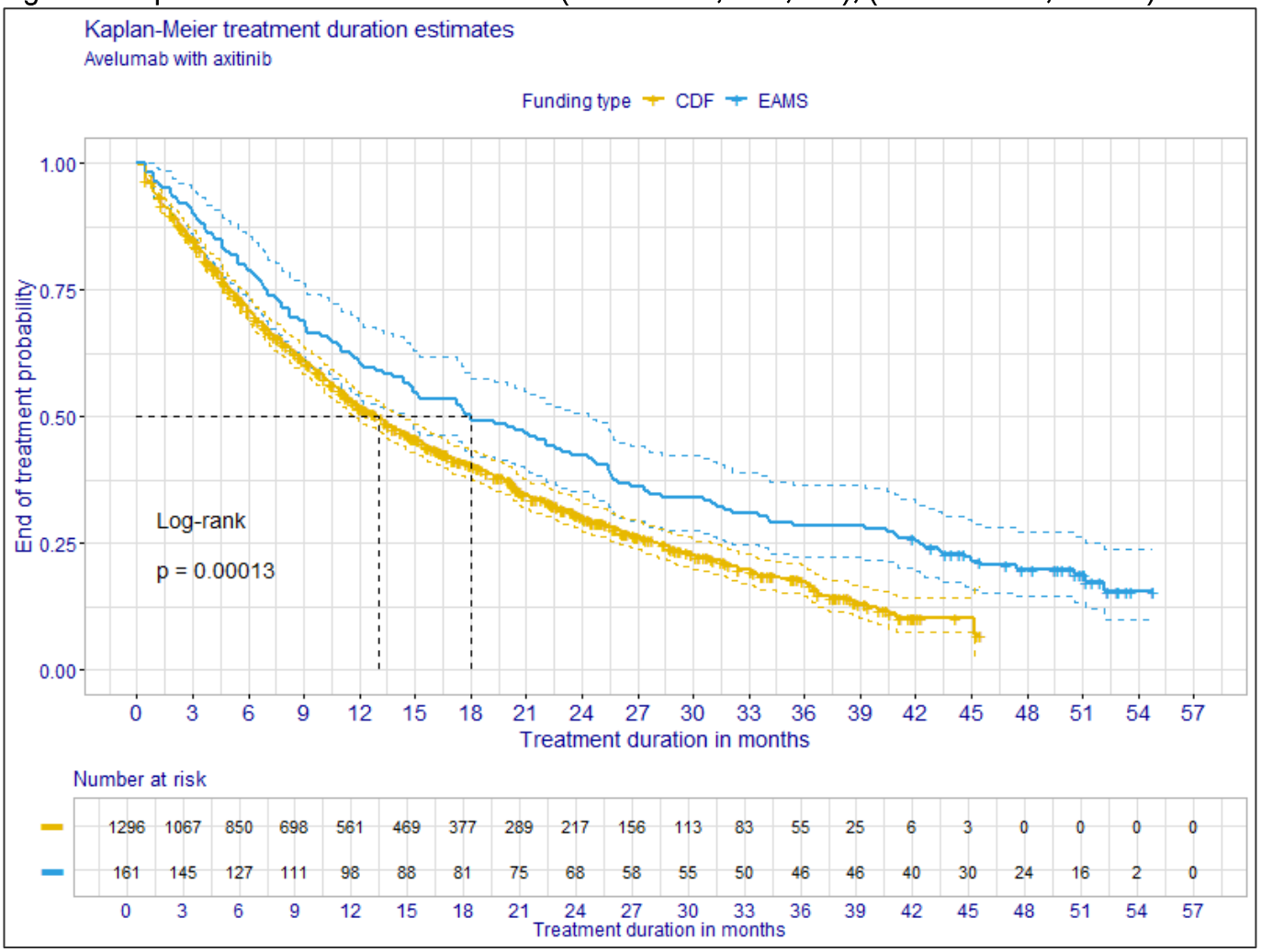


Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 67% (N=873) of patients had ended treatment at 29 February 2024.

Table 10: Treatment outcomes for patients that have ended treatment – CDF cohort (N=873)[j,k]

Outcome	Frequency (N)	Percentage (%)
Progressive disease during chemotherapy	414	47%
Acute chemotherapy toxicity	150	17%
Died not on treatment	111	13%
No treatment in 3 months	77	9%
Treatment completed as prescribed	36	4%
Patient benefitted from the non-curative treatment	32	4%
Died on treatment	19	2%
Patient choice (stopped or interrupted treatment)	18	2%
Patient did not benefit from the non-curative treatment	13	1%
Comorbidity	3	Less than 1%
Total	**873**	**100%**

[j] Figures may not sum to 100% due to rounding.
[k] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 7 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.

Table 11: Treatment outcomes and treatment status for patients that have ended treatment – CDF cohort (N=873)

Outcome[l]	Patient died [m] not on treatment	Treatment stopped	Patient died on treatment
Progressive disease during chemotherapy	309	105	
Acute chemotherapy toxicity	83	67	
Died not on treatment	111		
No treatment in 3 months		77	
Treatment completed as prescribed	7	29	
Patient benefitted from the non-curative treatment	9	23	
Died on treatment			19
Patient choice (stopped or interrupted treatment)	7	11	
Patient did not benefit from the non-curative treatment	8	5	
Comorbidity	1	2	
Total	**535**	**319**	**19**

l Relates to outcomes submitted by the trust in Table 10.
m Relates to treatment status in Table 7 for those that have ended treatment.

Table 12 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 81% (N=131) of patients had ended treatment at 29 February 2024.

Table 12: Treatment outcomes for patients that have ended treatment – EAMS cohort (N= 131) [n,o]

Outcome	Frequency (N)	Percentage (%)
Progressive disease during chemotherapy	60	46%
Acute chemotherapy toxicity	21	16%
Patient benefitted from the non-curative treatment	12	9%
Died not on treatment	11	8%
Treatment completed as prescribed	10	8%
Patient choice (stopped or interrupted treatment)	7	5%
No treatment in 3 months	7	5%
Patient did not benefit from the non-curative treatment	2	2%
Died on treatment	1	1%
Total	**131**	**100%**

[n] Figures may not sum to 100% due to rounding.
[o] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.

Table 13: Treatment outcomes and treatment status for patients that have ended treatment – EAMS cohort (N= 131)

Outcome[p]	Patient died [q] not on treatment	Treatment stopped	Patient died on treatment
Progressive disease during chemotherapy	41	19	
Acute chemotherapy toxicity	8	13	
Patient benefitted from the non-curative treatment	6	6	
Died not on treatment	11		
Treatment completed as prescribed	6	4	
Patient choice (stopped or interrupted treatment)	5	2	
No treatment in 3 months		7	
Patient did not benefit from the non-curative treatment	2		
Died on treatment			1
Total	**79**	**51**	**1**

p Relates to outcomes submitted by the trust in Table 12.
q Relates to treatment status in Table 8 for those that have ended treatment.

Overall survival (OS)

Of the 1,296 CDF patients with a treatment record in SACT, the minimum follow-up was 4.1 months (124 days) from the last CDF application. Patients were traced for their vital status on 2 July 2024. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time for the CDF cohort was 20.5 months (623 days).

The median follow-up time for the EAMS cohort was 46.9 months (1,429 days).

The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The maximum follow-up period for survival amongst the CDF cohort was 47 months. The maximum follow-up period for survival amongst the EAMS cohort was 59 months, all patients were traced on 2 July 2024.

By the end of the follow-up period, 2 July 2024, 554 patients in the CDF cohort had died, and 742 patients were still alive. In the EAMS cohort, at the end of the follow-up period, 80 patients had died and 81 were still alive.

Table 14: OS at 6, 12, 18, 24, 26, 48-month intervals

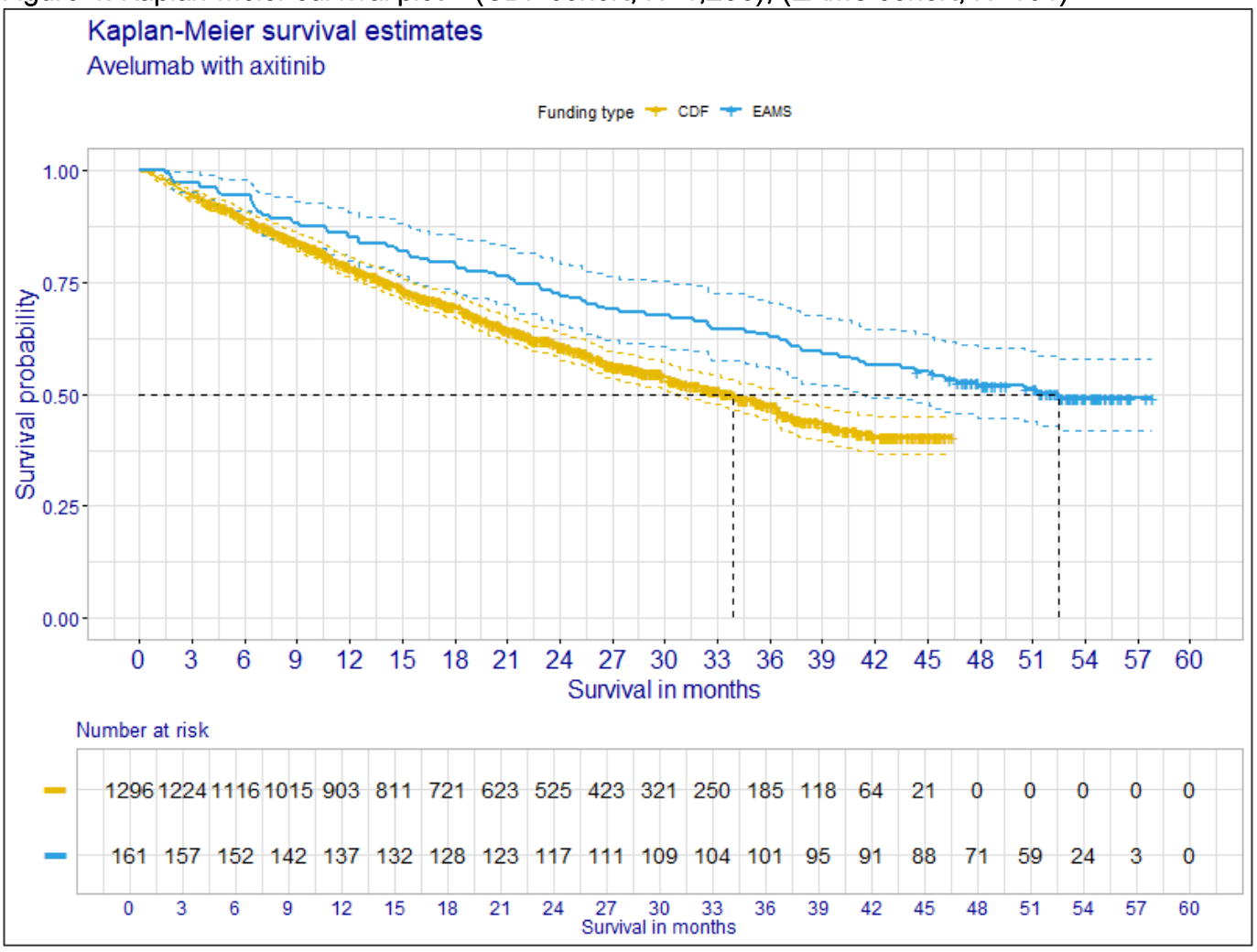
Time period	OS (%) CDF cohort	OS (%) EAMS cohort
6 months	89% [95% CI: 88%, 91%]	94% [95% CI: 91%, 98%]
12 months	79% [95% CI: 76%, 81%]	85% [95% CI: 80%, 91%]
18 months	70% [95% CI: 67%, 72%]	80% [95% CI: 74%, 86%]
24 months	61% [95% CI: 58%, 64%]	73% [95% CI: 66%, 80%]
36 months	48% [95% CI: 44%, 51%]	63% [95% CI: 56%, 71%]
48 months		52% [95% CI: 45%, 60%]

Results in Table 14 show OS amongst the EAMS cohort is longer than the CDF cohort, this difference is statistically significant at 18, 24, and 36 months.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 2 July 2024. The median OS was for all patients in the CDF cohort was 33.9 months [95% CI: 30.7, 36.5] (1,031 days).

The median OS for all patients in the EAMS cohort was 52.5 months[r] (1,597 days).

Figure 4: Kaplan-Meier survival plot – (CDF cohort, N=1,296), (EAMS cohort, N=161)



[r] confidence intervals could not be calculated due to the number of events

5. Sensitivity analyses

6-months follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, applications were limited to 31 August 2023 and SACT activity was followed up to 29 February 2024.

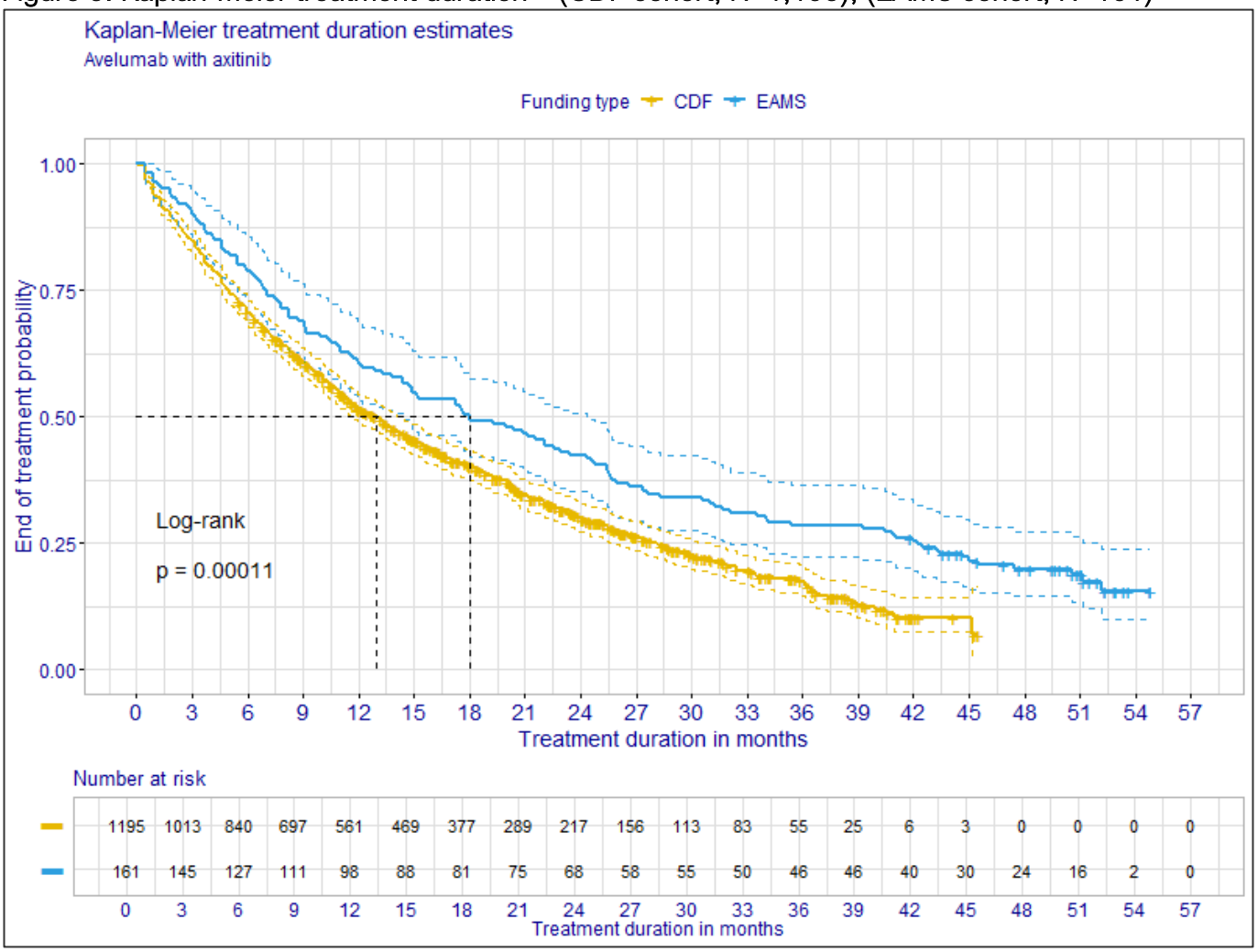
Following the exclusions above, 1,195 patients (92%) in the CDF cohort were identified for inclusion. All patients in the EAMS cohort had at least six months follow-up but were still included as a comparison.

The median follow-up time for the CDF cohort in SACT was 11.3 months (343 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

The Kaplan-Meier curve for treatment duration is shown in Figure 5. The median treatment duration for patients in the CDF cohort was 13 months [95% CI: 11.7, 14.2] (395 days) (N=1,195).

By the end of the follow-up period, 29 February 2024, 857 patients in the CDF cohort had ended treatment, and 338 patients were still receiving treatment.

Figure 5: Kaplan-Meier treatment duration – (CDF cohort, N=1,195), (EAMS cohort, N=161)



The median OS amongst the EAMS cohort higher than the CDF cohort and this difference is statistically significant.

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up. To identify the cohort, CDF applications were limited to 2 January 2024 and patients were traced for their vital status on 2 July 2024.

Following the exclusions above, 1,258 (97%) patients in the CDF cohort were identified for inclusion. The median follow-up time was 20.9 months (635 days).

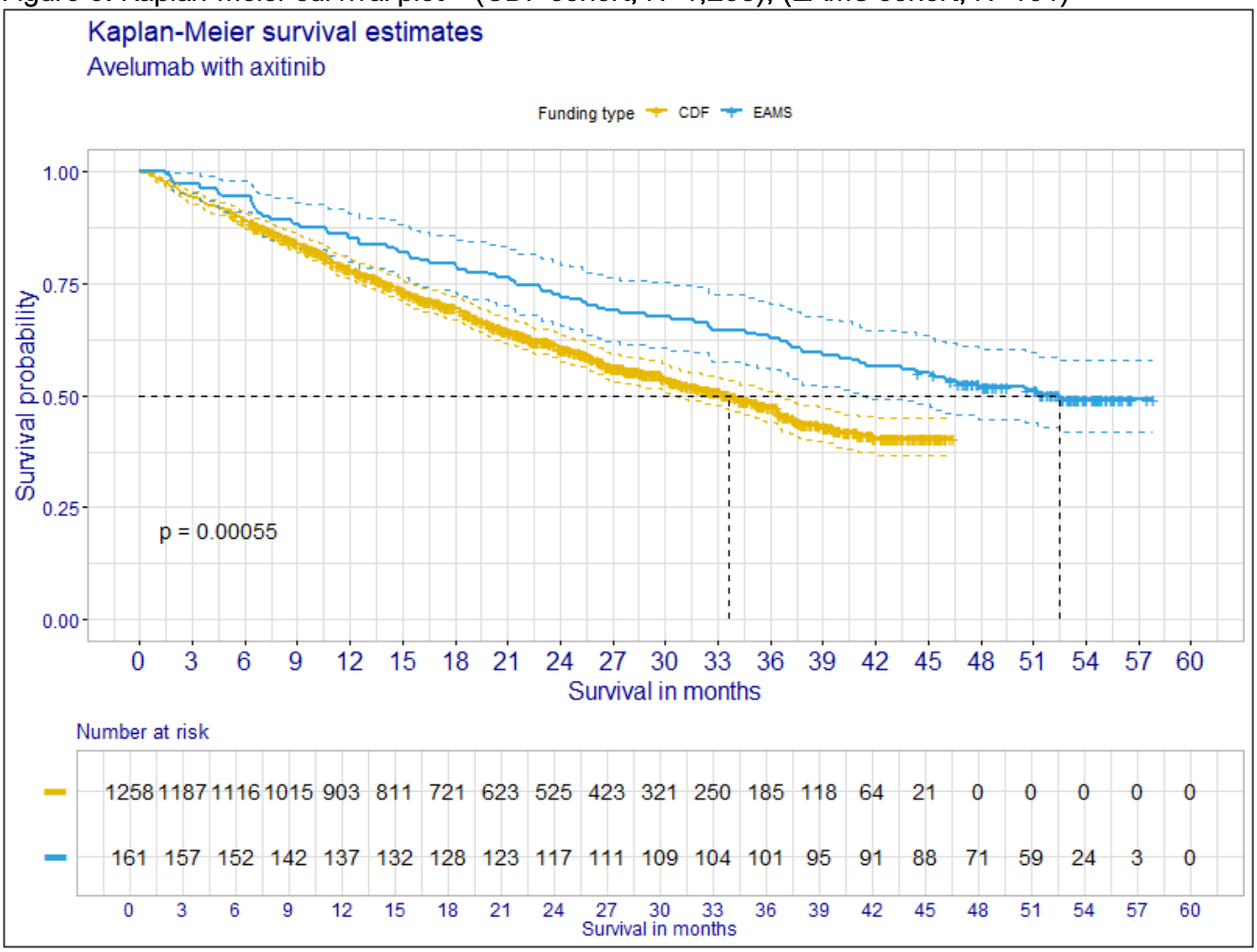
All patients in the EAMS cohort had at least six months follow-up but were still included as a comparison.

The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The Kaplan-Meier curve for OS is shown in Figure 6. The median OS for patients in the CDF cohort was 33.6 months [95% CI: 30.3, 36.5] (1,022 days) (N=1,258).

By the end of the follow-up period, 2 July 2024, 553 patients in the CDF cohort had died, and 705 patients were still alive.

Figure 6: Kaplan-Meier survival plot – (CDF cohort, N=1,258), (EAMS cohort, N=161)



6. Secondary sensitivity analyses

A secondary sensitivity analyses was carried out on the CDF cohort looking at treatment duration and OS by IMDC factors. IMDC factors was not collected for the EAMS cohort.

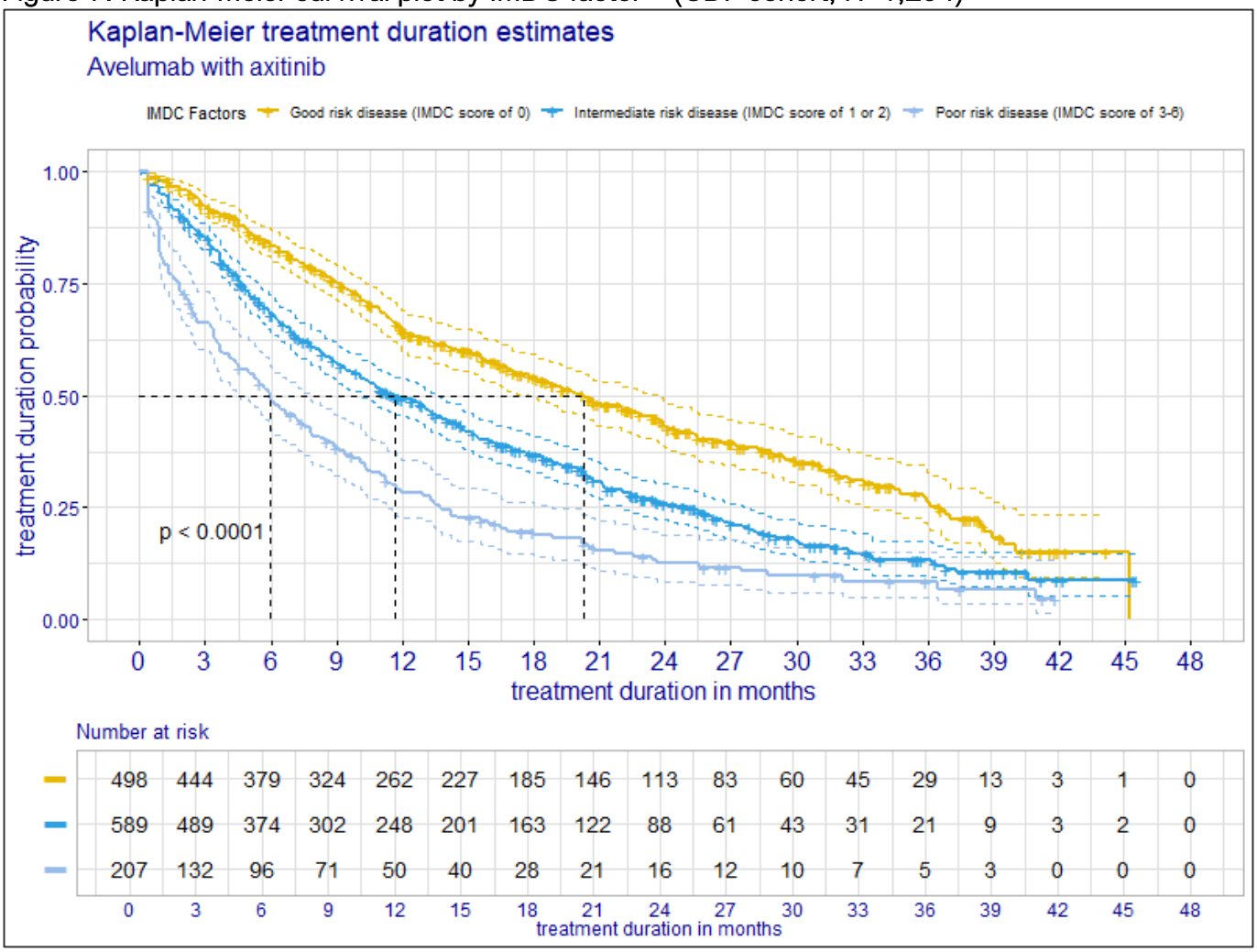
Only patients with a valid IMDC factor value were included in these analyses. Out of the 1,296 patients, 1,294 (99.8%) patients were included as two patients had a missing IMDC factor.

Treatment duration

The Kaplan-Meier curve for treatment duration is shown in Figure 7. The median treatment duration amongst patients with a good risk disease IMDC score of 0 was 20.2 months [95% CI: 17.7, 23.7] (614 days). The median treatment duration amongst patients with an intermediate risk disease IMDC score of 1 or 2 was 11.7 months [95% CI: 10.1, 13.5] (356 days), and the median treatment duration amongst patients with a poor risk disease IMDC score of 3-6 was 6 months [95% CI: 4.6, 7.8] (182 days).

Difference in treatment duration was statistically significant between all three risk groups.

Figure 7: Kaplan-Meier survival plot by IMDC factor – (CDF cohort, N=1,294)

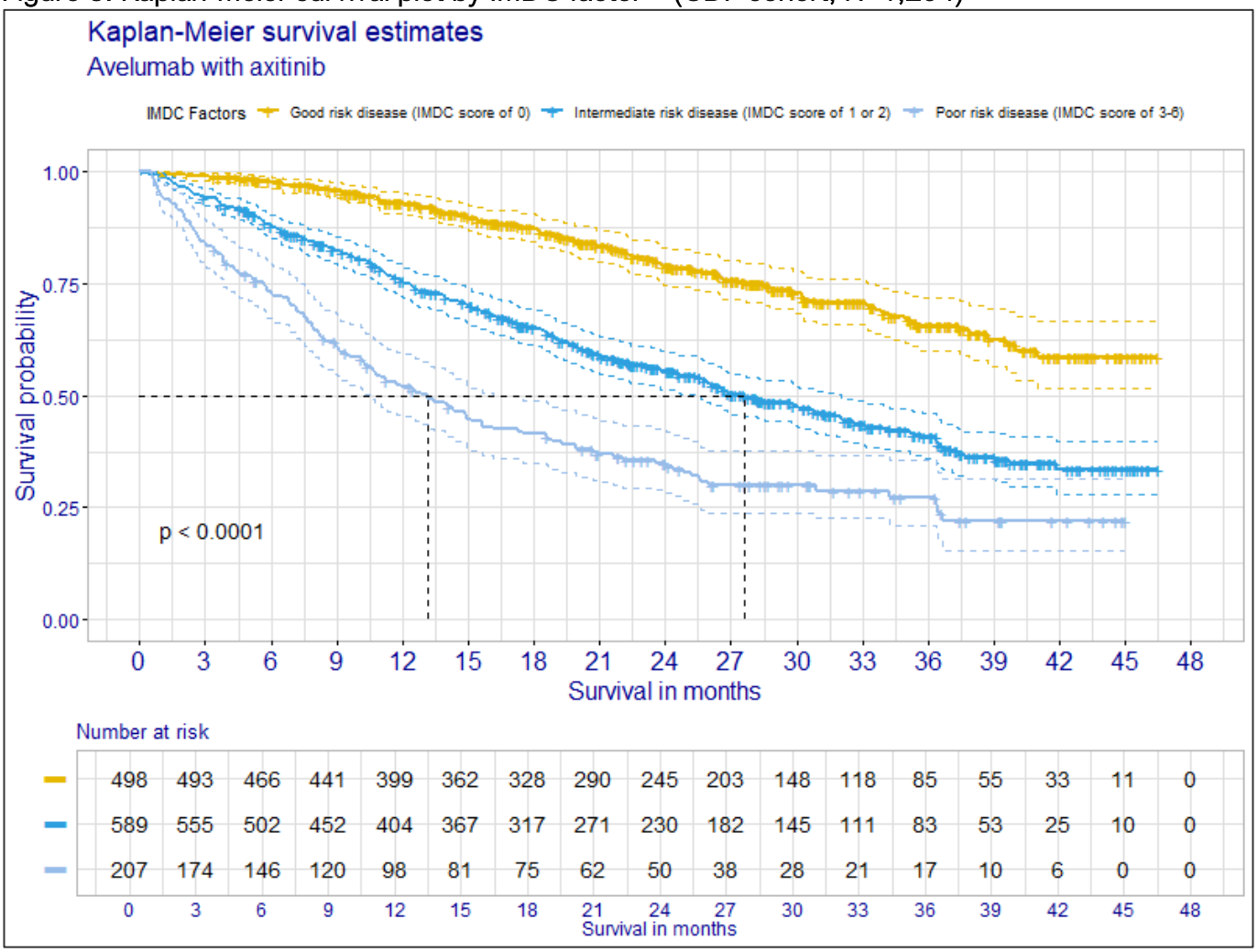


OS

The Kaplan-Meier curve for OS is shown in Figure 8. The median OS amongst patients with a good risk disease MDC score of 0 was not reached. The median OS amongst patients with an intermediate risk disease IMDC score of 1 or 2 was 27.6 months [95% CI: 25.4, 32.0] (840 days), and the median OS amongst patients with a poor risk disease IMDC score of 3-6 was 13.1 months [95% CI: 10.6, 17.3] (398 days).

Difference in OS was statistically significant between the intermediate risk and poor risk group.

Figure 8: Kaplan-Meier survival plot by IMDC factor – (CDF cohort, N=1,294)



7. Third sensitivity analyses

A third sensitivity analyses was carried out on the CDF cohort looking at treatment duration and OS by RCC histology. RCC histology was not collected for the EAMS cohort.

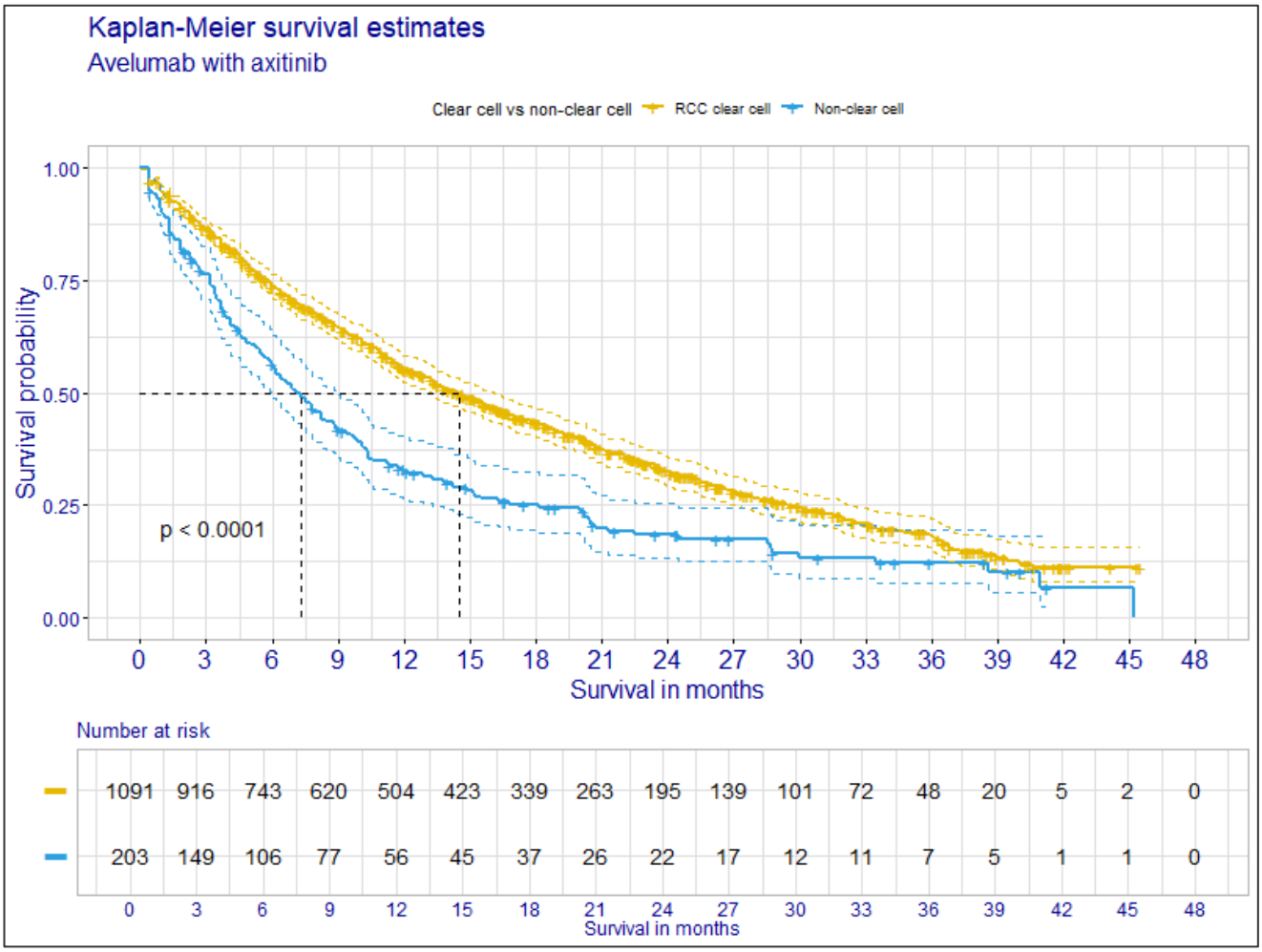
Only patients with a valid RCC histology value were included in these analyses. Out of the 1,296 patients, 1,294 (99.8%) patients were included as two patients had a missing RCC histology value and it could not be determined what that value should be.

Treatment duration

The Kaplan-Meier curve for treatment duration is shown in Figure 9. The median treatment duration amongst patients with clear cell RCC was 14.5 months [95% CI: 13.2, 16.1] and the median treatment duration amongst patients who did not have clear cell RCC was 7.3 months [95% CI: 5.9, 8.9].

Difference in treatment duration was statistically significant between the two groups.

Figure 9: Kaplan-Meier survival plot by RCC histology – (CDF cohort, N=1,294)



OS

The Kaplan-Meier curve for OS is shown in Figure 10. The median OS amongst patients with clear cell RCC was 36.4 months [95% CI: 33.9, 39.6] and the median OS amongst patients who did not have clear cell RCC was 15.6 months [95% CI: 12.6, 20.7].

Difference in OS was statistically significant between the two groups.

Figure 10: Kaplan-Meier survival plot by RCC histology – (CDF cohort, N=1,294)

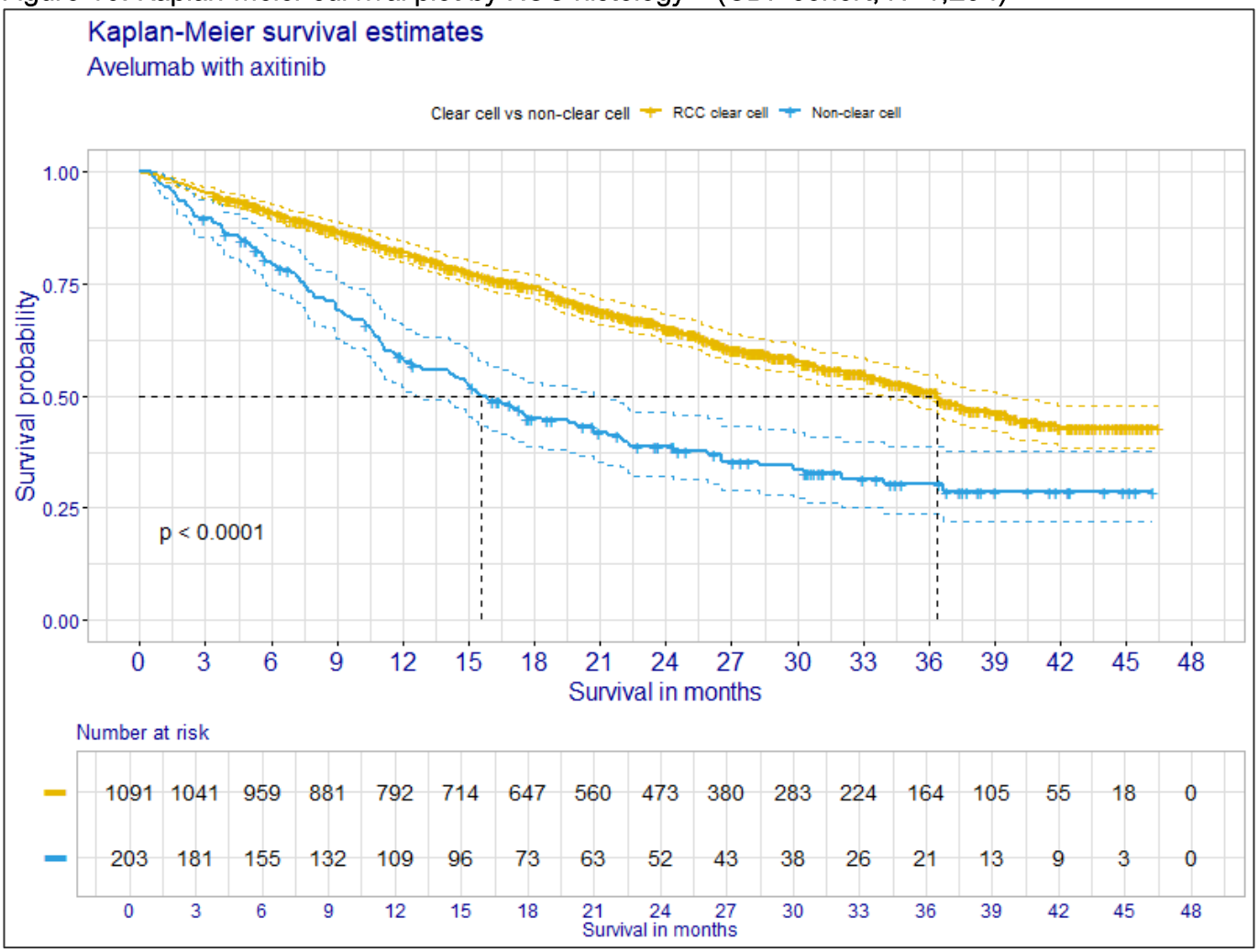


Table 15: Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Main CDF cohort Standard analysis: Full cohort	EAMS cohort Standard analysis:	Sensitivity analysis: 6 months follow-up cohort: treatment duration – CDF cohort only	Sensitivity analysis: 6 months follow-up cohort: OS – CDF cohort only
N	1,296	161	1,195	1,258
Median treatment duration	13 months [95% CI: 11.7, 14.2] (395 days)	18 months [95% CI: 14.4, 24.3] (547 days)	13 months [95% CI: 11.7, 14.2] (395 days)	
OS	33.9 months [95% CI: 30.7, 36.5] (1,031 days)	52.5 months[s] (1,597 days)		33.6 months [95% CI: 30.3, 36.5] (1,022 days)

[s] confidence intervals could not be calculated due to the number of events

8. Conclusions

1,301 patients received avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [TA645] through the CDF in the reporting period (31 July 2020 to 29 February 2024). 1,296 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99.6%. An additional 18 patients with a CDF application did not receive treatment and 38 patients died before treatment, these cases were confirmed by the trust responsible for the CDF application by the team at NHS England.

161 patients received avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma as part of an early access to medicine scheme (EAMS). All 161 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 100%. An additional three patients with an EAMS application did not receive treatment and five patients died before treatment, these cases were also confirmed by the trust responsible for the CDF application by the team at NHS England.

Patient characteristics from the SACT dataset amongst the CDF cohort showed that 71% (N=920) of patients who received avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma were male and 29% (N=376) of patients were female. Most of the cohort was aged between 50 and 79 years 89%, (N=1,147) and 86% (N=1,110) of patients had a performance status between 0 and 1 at the start of their regimen.

Patient characteristics from the SACT dataset amongst the EAMS cohort showed that 73% (N=117) of patients who received avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma were male and 27% (N=44) of patients were female. Most of the cohort was aged between 50 and 79 years 86%, (N=141) and 86% (N=138) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 67% (N=873) of CDF patients were identified as no longer being on treatment. Of these 873 patients:

- 47% (N=414) of patients stopped treatment due to disease progression
- 17% (N=150) of patients stopped treatment due to acute toxicity
- 13% (N=111) of patients died not on treatment
- 9% (N=77) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 4% (N=36) of completed treatment as prescribed
- 4% (N=32) of patients were treated palliatively and did benefit from the treatment they received
- 2% (N=19) of patients died on treatment
- 2% (N=18) of patients chose to end their treatment

- 1% (N=13) of patients were treated palliatively and did not benefit from the treatment they received
- Less than 1% (N=3) of patients stopped treatment due to having other comorbidities

Of the 161 patients in the EAMS cohort 131 (81%) patients were identified as no longer being on treatment. Of these 131 patients:

- 46% (N=60) of patients stopped treatment due to disease progression
- 16% (N=21) of patients stopped treatment due to acute toxicity
- 9% (N=12) of patients were treated palliatively and did benefit from the treatment they received
- 8% (N=11) of patients died not on treatment
- 8% (N=10) of completed treatment as prescribed
- 5% (N=7) of patients chose to end their treatment
- 5% (N=7) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 2% (N=2) of patients were treated palliatively and did not benefit from the treatment they received
- 1% (N=1) of patients died on treatment

The median treatment duration amongst the CDF cohort was 13 months [95% CI: 11.7, 14.2] (395 days) and the median treatment duration amongst the EAMS cohort was 18 months [95% CI: 14.4, 24.3] (547 days).

The difference in treatment duration was statistically significant between the two groups.

Treatment duration was also calculated at 6, 12, 18, 24, 36 and 48 months, results showed that there was a statistically significant difference between both the CDF and EAMS cohorts at month 24 and 36.

The median OS amongst the CDF cohort was 33.9 months [95% CI: 30.7, 36.5] (1,031 days) and the median OS amongst the EAMS cohort was 52.5 months (1,597 days).

OS was also calculated at 6, 12, 18, 24, 36 and 48 months, results showed that there was a statistically significant difference between both the CDF and EAMS cohorts at 18, 24, and 36 months.

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for OS was slightly different to the full cohort

33.6 months [95% CI: 30.3, 36.5] vs 33.9 months [95% CI: 30.7, 36.5] but this difference was not statistically significant.

Sensitivity analysis for treatment duration for the full cohort was the same as the full cohort.

A secondary sensitivity was carried out comparing treatment duration and overall survival by IMDC factors, information captured in Blueteq. Results showed results were statistically significantly different between the three groups.

Treatment duration amongst patients with good risk disease, having an IMDC score of 0 was 20.2 months [95% CI: 17.7, 23.7]. Patients with intermediate risk disease, having an IMDC score between 1 and 2 was 11.7 months [95% CI: 10.1, 13.5] and patients with poor risk disease, having an IMDC score between 3 and 6 was 6 months [95% CI: 4.6, 7.8].

OS amongst patients with good risk disease, having an IMDC score of 0 was not reached. Patients with intermediate risk disease, having an IMDC score between 1 and 2 was 27.6 months [95% CI: 25.4, 32.0] and patients with poor risk disease, having an IMDC score between 3 and 6 was 13.1 months [95% CI: 10.6, 17.3]

A third sensitivity was carried out comparing treatment duration and overall survival by RCC histology, information captured in Blueteq. Results showed results were statistically significantly different between the two groups.

Treatment duration amongst patients with clear cell RCC was 14.5 months [95% CI: 13.2, 16.1]. Patients who did not have clear cell RCC, their median treatment duration was 7.3 months [95% CI: 5.9, 8.9].

OS amongst patients with clear cell RCC was 36.4 months [95% CI: 33.9, 39.6]. Patients who did not have clear cell RCC, their median OS was 15.6 months [95% CI: 12.6, 20.7].

9. References

1. The Personal Demographics Service (PDS). NHS Digital: 2023 [cited 2024 July]. Available from: https://digital.nhs.uk/Demographics
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Single Technology Appraisal

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Clinical expert statement

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Part 1: Treating untreated advanced renal cell carcinoma and current treatment options

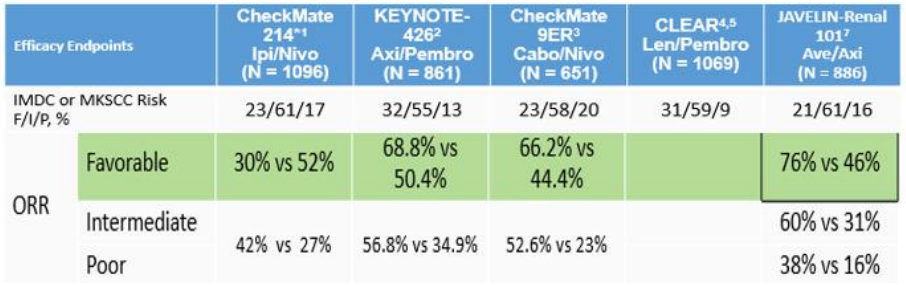
Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Ricky Frazer
2. Name of organisation	Velindre Cancer Services
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated advanced renal cell carcinoma? ☒ A specialist in the clinical evidence base for untreated advanced renal cell carcinoma or avelumab with axitinib? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for untreated advanced renal cell carcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The possibility of providing durable treatment responses which may turn out to be cure for approximately 20% with first line immunotherapy. Also to gain early control of the disease to improve symptoms and patient quality of life.
9. 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)	For some patients, stabilising the disease and stopping further growth can both buy the patient more time and quality of life. Partial or complete response by RECIST criteria is the ultimate aim in addition to this remaining durable.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated advanced renal cell carcinoma?	Yes, which is partially addressed at present by the ability to prescribe the combination of Axitinib and avelumab.
11. How is untreated advanced renal cell carcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the avelumab with axitinib have on the current pathway of care?	• ESMO and ASCO guidelines • I work in Wales, which follows the same approach as colleagues in England and Northern Ireland. It is well defined across all nations that IO/TKI should be considered standard of care across the whole of the UK and across the world. As none of the other IO/TKI have been reimbursed in the favourable risk, if Axitinib and avelumab was not approved in the favourable risk group we would not have either a combination IO/IO option of IO/TKI option in favourable risk and this would leave us behind all developed and many developing countries.
12. Will avelumab with axitinib (the technology) be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between avelumab with axitinib and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Treatment will primarily be used in favourable risk patients though there are also a small percentage of patients where it continues to be used in IMDC Intermediate and Poor Risk. It is currently used primarily in favourable risk patients as there are no other combinations available an in my opinion there is a clinically significant improvement in progression free survival, response rate and overall survival when Axitinib/Avelumab combination is compared to single agent TKI. Should be used in routine use for first line metastatic kidney cancer

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	No additional investment will be required in terms of facilities, equipment and training.
13. Do you expect avelumab with axitinib to provide clinically meaningful benefits compared with current care? • Do you expect avelumab with axitinib to increase length of life more than current care? • Do you expect avelumab with axitinib to increase health-related quality of life more than current care?	The current care is to give combination of Axitinib and avelumab to performance status 0-1 patients. If we were no longer able to prescribe this treatment due to a lack of reimbursement, I would expect to see a reduction in length of life, time to progression, response rate and health related quality of life.
14. Are there any groups of people for whom avelumab with axitinib would be more or less effective (or appropriate) than the general population? • Would you expect a difference in treatment outcomes based on whether the renal cell carcinoma has a clear or non-clear cell component?	More effective for favourable risk patients. We have a number of data sets with cabozantanib and Nivolumab and Lenvatinib and pembrolizumab that shows that IO/TKI is superior to single agent TKI in non-clear cell. As none of those treatments are reimbursed in England, Wales or Northern Ireland (they are reimbursed and available in Scotland) if we were no longer able to use Axitinib and avelumab in all risk groups, patients in England, Wales and Northern Ireland would be placed at a further disadvantage. I have personal experience of using Axitinib and Avelumab in non-clear cells with good efficacy and tolerability.
15. Will avelumab with axitinib be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Currently being used as a standard of care so there would be no practical implications.
16. Will any rules (informal or formal) be used to start or stop treatment with avelumab with axitinib? Do these include any additional testing?	None are required.

17. Do you consider that the use of avelumab with axitinib will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of avelumab with axitinib or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. In favourable risk patients axitinib is not available as a single agent treatment. Indeed, pembrolizumab and Axitinib combination (the only other combination with Axitinib in the first line setting) is also not reimbursed by NICE. Axitinib has the shortest half-life of 4-6 hours, compared for example to cabozantanib 100 hours or Tivozanib 89 hours. The advantage of this is that if patients developed toxicity, such as diarrhoea which is a class effect, it resolves very quickly on stopping Axitinib, this is not the case for the other treatments with significantly longer half-lives.
18. Do you consider avelumab with axitinib 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? • Is avelumab with axitinib a 'step-change' in the management of the condition? • Does the use of avelumab with axitinib address any particular unmet need of the patient population?	Step Change between combination therapy in first line vs single agent. There is a massive unmet need in favourable risk if Axitinib and Avelumab is not approved. Lenvatinib/Pembrolizumab, Axitinib/Pembrolizumab and Cabozantanib/Nivolumab (all IO/TKI) did not get reimbursed by NICE for the approximate 15-20% of patients with favourable risk disease. In addition, Ipilimumab and Nivolumab (IO/IO) does not have a licence in the UK (though is used in USA). The loss of Axitinib and Avelumab for these patients would leave our patients at a significant disadvantage to nearly all developed countries. In Scotland for example they can use any of the 4 IO/TKIs (including Axitinib and avelumab) for favourable risk disease. If you look at the subgroup analysis in the Javelin Renal 101 trial it has the best hazard ration of any of the IO/TKI combinations and I believe this is due to the PDL1 mechanism of action. It also has the best response rate of any of the IO/TKIs in the favourable risk group. There is a massive unmet need. We know that immunotherapy is the best chance of obtaining long term durable outcomes in kidney cancer. We also know from the United Kingdom Renal Oncology Collaborative (UK ROC) data (1319 patients across 17 centres in the UK) that less than 70% of favourable risk patients receive a second line therapy (after censoring for those patients continuing first line treatment due to ongoing response).Therefore, if patients do not receive immunotherapy first line, they may die without receiving immunotherapy at all which I believe is a disservice to renal cancer patients.

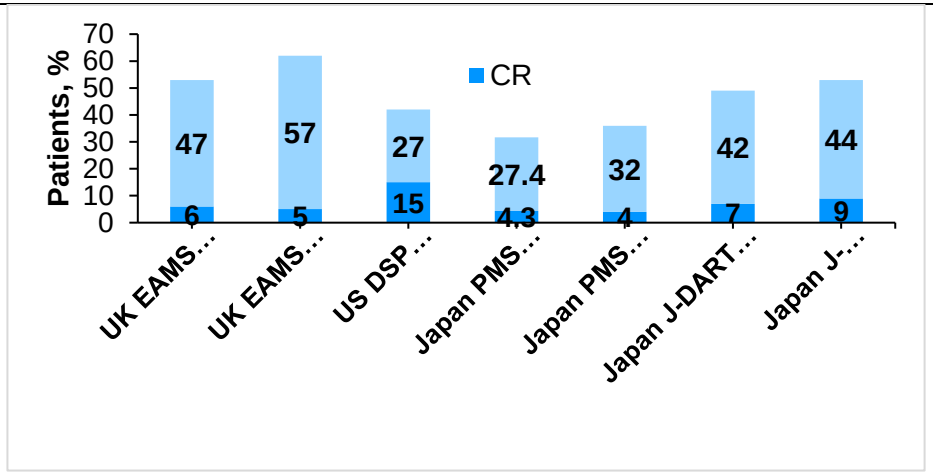
Efficacy Endpoints		CheckMate 214*[1] Ipi/Nivo (N = 1096)	KEYNOTE-426[2] Axi/Pembro (N = 861)	CheckMate 9ER[3] Cabo/Nivo (N = 651)	CLEAR[4,5] Len/Pembro (N = 1069)	JAVELIN-Renal 101[7] Ave/Axi (N = 886)
IMDC or MKSCC Risk F/I/P, %		23/61/17	32/55/13	23/58/20	31/59/9	21/61/16
ORR	Favorable	30% vs 52%	68.8% vs 50.4%	66.2% vs 44.4%		76% vs 46%
	Intermediate	42% vs 27%	56.8% vs 34.9%	52.6% vs 23%		60% vs 31%
	Poor					38% vs 16%

Efficacy Endpoints		CheckMate 214*[1] Ipi/Nivo (N = 1096)	KEYNOTE-426[2] Axi/Pembro (N = 861)	CheckMate 9ER[3] Cabo/Nivo (N = 651)	CLEAR[4,5] Len/Pembro (N = 1069)	JAVELIN-Renal 101[7] Ave/Axi (N = 886)
IMDC or MKSCC Risk F/I/P, %		23/61/17	32/55/13	23/58/20	31/59/9	21/61/16
mOS (HR)	**Favorable**	77.9 vs 66.7 (0.82)	60.3 vs 62.4 (1.10)	52.9 vs 58.9 (1.10)	NR vs 59.9 (0.94)	79.4 vs 65.5 (**0.73**)
	Intermediate	46.7 vs 26 (0.69)	42.2 vs 29.3 (0.76)	43.9 vs 29.3 (0.73)	47.9 vs 34.3 (0.74)	41.3 vs 38.0 (0.95)
	Poor					21.3 vs 11.0 (**0.58**)

19. How do any side effects or adverse effects of avelumab with axitinib affect the management of the condition and the patient's quality of life?	In my experience, the combination of Axitinib and Avelumab is most well tolerated of all the IO/TKI combinations across all three risk groups. As mentioned above, a significant advantage of this combination is the shorter half-life of avelumab and Axitinib. If you compare quality of life in Javelin 101 it is comparable with sunitinib, however we should be clear that this was assessed during the 2 weeks break from sunitinib (given 4 weeks on 2 weeks off) and so in reality when a patient is taking either treatment and not on a break, I believe quality of life is significantly better on the combination of Axitinib and Avelumab.

20. Do the clinical trials on avelumab with axitinib reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • Is the clear cell trial population representative of the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The Javelin 101 trial included patients from western Europe, USA, Canada and other countries. In real world experience, approximately 85% of patients have a clear cell component to their tumour. In the Javelin 101 trial, all patients had a clear cell component. Most important outcomes and RR, PFS and OS, all were measured in the trial with a statistically significant Improvement in response rate and PFS and a clinically meaningful improvement in all three endpoints. PFS2 has also been calculated and shows improvement of Axitinib and Avelumab compared to single agent TKI No new adverse events have come to light
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of the following NICE technology appraisal guidances? • Cabozantinib with nivolumab for untreated advanced renal cell carcinoma (2024) NICE technology appraisal guidance TA964 • Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (2022) NICE technology appraisal guidance TA858 • Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2022) NICE technology appraisal guidance TA780 • Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma (2020) NICE technology appraisal guidance TA650	I believe both the UK ROC publications and other real world data sets will be included in the systematic review. I have included the references below. 1. Nathan PD, et al. J Clin Oncol. 2022;40(Suppl):Abstract 301. 2. Nathan PD, et al. 2024;42(Suppl 4):Abstract 386. 3. Zanotti G, et al. IKCS 2021. Poster N23. 4. Oya M, et al. JUA 2023. Presentation 110890. 5. Nonomura N, et al. JSCO 2023: Abstract FR2-7. 6. Kato T, et al. Int J Urol. 2024;31(3):265-72. 7, Eto M, et al. JUA 2024. 8. McGrane J, et al. Caner Med. Published online June 21, 2024.

• Cabozantinib for untreated advanced renal cell carcinoma (2018) NICE technology appraisal guidance TA542 • Tivozanib for treating renal cell carcinoma (2018) NICE technology appraisal guidance TA512 • Pazopanib for the first-line treatment of advanced renal cell carcinoma (2011, updated 2013) NICE technology appraisal guidance TA215. • Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE technology appraisal guidance TA169.	
23. How do data on real-world experience compare with the trial data?	As outline in the references above the real-world data is consistent with the trial data and indeed in the large UK ROC study led by Dr McGrane, there was a statistically significant improvement in overall survival. Similarly, the data from UK ROC also shows that there is a significant drop off rate between first- and second-line therapies and patients who do not receive immunotherapy in the first line face the prospect of dying without ever having received checkpoint Inhibitor Immunotherapy.



- In observational studies, ORRs with 1L avelumab + axitinib ranged from 32% to 62%, with CR rates ranging from 4.0% to 15.0%[1-7]
- In a UK-based real-world study[2]
  - Median PFS was 13.5 months
  - OS rates at 12, 24, and 36 months were 81.5%, 65.3%, and 53.0%, respectively
- In the real-world J-DART2 study in Japan[7]
  - Median PFS was 17.1 months
  - OS rates at 12 and 24 months were 90.6% and 84.7%, respectively
- In a retrospective UK study, ICI + TKI combination therapy in patients with favourable IMDC risk (avelumab + Axitinib in 95.5%) was associated with significant improvements in PFS and OS vs TKI monotherapy[8]
  - HR for PFS: 0.60 (95% CI, 0.39-0.91)
  - HR for OS: 0.42 (95% CI, 0.18-0.99)

	• The safety profile of avelumab + axitinib in general clinical practice in Japan was comparable to that observed in the JAVELIN Renal 101 trial[3] Percentage of patients by the IMDC risk group receiving a subsequent line of therapy[1] |	Favourable	Intermediate	Poor | |---|---|---|---| | 2L | 67.6 | 62.3 | 46.0 | | 3L | 34.6 | 24.7 | 13.8 | | 4L | 9.3 | 6.5 | 3.8 | • Of the 294 'favourable' risk patients, 97 died within the follow up[2] • 50 (51.5%) of those that died did not receive immunotherapy at any point[2] McGrane J, et al. Caner Med. Published online June 21, 2024.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering untreated advanced renal cell carcinoma and avelumab with axitinib? Please explain if you think any groups of people with untreated advanced renal cell carcinoma are particularly disadvantaged.	None not already discussed above. I do have to say though, if as a kidney cancer treating oncologist, I was back to prescribing sunitinib alone as per guidelines pre 2010 it would be a very embarrassing situation for our country, health service and our profession.

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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Combination of Axitinib and Avelumab has the Longest PFS, Best Response Rate and most desirable toxicity profile of all IO/TKIs in first line kidney cancer

In UK ROC Real world data set approximately a third of patients in the favourable risk group will NOT receive immunotherapy at any point before death if not given in first line

Approximately 60% of patients receive only one line of therapy in first line and therefore best treatment should be given first

Overall survival advantage seen in UK ROC data set in the favourable risk group when combination Axitinib and avelumab was compared to single agent TKI

If treatment not approved, patient in the UK will be one of the few developed countries not to be able to access immunotherapy in first line.

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Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

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Part 1: Treating untreated advanced renal cell carcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Naveen Vasudev
2. Name of organisation	Leeds Teaching Hospitals
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated advanced renal cell carcinoma? ☐ A specialist in the clinical evidence base for untreated advanced renal cell carcinoma or avelumab with axitinib? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for untreated advanced renal cell carcinoma?	The main aims are to gain disease control, improve cancer-related symptoms or delay onset of symptoms, improve quality of life and extend survival

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. 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)	Disease control (stable disease, partial response or complete response) in conjunction with clinical benefit, translating to improvements in PFS +/- OS
10. In your view, is there an unmet need for patients and healthcare professionals in untreated advanced renal cell carcinoma?	Yes. For most patients this remains an incurable, life-limiting condition. Furthermore, current treatments can come at the cost of significant toxicity. There are also no predictive biomarkers available.
11. How is untreated advanced renal cell carcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the avelumab with axitinib have on the current pathway of care?	All patients with advanced RCC (aRCC) can be classified as having good, intermediate or poor risk disease, based on International Metastatic RCC Database Consortium (IMDC) criteria. Clinical guidelines (ESMO, NCCN) recommend combination therapy across all subgroups. The pathway of care is well defined. In patients with intermediate and poor-risk disease, patients have a choice between doublet immunotherapy (IO) (ipilimumab + nivolumab) or IO + VEGF TKI (either lenvatinib + pembrolizumab / cabozantinib + nivolumab or axitinib + avelumab). Alternatively, patients can receive single agent TKI, although this will be in the minority of patients. Patients with favorable risk disease have options including surveillance, single agent TKI or combination axitinib + avelumab. In other words, this combination is the only IO+TKI combination available to such patients on the NHS and the only first line immunotherapy. Practice will vary in terms of single agent TKI vs IO/TKI, taking into account disease pattern, co-morbidities and patient wishes, particularly given the lack of OS signal in this group. However, ORR and PFS are superior with the combinations, strongly supporting their continued availability to patients.
12. Will avelumab with axitinib (the technology) be used (or is it already used) in the same way as current care in NHS clinical practice?	Avelumab plus axitinib is available via the CDF and already being used in patients with untreated aRCC across IMDC risk groups.

• How does healthcare resource use differ between avelumab with axitinib and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect avelumab with axitinib to provide clinically meaningful benefits compared with current care? • Do you expect avelumab with axitinib to increase length of life more than current care? • Do you expect avelumab with axitinib to increase health-related quality of life more than current care?	This combination treatment is currently being used as a standard of care. If this is no longer an available option then the only available treatment for favourable-risk patients would be single agent TKI. Using this as a comparator, then yes. Av + Axi led to a statistically and clinically meaningful improvement in ORR and PFS with longer duration of response in comparison to sunitinib, amongst ITT population in JAVELIN 101. OS favoured the combination but did not meet statistical significance These improvements in ORR, PFS and duration of response were maintained across IMDC risk groups. OS was demonstrated to be significantly better amongst intermediate- and poor-risk, but not favourable-risk, patients. The study provides the longest FU to date for any IO/TKI combination It is important to recognise that aRCC is a heterogeneous disease, even within risk groups. This is supported by gene expression studies. Thus, even amongst favourable risk patients, some may not do as well with single agent TKI and, in some, a higher chance of response can still be important No trials have formally compared IO/TKI combinations. However, they are broadly considered equivalent in terms of efficacy. The lack of an OS signal, however, together with the fact avelumab is given 2-weekly, means that combinations such as len+pem and cabo+nivo are used in preference given the choice

14. Are there any groups of people for whom avelumab with axitinib would be more or less effective (or appropriate) than the general population? • Would you expect a difference in treatment outcomes based on whether the renal cell carcinoma has a clear or non-clear cell component?	There is a paucity of data for this combination in patients with nccRCC. Based on what we have seen with other IO/TKI combinations, we can expect it to have activity in other histological subtypes, but typically less so than in clear cell RCC
15. Will avelumab with axitinib be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Since it is already being used, HCPs are well versed in the delivery of the combination.
16. Will any rules (informal or formal) be used to start or stop treatment with avelumab with axitinib? Do these include any additional testing?	No additional testing. Treatment is continued until clear loss of clinical benefit or unacceptable toxicity. It is worth noting, however, that in more recent trials of combination IO/TKI, the IO component was stopped at 2 years. The benefit of continuing IO beyond this time-point remains poorly understood
17. Do you consider that the use of avelumab with axitinib will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of avelumab with axitinib or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No

18. Do you consider avelumab with axitinib 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? • Is avelumab with axitinib a 'step-change' in the management of the condition? • Does the use of avelumab with axitinib address any particular unmet need of the patient population?	Axitinib is a well-tolerated TKI. It has high potency against VEGFR1-3 and is clean, relative to others in this class. Its short half-life is also attractive, in terms of toxicity management, albeit patients are required to take it twice a day. It is important that patients with favorable-risk disease continue to have access to an IO/TKI combination, in my opinion
19. How do any side effects or adverse effects of avelumab with axitinib affect the management of the condition and the patient's quality of life?	Toxicity is principally driven by the TKI component. But these are a class of drug with which treating HCPs have vast experience and, therefore, expertise in mitigating and managing side-effects. IO-related toxicities are also seen, but again, these agents are now widely used across cancer medicine, with well-defined management algorithms QoL was broadly maintained amongst patients in JAVELIN 101
20. Do the clinical trials on avelumab with axitinib reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • Is the clear cell trial population representative of the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The study population in JAVELIN 101 is broadly reflective of UK practice, although only 30% were from Western Europe/Canada Yes, the clear cell population appears representative The most important measures are ORR, PFS, duration of response and OS, all measured in the study No AEs have subsequently come to light
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of the following NICE technology appraisal guidances? • Cabozantinib with nivolumab for untreated advanced renal cell carcinoma (2024) NICE technology appraisal guidance TA964 • Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (2022) NICE technology appraisal guidance TA858 • Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2022) NICE technology appraisal guidance TA780 • Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma (2020) NICE technology appraisal guidance TA650 • Cabozantinib for untreated advanced renal cell carcinoma (2018) NICE technology appraisal guidance TA542 • Tivozanib for treating renal cell carcinoma (2018) NICE technology appraisal guidance TA512 • Pazopanib for the first-line treatment of advanced renal cell carcinoma (2011, updated 2013) NICE technology appraisal guidance TA215. • Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE technology appraisal guidance TA169.	No
23. How do data on real-world experience compare with the trial data?	Generally compare well and support trial data. This includes UK data -- Nathan et al. 2024. McGrane et al have also published RWD amongst a large retrospective cohort of patients and report an OS benefit for patients receiving IO/TKI ((n=66-majority axi-ave) versus TKI alone amongst favorable-risk patients

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering untreated advanced renal cell carcinoma and avelumab with axitinib? Please explain if you think any groups of people with untreated advanced renal cell carcinoma 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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is the only combination available to patients with favourable-risk disease (only access to immunotherapy in the first line)

Ave+Axi is an active combination in untreated aRCC, across all IMDC risk groups

Axi is a potent, 'clean', TKI with short half-life, making the combination generally well tolerated

RCC is a heterogeneous disease, clinically and biologically, even within risk groups

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with untreated advanced renal cell carcinoma. The text boxes will expand as you type.

In part 2 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 12 March 2025.** 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, 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 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.

Patient expert statement

Part 1: Living with untreated advanced renal cell carcinoma or caring for a person with this condition

Table 1 About you, untreated advanced renal cell carcinoma, current treatments and equality

1. Your name	Christopher Hallworth
2. Are you (please tick all that apply)	☐ A person with untreated advanced renal cell carcinoma? x A person with experience of the treatment being evaluated? ☐ A carer of a person with untreated advanced 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) x 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 x I agree with it and **will be** completing ☐
5. How did you gather the information included in your statement? (please tick all that apply)	x 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: x 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 untreated advanced renal cell carcinoma **If you are a carer (for someone with untreated advanced renal cell carcinoma) please share your experience of caring for them**	From first symptoms (blood in urine) in October 2018 to radical nephrectomy to remove right kidney and 7cm tumour was just 2 months. Subsequent scans in March 2019 showed new left hilar lymph nodes. Palliative radiotherapy given in July 2019. Progressive lymph node enlargement led to starting Avelumab and Axitinib combination in September 2019.
7a. What do you think of the current treatments and care available for untreated advanced 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?**	From my experience very few people seem to be on this combination. I don't know how the other combination treatments work although anecdotally from the Action for Kidney Cancer facebook group the side effects of combination treatments seem similar.
8. If there are disadvantages for patients of current NHS treatments for untreated advanced renal cell carcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Not able to comment
9a. If there are advantages of avelumab with axitinib 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 avelumab with axitinib help to overcome or address any of the listed disadvantages of current**	This treatment combination has been relatively easy to endure. It involved writing off one day a fortnight to the infusion and subsequent fatigue. But this passed by the next day and enabled me to continue with an active life as normal. The success of the treatment, leading to no evidence of disease after 2 years was comfortably the most important outcome but I was very grateful that the impact on my lifestyle was very limited and manageable.

treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of avelumab with axitinib over current treatments on the NHS please describe these. For example, are there any risks with avelumab with axitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I had to suspend treatment in August 2024 as a routine scan identified an aortic aneurysm (5.6cm) which required surgery. The scan continued to show no evidence of cancer, so my oncologist felt it was prudent to focus on the heart issues and review again once I had recovered. Heart op (AVR and Ascending Aorta replacement) done Feb 2025. I don't know if the Axitinib contributed to the heart problems, or they are unrelated. Diarrhoea was a constant companion with the Axitinib but manageable. Headaches early in the treatment but these eased after a few months. High blood pressure and under active thyroid were bought on as a result of the treatment but returned to normal with low dose daily medication.
11. Are there any groups of patients who might benefit more from avelumab with axitinib or any who may benefit less? If so, please describe them and explain why Consider, for example: ● if people with renal cell carcinoma also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments or ● if the renal cell carcinoma has a clear cell component compared with a non-clear cell component	Not qualified to comment
12. Are there any potential equality issues that should be taken into account when considering untreated	Unknown

advanced renal cell carcinoma and avelumab with axitinib? Please explain if you think any groups of people with this condition are particularly disadvantage 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?	Having better information about the treatment would be useful. Maybe some guidelines on reducing dosages or frequency of infusion, which I have read has been looked at in other countries.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The success of this combination has been well above my expectation, and I feel very lucky to have been involved from an early stage.
- The side effects of diarrhoea, headaches, high blood pressure and low thyroid have all been manageable.
- I have been able to maintain a very active lifestyle (squash, tennis, golf, walking etc) throughout the 5 years of treatment.
- I cannot say if my aortic aneurysm was linked to the treatment, but I think it is worth monitoring.

Thank you for your time.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The authors declare none. Dr Gee reports Merck sponsored attendance at the ASCO-GU 24 update at BMA House (£150 for travel).

Rider on responsibility for report

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.

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Contributions of authors

Asyl Hawa critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanna Picot critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor; Lois Woods critically appraised the clinical effectiveness systematic review and

drafted the report; Ines Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
aRCC	Advanced renal cell carcinoma
BICR	Blinded independent central review
BNF	British National Formulary
CDF	Cancer Drugs Fund
CI	Confidence interval
CIC	Commercial in confidence
CAA	Commercial access arrangement
cPAS	Comparator PAS
CS	Company submission
CSR	Clinical study report
DCO	Data cut-off
DSU	Decision Support Unit
EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
ECOG PS	Eastern Cooperative Oncology Group performance status (score)
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
FAS	Full Analysis Set
FKSI-19	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 19 items
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IMDC	International Metastatic RCC Database Consortium
IO	Immunotherapy
ITC	Indirect treatment comparison

ITT	Intention-to-treat
IV	Intravenous
MCID	Minimum clinically important difference
MSKCC	Memorial Sloan Kettering Cancer Center
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression free survival
PRO	Patient-reported outcome
PSS	Personal Social Services
QALY	Quality-adjusted life year
Q-TWiST	Quality-adjusted Time Without Symptoms or Toxicity
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RWE	Real-world evidence
SACT	Systemic anti-cancer therapy
SAP	Statistical analysis plan
SLR	Systematic literature review
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
VAS	Visual analogue scale
VEGFR	Vascular endothelial growth factor receptor

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides our critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement. Section 1.2 provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.4 to 1.7 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Critique of the company's adherence to the committee's preferred assumptions

When avelumab plus axitinib was recommended for untreated advanced renal cell carcinoma (aRCC) within the Cancer Drugs Fund the NICE committee stated that when the guidance was reviewed the updated model should include the preferred assumptions listed below (unless new evidence indicated otherwise) (TA645 paragraph 3.20):

- No stopping rule
- Trial evidence and costs adjusted to reflect subsequent treatments used in NHS practice, including adjusting for life-extending treatments used in the trial not available in the NHS and justifying the methods used to adjust for follow-on treatments
- A range of overall survival extrapolations explored, including the exponential curve
- The modelled overall survival treatment effect over comparators over time, explicitly presented

The company's updated appraisal has adhered to the above points outlined in the managed access agreement.

1.2 Overview of the EAG's key issues

Table 1 Summary of Key issues

ID	Summary of issue	Report sections
1	Effectiveness of avelumab with axitinib versus comparators for people with non-clear-cell aRCC	2.1, 3.2.7.1.2, 3.6
2	Parametric curve used for modelling overall survival in the favourable-risk population	4.2.4.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are changes in the prices used for sunitinib and everolimus; see section 1.8 below.

1.3 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The revised company model base case deterministic results are shown in Table 2. The pairwise ICER for avelumab with axitinib versus sunitinib is [redacted] per QALY. Tivozanib and pazopanib are 'dominated' by sunitinib: that is, they have high costs but by assumption produce the same QALY gain. The pairwise ICER for avelumab with axitinib versus tivozanib is [redacted] per QALY and versus pazopanib is [redacted] per QALY.

Table 2 Base case results of the revised company model, PAS price for avelumab (favourable-risk population).

Treatment	Total		Incremental		ICER
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
Versus sunitinib					
Sunitinib	£93,185	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib					
Tivozanib	£136,173	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib					
Pazopanib	£165,275	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from Table 12 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.

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

No new issues since TA645[1] were identified with respect to the decision problem. We note that treatment choice in adults with untreated aRCC is now determined by considering International Metastatic RCC Database Consortium (IMDC) risk category alongside individual patient characteristics and the company have chosen to focus their submission and economic model base case on the subgroup of patients with favourable-risk aRCC. The company have also presented evidence for the intermediate-/poor-risk subgroup as well as the full intention-to-treat (ITT) population.

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

Issue 1 Effectiveness of avelumab with axitinib versus comparators for people with non-clear-cell aRCC

Report section	2.1, 3.2.7.1.2, 3.6
Description of issue and why the EAG has identified it as important	A key uncertainty from TA645 (paragraph 3.19 of the NICE guidance document) was the lack of data on whether avelumab with axitinib is effective for non-clear-cell disease. The committee agreed that this was one of two uncertainties that could be resolved by collecting further data to monitor whether there is a difference in effectiveness in comparison to those with clear-cell histology (paragraph 3.7 of the NICE guidance document). Data collected from patients treated within the Cancer Drugs Fund shows that median overall survival (OS) in the non-clear cell population (n=[redacted]) is [redacted] than for the clear cell aRCC population (n=[redacted]). However, as the Cancer Drugs Fund does not include data for people with non-clear-cell disease treated with the possible comparator treatments the effectiveness of avelumab with axitinib in comparison to relevant comparators in this group of patients is still unknown.
What alternative approach has the EAG suggested?	No alternative suggested.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion on whether the JAVELIN Renal 101 trial results in people advanced renal cell carcinoma (aRCC) with clear-cell histology are likely to be generalisable to people with aRCC of non-clear-cell histology.

1.6 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 2 Uncertainty over long-term predictions of overall survival

Report section	4.2.4.1
Description of issue and why the EAG has identified it as important	There is a high uncertainty over long-term survival; although many of the parametric survival curves fit the KM data initially, their long-term projections vary significantly beyond 10 years. The company uses a log-normal distribution for avelumab with axitinib for OS, and the generalised gamma for sunitinib (and therefore also pazopanib and tivozanib).They test alternative extrapolations in scenario analysis, which show that the cost-effectiveness results are sensitive to the choice of survival curves.
What alternative approach has the EAG suggested?	Further external evidence is needed to inform the choice of OS curves for the avelumab with axitinib and sunitinib treatment arms.
What is the expected effect on the cost-effectiveness estimates?	In the company revised base case, the ICER is [redacted] per QALY for avelumab with axitinib versus sunitinib. The following ICERs are produced in scenario analyses (see section 6): • OS avelumab with axitinib: o Exponential: [redacted] per QALY o Generalised gamma: [redacted] per QALY • OS sunitinib: o Weibull: [redacted] per QALY o Exponential: [redacted] per QALY Results for pazopanib and tivozanib are presented in Table 21.
What additional evidence or analyses might help to resolve this key issue?	Hazard function plots from the JAVELIN Renal 101 trial OS data to show how hazards changed over time for patients with favourable-risk disease in the avelumab with axitinib and sunitinib arms. Further expert opinion on the plausibility of long term survival extrapolations from the trial data (from 10 years onwards)

1.7 Other key issues: summary of the EAG's view

We have no other key issues.

1.8 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's economic model in section 4, we have implemented a single change to the revised company base case. This involves updating the costs of sunitinib and everolimus using the most recent eMIT prices (see Table 14). Table 3 below presents a comparison of the revised company base case results and the EAG preferred base case, including a PAS discount of [redacted] for avelumab.

Table 3 Company revised base case and EAG preferred base case results (favourable-risk population)

Base case	Treatment	Total cost	Total QALYs	ICER (£/QALY) [a]
Company base case	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
EAG preferred base case	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Source: reproduced using company economic model and EAG base case model.
Ave + axi, avelumab with axitinib; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
[a] Pairwise ICERs for Avelumab with axitinib relative to each comparator. Pazopanib and tivozanib are dominated by sunitinib in all scenarios, as they have a higher cost and by assumption provide the same QALY gain

For further details of the exploratory and sensitivity analyses done by the EAG, see section 6 of this EAG report.

The EAG notes two additional uncertainties related to the cost-effectiveness analysis:

- Relative dose intensity (RDI) has been implemented for the intervention and comparators but not for subsequent treatments; see section 4.2.6.2.3.
- TA645 included oral administration costs but these were not included in the company's submission for the current appraisal. The reason for this change has not been explained. See section 4.2.6.2.4.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Merck on the clinical effectiveness and cost effectiveness of avelumab (Bavencio) in combination with axitinib (Inlyta) for treating adults with untreated advanced renal cell carcinoma (aRCC). It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 2nd December 2024. A response from the company via NICE was received by the EAG on 18th December 2024 and this can be seen in the NICE committee papers for this appraisal.

The key areas of clinical uncertainty identified by the appraisal committee during TA645 and listed in the managed access agreement were:

- the immaturity of the overall survival data and the companies' approach to modelling overall survival over the long term
- the lack of data on whether the treatment is effective for non-clear-cell disease and
- the companies' methods for adjusting both the costs and benefits of subsequent treatments to reflect NHS practice

It was concluded that further data collection within the Cancer Drugs Fund (CDF) could potentially resolve the uncertainty regarding the first two points (immaturity of the survival data and treatment effectiveness for non-clear-cell disease).

For this appraisal the CS addresses the key areas of clinical uncertainty from TA645 by:

- providing data from the final analysis of the JAVELIN Renal 101 trial of avelumab with axitinib versus sunitinib (data cut off 31 August 2023). See section 3.2.1 of this report.
- Presenting real-world evidence on overall survival for patients who received avelumab with axitinib in the UK from the CDF or an Early Access to Medicines Scheme (EAMS). Some of these patients had non-clear-cell disease. See section 3.2.7.1.2 of this report.
- Using data from the McGrane et al. analysis of RWE to adjust the costs of subsequent treatment in a scenario analysis (see section 4.2.6.2.5 of this report). No adjustments for subsequent treatment use are made to the clinical data used to inform the model.

2.2 Background

2.2.1 Background information on advanced renal cell carcinoma (aRCC)

Renal cell carcinoma (RCC) starts in the lining (epithelium) of the tubules of the kidney and is the most common type of kidney cancer, accounting for about 80% of cases.[2] The company report the key facts of the disease appropriately in CS section B.1.3.1. The reported epidemiological data aligns with the latest statistics from Cancer Research UK,[3] one of the company's sources, and the EAG are satisfied that the epidemiological data for aRCC in the CS is relevant to the UK.

Renal cell carcinoma (RCC) has different histological subtypes: clear-cell RCC which is the most common, and non-clear cell RCC which groups together other subtypes. Company data reported for the proportions of people with clear cell RCC and non-clear cell RCC are from a confidential NHS England systemic anti-cancer therapy (SACT) data report[4] produced for this review. However, the proportions of clear cell and non-clear cell aRCC [redacted] to the published McGrane 2024 study of 1319 aRCC patients in the UK of whom 83.1% had a clear cell component.[5]

CS section B.1.3.1.1 describes staging and prognostic risk factors for aRCC. The International Metastatic RCC Database Consortium (IMDC) criteria (also known as Heng Criteria) are commonly used in the UK clinical practice to categorise patients into favourable-, intermediate- and poor-risk subgroups for survival based on the criteria presented in CS Figure 3. A person's disease risk status then helps to decide treatment choice (section 2.2.3).

2.2.2 Background information on avelumab with axitinib

Avelumab in combination with axitinib is indicated for first line treatment of adults with aRCC.[6] In September 2020 avelumab with axitinib was recommended by NICE for use in this population within the Cancer Drugs Fund subject to the conditions set out in its Managed Access Agreement being followed.[1 7] The licensed indication[6] includes:

- all risk groups that now determine the treatment pathway for aRCC patients in the NHS (see treatment pathway in section 2.2.3 below).
- all histological subtypes, i.e. whether clear cell or non-clear cell aRCC, although the company pivotal trial does not evaluate its use in non-clear cell aRCC
- tumours that are programmed cell death ligand-1 (PD-L1) positive and those that are PD-L1 negative.

Avelumab is a type of immunotherapy that blocks the PD-L1 protein. PD-L1 is present on immune cells and it may also be present on cancer cells where it can stop the body's T cells fighting the cancer.[6] However, the recent European Society for Medical Oncology (ESMO) RCC guideline (Powles et al. 2024)[8] states that PD-L1 has been unreliable as a biomarker in renal cancer, and testing people with aRCC to see if their tumour is PD-L1-positive is not routinely available on the NHS. The EAG's clinical expert confirmed this, advising us that they do not take PD-L1 status into account when considering first-line therapy, nor do they test for it.

Axitinib is a tyrosine kinase inhibitor (TKI) that inhibits the vascular endothelial growth factor receptors (VEGFR), VEGFR-1, VEGFR-2 and VEGFR-3, that are implicated in the abnormal growth of blood vessels, tumour growth and disease progression in cancer.[9] Axitinib as a monotherapy is recommended by NICE as a subsequent treatment for aRCC when sunitinib or other cytokine therapy has failed.[10]

For the treatment of adults with aRCC the recommended dose of avelumab in combination with axitinib, according to its marketing authorisation, is 800 mg of avelumab administered intravenously every two weeks and 5 mg of axitinib administered orally twice a day until disease progression or unacceptable toxicity.[6] The dose of axitinib may be increased or reduced, or temporarily discontinued, based on patient safety and tolerability.[6]

2.2.3 The position of avelumab with axitinib in the treatment pathway

There are no treatment guidelines for aRCC specific to the UK. NICE has a kidney cancer guideline (NG10398) in development. However, in practice, our clinical expert advised us that they refer primarily to the NICE recommendations for individual treatments and that the ESMO RCC guideline[8] can be useful with the caveat that funding is not in place in the UK for many of the ESMO treatment pathways.

NICE guidance for individual treatments state that choice of first line treatment for aRCC depends on a person's disease risk status, according to the IMDC criteria for aRCC, and European Cooperative Oncology Group (ECOG) performance status score. Treatment options, according to NICE guidance, for those with favourable-risk disease are: avelumab with axitinib (via the CDF),[1 7] or one of the tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, or tivozanib.[11-13] Treatment options for those with intermediate- or poor-risk disease include the same options as for favourable-risk disease with the additional options of cabozantinib,[14] two further combination immunotherapy/tyrosine kinase inhibitor (IO/TKI) options and a combined immunotherapy option (IO/IO): cabozantinib with nivolumab (TA964),[15] lenvatinib with pembrolizumab (TA858),[16] and nivolumab with ipilimumab

(TA780).[17] The combination IO/TKI and IO/IO therapies were not available at the time of the original avelumab with axitinib appraisal (TA645). Both nivolumab and pembrolizumab are also programmed cell death-1 (PD-1)/PD-L1 checkpoint inhibitor therapies like avelumab.

Therefore, avelumab with axitinib, via the CDF, represents an additional IO/TKI combination treatment option at first line for all aRCC risk groups, and is the only IO/TKI combination treatment recommended for the favourable risk group. This is shown in CS Figure 5 which is replicated in Figure 1 below.

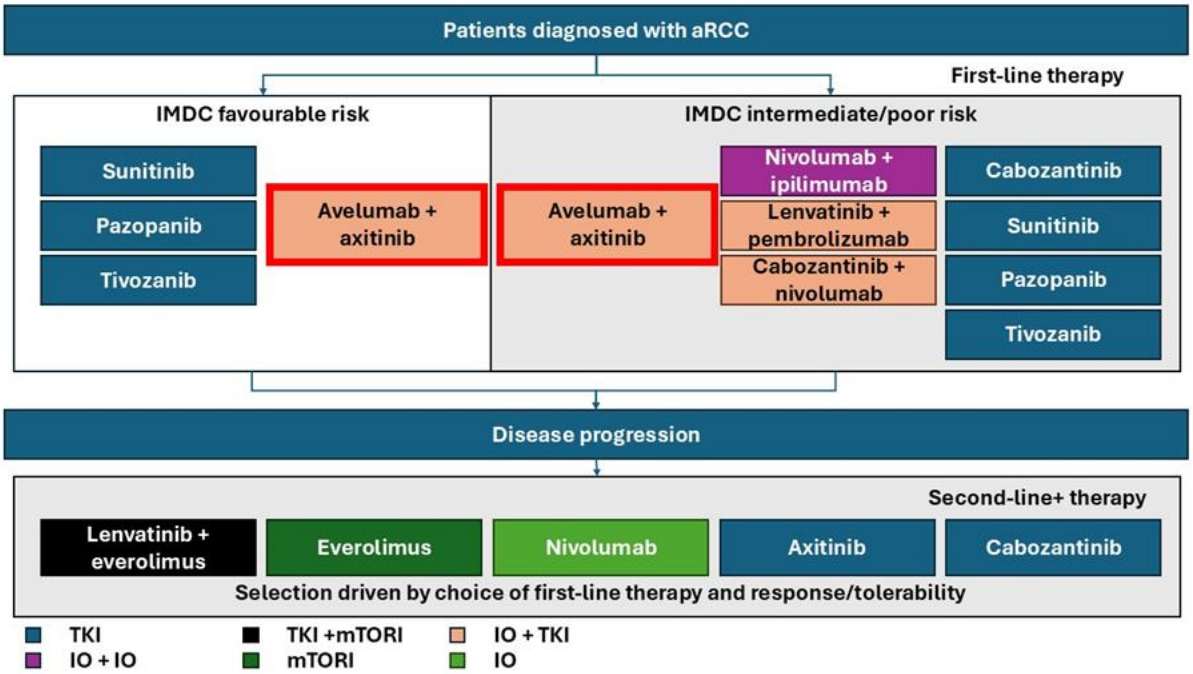

Figure 1 Clinical pathway of care including the anticipated place for avelumab with axitinib

Source: Reproduced from CS Figure 5.
Abbreviations: aRCC, advanced renal cell cancer; CDF, cancer drugs fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; mTORI, mammalian target of rapamycin inhibitor; TKI, tyrosine kinase inhibitor.

Briefly, second line treatment options for aRCC outlined in Figure 1 above include nivolumab (according to TA417, but not after prior immunotherapy),[18] axitinib (according to TA333),[10] cabozantinib (according to TA463),[19] everolimus (according to TA432)[20] or lenvatinib with everolimus (according to TA498).[21] Choice of subsequent treatment options depend on the class of drug received for first line treatment and how the patient tolerated and responded to it. The EAG's clinical expert confirmed this and added that they might also consider trial data for second-line treatments and discussions with colleagues. People who receive an immunotherapy option at first line do not receive another at second line as advised in the

international guidelines.[8 22 23] Our clinical expert added that immunotherapy may not be given in combination with TKI or as dual immunotherapy in the second line setting, even if no immunotherapy was given at first-line, and this is as illustrated in the treatment pathway in Figure 1 above. Furthermore, our clinical expert noted that a patient with complete response to immunotherapy cannot stop treatment and then restart at the point of progression, therefore in order to retain access to a treatment that works a patient with no disease on scans may continue treatment, perhaps unnecessarily, for many years. Nivolumab is the only PD-1/PD-L1 immunotherapy available at second line and beyond. Subsequent treatments are relevant to the economic model and are further discussed in section 4.2.6.2.5.

EAG conclusion on background information

The company have accurately summarised aRCC and the treatment pathway for this. Since avelumab with axitinib entered the CDF in 2020 the treatment pathway for people with aRCC has changed, firstly to take into account a person's prognostic risk status to decide first-line treatment options, and secondly to include three new combination treatments that are available for people with intermediate-/poor- prognostic risk status.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with untreated aRCC	Adults with untreated aRCC with IMDC favourable-risk disease and intermediate-/poor-risk disease	Aligned with the evolution of the treatment pathway, evidence is additionally presented as subgroups of particular interest: people with favourable-risk disease and people with intermediate-/poor-risk disease.	We agree with the company that treatment choice in adults with untreated aRCC is now determined by considering IMDC risk category alongside individual patient characteristics. The company present their evidence focussing on the favourable-risk subgroup (which is the population in the economic model base case) but also present evidence for the intermediate-/poor-risk subgroup as well as the full ITT population. As noted in TA645[1] the company's key trial, JAVELIN Renal 101 is limited to people with clear cell aRCC.
Intervention	Avelumab with axitinib	Avelumab with axitinib	In line with the NICE final scope.	No additional comment
Comparators	Favourable-risk disease as defined in the IMDC criteria: • Pazopanib • Sunitinib • Tivozanib	Favourable-risk disease as defined in the IMDC criteria: • Pazopanib • Sunitinib • Tivozanib	In line with the NICE final scope.	As was the case in TA645, direct evidence is available from the JAVELIN Renal 101 trial for the comparison with sunitinib. For the comparisons with pazopanib and

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	Intermediate-/poor-risk disease as defined in the IMDC criteria: • Cabozantinib • Nivolumab with ipilimumab • Lenvatinib with pembrolizumab • Cabozantinib with nivolumab • Pazopanib • Sunitinib • Tivozanib	Intermediate-/poor-risk disease as defined in the IMDC criteria: • Cabozantinib • Nivolumab with ipilimumab • Lenvatinib with pembrolizumab • Cabozantinib with nivolumab • Pazopanib • Sunitinib • Tivozanib		tivozanib in the favourable-risk disease subgroup and in the ITT population the company followed the precedent set in previous NICE appraisals and assumed similar efficacy for the TKI monotherapies (i.e. pazopanib and tivozanib assumed to have similar efficacy to sunitinib). For the intermediate-/poor-risk subgroup a network meta-analysis was used to compare avelumab + axitinib to cabozantinib; nivolumab + ipilimumab; lenvatinib + pembrolizumab; cabozantinib + nivolumab; and sunitinib. Pazopanib and tivozanib were assumed to have similar efficacy as sunitinib.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response • time on treatment/time to next treatment • adverse effects of treatment • health-related quality of life.	As per the final scope, the submission considers the following outcomes: • overall survival • progression-free survival • response rates • duration of response • time on treatment/time to next treatment • adverse effects of treatment	In line with the NICE final scope.	All outcome measures are considered. The network meta-analysis was only conducted for overall survival and progression-free survival (because these were the outcomes informing the economic model).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		• health-related quality of life.		
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 and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The cost-effectiveness analysis takes into consideration commercial arrangements for the following treatments: • avelumab • pazopanib There are commercial arrangements for the following treatments that could not be taken into consideration since the volume of any Patient Access Scheme (PAS) discounts are unknown: • axitinib • tivozanib • cabozantinib • nivolumab • ipilimumab • pembrolizumab • lenvatinib	The cost-effectiveness analysis is in line with the NICE final scope, except for the specification of PAS discounts which are confidential.	The company's cost-utility analysis adheres to the NICE reference case. The population modelled in the base case is the favourable-risk subgroup, we consider this focus acceptable. The existing simple PAS price discount for avelumab and a published discount for pazopanib are applied in the economic evaluation.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Subgroups	If the evidence allows the following subgroup will be considered: • Favourable-risk advanced metastatic RCC as defined in the IMDC criteria • Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • PD-L1 status	• IMDC favourable-risk subgroup • IMDC intermediate-/poor-risk subgroup • PD-L1 status	In line with the NICE final scope. Evidence is presented for the PD-L1 positive (+) subgroup; however, clinical opinion suggests that PD-L1 status is not relevant to systemic treatment decision-making for aRCC and hence it has not been explored in cost-effectiveness analyses.[1 24]	No additional comment

Source: CS Table 1 with EAG comments added.
aRCC, advanced renal cell carcinoma; CS, company submission; IMDC, international metastatic renal cell cancer database consortium; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; PD-L1, programmed cell death-ligand-1; TA, technology appraisal; TKI, tyrosine kinase inhibitor.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company performed two systematic literature reviews (SLRs),

- one to identify randomised controlled trial (RCT) evidence for efficacy, safety and tolerability of all treatments for untreated aRCC which was originally carried out for the company's previous submission to NICE and updated for this submission, and
- a new one to identify real-world evidence (RWE) exploring the benefits of treatment with avelumab in combination with axitinib since its availability in 2019 (see section 3.2.6).

3.1.1 RCT systematic literature review (SLR)

For the RCT SLR, the main healthcare databases, relevant conferences, and the bibliographies of systematic reviews, were last searched on 4 June 2024 (CS section B.2.1 and CS Appendix D.1.1) or 13 May 2024 (CS section B.2.10.1). Screening was carried out using eligibility criteria that align with the NICE scope (CS Appendix D.3 Table 27) and generally the review methods were appropriate. Despite some lack of clarity around reporting, e.g. details in the included PRISMA flow diagram, and that no lists of excluded or included studies were provided with the submission, we consider that the SLR is up to date and not likely to be missing any relevant RCTs. A summary of the EAG's appraisal of the systematic review methods for the RCT SLR is in Appendix 1.

The RCT SLR identified 76 unique studies (503 publications), from the original search and all update searches, that evaluated all relevant treatments for aRCC (CS Appendix D.5 Figure 1). One relevant RCT was identified evaluating avelumab with axitinib compared to sunitinib, JAVELIN Renal 101 (CS section B.2.2 and CS Appendix D.5.1-5.2). The company explain that evidence from a dose-finding phase 1b trial, JAVELIN Renal 100, has been superseded by the final analysis of JAVELIN Renal 101 and real-world evidence (CS section B.2.2) and the EAG agree. We therefore agree that JAVELIN Renal 101 is the only relevant RCT evaluating avelumab with axitinib and we discuss it further in section 3.2 below. This trial provides evidence for both the favourable-risk and intermediate-/poor-risk aRCC subgroups.

The company's SLR additionally identified five relevant RCTs that evaluated comparator treatment options listed in the NICE scope for the intermediate-/poor-risk subgroup and they were included in the company's indirect treatment comparison (ITC) in CS section B.2.10. A list of excluded studies was not provided for the ITC – therefore although we can confirm

that the included studies are relevant, we cannot assess whether all relevant studies were included. We discuss the identification of studies for the ITC in section 3.3.2.

3.1.2 RWE SLR

The RWE SLR sought to identify real-world evidence of the treatment benefits of avelumab with axitinib for UK patients. Therefore, the search dates, from 2019, which was the time of approval of the combination therapy in the UK, to 29 July 2024 are appropriate and retrieve up-to-date evidence. Relevant databases and conferences were searched, and the search terms were broader than for the RCT SLR by not including disease stage. Overall, we consider that the search terms for RWE were comprehensive. The review methods were generally appropriate, and we believe that the RWE SLR would have identified all relevant evidence for avelumab with axitinib in the UK. However, as the RWE SLR did not seek to identify any real-world evidence for comparator treatments it is biased towards avelumab with axitinib.

A summary of the EAG's appraisal of the systematic review methods for the RWE SLR is in Appendix 2. The real-world evidence is discussed further in section 3.2.6.

3.2 Critique of new clinical evidence

The original CS for TA645 included clinical evidence from the company's pivotal phase 3 JAVELIN Renal 101 trial, primarily from interim analysis (IA) 1 (data cut-off 20 June 2018) with a summary of some results from IA2 (data cut-off 28 January 2019). Supportive evidence from a dose-finding Phase 1b trial B9991002 was also included. A detailed critique of the JAVELIN Renal 101 trial was provided in the original EAG report which can be found in the committee papers for TA645.[25] As the Phase 1b trial had no comparator it was not critiqued in the original EAG report and it has not been included in the CS for this managed access review.

The current CS includes the following clinical evidence:

- Updated clinical evidence from the final analysis of JAVELIN Renal 101 (data cut-off 31 August 2023)
- Data from the SACT database for two cohorts of patients: the cancer drugs fund (CDF) cohort (n=[redacted]) and the Early Access to Medicines Scheme (EAMS) cohort (n=[redacted]).
- Real-world evidence published by Nathan et al.[26 27] for 130 patients who received avelumab with axitinib via an EAMS. This publication is considered by the company to have captured evidence from two other studies[28 29] which report patients from single centres who were included in EAMS.

- Real-world evidence published by McGrane et al.[5] from a retrospective review of 1,319 patients from 17 UK centres who initiated treatment for metastatic RCC. Of these, 168 received avelumab with axitinib.
- An indirect treatment comparison in the form of a network meta-analysis for the subgroup of people with intermediate-/poor-risk aRCC. This enables a comparison between avelumab with axitinib and four of the comparators (cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib and nivolumab + cabozantinib) where there is no head-to-head evidence.

In this report we focus on the updated clinical evidence from the final analysis of JAVELIN Renal 101 (sections 3.2.1 to 3.2.5) and the data from the SACT database (sections 3.2.6 to 3.2.7). Because some or all of the patients whose data contributes to the analyses in Nathan et al. and McGrane et al. may also be included in the SACT database we do not consider these sources in detail.

3.2.1 Updated trial evidence

The final analysis for the JAVELIN Renal 101 RCT was planned for after 368 deaths had occurred in the PD-L1 positive population (CS section B.2.3.1). The company amended the primary outcome to apply to the PD-L1 positive subgroup only (discussed and found to be appropriate in the previous appraisal[25]) and this was the primary analysis for overall survival (OS). The data cut-off for the final analysis was 31 August 2023 when 375 deaths had occurred in this population. Median follow-up in the avelumab with axitinib arm is 73.2 months and in the sunitinib arm 73.0 months (CS Table 6). A participant flow diagram is not provided but participant flow is described in CS section B.2.4.3 and summarised in CS Table 11.

3.2.1.1 Trial characteristics

The JAVELIN Renal 101 RCT was described in the original appraisal (see TA645 ERG report section 4.3.1).[25] A summary of the trial methodology is provided in the current CS, Table 6. As stated in CS Table 6 results are presented for favourable and intermediate-/poor-risk subgroups. The favourable-risk subgroup included 190 participants (avelumab with axitinib arm n=94, sunitinib arm n=96) and thus made up 21.4% of the intention-to-treat (ITT) population. The remainder of the trial population, 691 participants, had intermediate-/poor-risk disease (avelumab with axitinib arm n=343, sunitinib arm n=348).

3.2.1.2 Patients' baseline characteristics

The CS reports participant baseline demographic and clinical characteristics for the Full Analysis Set (FAS; i.e. the overall trial population) and also for the IMDC prognostic risk groups in CS Table 8.

In the overall trial population, the EAG for the original appraisal concluded that patients were generally younger and fitter than those seen in NHS clinical practice (as is usual in clinical trials) and that the proportion of patients who had received a prior nephrectomy may be higher in NHS clinical practice but that this would not impact the results of trial. Additionally, the participant characteristics were generally well balanced between the avelumab with axitinib and the sunitinib arms.

Here we focus on the participant characteristics of the 190 participants in the IMDC favourable disease risk group, used in the company base case. The CS assessed differences between the favourable-risk group and the intermediate-/poor-risk group (CS section B.2.3.3), however we will assess any differences between treatment arms within the favourable-risk group and consider the generalisability of the favourable-risk group to NHS clinical practice.

Characteristics are generally well balanced between treatment arms for the favourable-risk subgroup, except that there were more males in the sunitinib arm ([redacted]) compared to the avelumab with axitinib arm ([redacted]). However, the EAG's clinical expert confirmed that sex is not a prognostic factor for aRCC, therefore we do not find it a concern. The proportion of participants with previous nephrectomy is balanced between the avelumab with axitinib and sunitinib arms and is [redacted] in both arms than in the overall trial population: for avelumab with axitinib the favourable subgroup has [redacted] with a previous nephrectomy compared to 79.6% in the overall trial population; and for sunitinib the favourable subgroup has [redacted] with a previous nephrectomy compared to 80.0% in the overall trial population. Our clinical expert noted that there is a high rate of previous nephrectomy in the favourable-risk group in NHS clinical practice and that the proportion is likely to be somewhere between the proportions observed in the favourable-risk subgroup and the overall trial population ([redacted]%). Therefore, in relation to previous nephrectomy, the favourable-risk subgroup may be similar to the population seen in NHS clinical practice than the overall trial population as noted in the previous appraisal. Characteristics are also generally well-balanced between treatment arms for the intermediate-/poor-risk subgroup.

Data for performance status comes from the ECOG performance status score and this characteristic is balanced across all trial groups.

EAG comment on included studies

Comparative evidence for avelumab with axitinib versus sunitinib comes from the same JAVELIN Renal 101 RCT that informed TA645, but the company now focus on the subgroup of 190 favourable-risk patients in this trial. Median follow-up in the trial has increased to 73 months and data are provided from the final trial analysis.

3.2.2 Risk of bias assessment

The EAG's risk of bias assessment, alongside the company's assessment, is in Appendix 3. We agree with the previous EAG's consideration for the original appraisal (TA645) that the JAVELIN Renal 101 trial was generally well designed and well conducted, and we also agree that the open-label nature design would contribute to bias because "*it provides an opportunity for differential use of second-line therapies, for subjective results and investigator-assessed outcomes to be biased*".[25] At the time of the interim analyses used for the original appraisal, blinded independent central review (BICR) was used to minimise bias in the measurement of progression-free survival (PFS) and objective response rate (ORR) outcomes, however after the second interim analysis BICR was not used, and disease progression was assessed by the investigator only (CS Table 7). We suggest that the evidence from JAVELIN Renal 101 presented in this CS and used in the economic model is at moderate risk of bias due to the open-label study design and use of investigator assessment for PFS. This is important because disease progression (PFS) is used in the economic model. We asked the company to plot PFS by BICR and PFS by investigator on the same graph to aid our understanding about the impact that blinding could have had on this outcome (clarification question A1). The company did not consider it appropriate to provide such a plot but did provide the plots side by side (company response to clarification question A1, Figure 1 and Figure 2). The data in the two plots appear broadly comparable.

3.2.3 Outcomes assessment

3.2.3.1 Efficacy outcome(s)

The company summarise and define the JAVELIN Renal 101 trial outcomes in CS Table 7. As noted in the original TA645 appraisal (EAG report section 4.6) the co-primary efficacy outcomes were PFS and OS in patients with PD-L1 positive tumours but clinical advice was that it was reasonable to consider all patients unselected for PD-L1 expression and the NICE committee was satisfied that it could use the results for the total population in its decision making (TA645 guidance paragraph 3.3). Clinical expert advice to us for this managed access review was that in NHS practice PD-L1 status is not considered when selecting first-

line treatment, nor is it tested for. PFS and OS in patients unselected for PD-L1 expression were secondary endpoints.

CS Table 7 includes all the outcomes listed in the NICE scope except time on treatment although this appears in CS Table 6 but referred to as time to treatment discontinuation (TTD). CS Table 7 also lists some outcomes in addition to those listed in the NICE scope: disease control, time to response and PFS on next-line therapy. Of these only disease control and time to response are reported in the CS.

The efficacy outcomes that contribute data to the economic model are OS and PFS with time to treatment discontinuation used to calculate the costs specific to treatment status.

3.2.3.2 Health-related quality of life (HRQoL) outcomes

The generic EuroQol 5-Dimension 5-Level (EQ-5D-5L) index score and visual analogue scale (VAS) score from JAVELIN Renal 101 (CS Tables 6 and 7) are reported in CS section B.2.6.4 for the whole trial population and not for the IMDC risk subgroups, because subgroup analyses were not pre-specified for the HRQoL outcomes. EQ-5D-5L data from favourable disease risk patients was used in the economic model (CS section B.3.4.1); appropriately mapped to 'UK tariff' EQ-5D-3L values using NICE preferred methods (CS section B.3.4.2).

A validated, disease-specific measure, the Functional Assessment of Cancer Therapy – Kidney Symptom Index – 19 items (FKSI-19, also known as the NFKSI-19)[30] was assessed in the trial (CS Tables 6 and 7), and time to deterioration using the FKSI-DRS subscale was assessed up to IA1 (clarification response A2). The CS does not report any minimum clinically important difference (MCID) for the FKSI-19 as used in the JAVELIN Renal 101 trial. A recent systematic review has shown that MCID thresholds for FKSI-19 used in the published literature are heterogeneous,[31] however, as a guide, the recent CheckMate 214 trial of nivolumab + ipilimumab versus sunitinib for aRCC used an MCID of 3 or more points.[32]

The EQ-5D and the FKSI-19 outcomes were measured every 6 weeks at Day 1 of each Cycle which corresponds to the 'off-treatment' period of sunitinib when those participants would have the lowest symptom burden, acknowledged in the CS (CS section B.2.13.1.1) and published literature.[33] Therefore, there could be bias in favour of the sunitinib arm.

3.2.3.3 Safety outcomes

Adverse events and TTD are used in the economic model. Safety results are also reported for avelumab and axitinib as single agents which is appropriate due to the dose adjustments and temporary discontinuations required to manage these treatments, but only for earlier analyses reported in the confidential company clinical safety report 2018[34] (CS section B.2.11.1.2; clarification response A5). TTD is reported specifically in relation to model inputs and not for clinical effectiveness, for the favourable-risk subgroup (CS section B.3.3.3), the intermediate-/poor-risk subgroup (CS Appendix O.4.1) and the ITT population (CS Appendix O.4.2). Adverse events associated with dose modifications and treatment discontinuation are reported in the CS.

Avelumab was investigated for immunogenicity which is appropriate for a monoclonal antibody treatment. Anti-drug antibody results for avelumab are reported in the clinical study report (CSR) (section 5.5) and immune-related adverse events for all study treatments are reported in the CS (CS section B.2.11.4.1).

EAG comment on outcomes assessment

The EAG has no concerns regarding the efficacy and safety outcomes assessment, though we note the potential for bias in favour of the sunitinib arm in the HRQoL outcomes due to the timing of those assessments.

3.2.4 Statistical methods of the included studies

The EAG for the original appraisal concluded that the statistical approach employed by the company was adequate and appropriate, and we have not identified any new issues for the statistical methods around the overall trial population (full analysis set) in the final analysis. Here we focus on the statistical handling of the IMDC risk subgroups.

Analysis populations: CS section B.2.4.1 describes the analysis sets, with the risk subgroup analysis sets for favourable-risk and intermediate-/poor-risk being relevant to the decision problem (CS Table 9). They were pre-specified subgroups for analysis of the OS and PFS outcomes. As subsets of the Final Analysis Set they include all randomised participants (with the appropriate risk status). Adverse events are reported for the Safety Set, which for JAVELIN Renal 101 is all patients who received $\geq$1 dose of study drug, and this is appropriate because it maximises safety data (CS B.2.11; clarification response A4).

Sample size calculations: the sample sizes of the risk subgroups are a smaller size than the overall trial population, and so the results for the risk subgroup populations are not powered to detect statistical difference between the two treatment arms.

Methods to account for multiplicity: analyses of the risk subgroups had no adjustment for multiplicity (CS sections B.2.5 and B.2.13.2.1).

Analysis of outcomes: subgroup analyses were carried out for OS, PFS, objective response (OR) and duration of response as outlined in the statistical analysis plan (SAP) section 6.4, and subject to the same censoring rules as for the overall trial population. In the SAP the intermediate-risk and poor-risk subgroups are listed separately whereas in the CS results are reported for a combined intermediate-/poor-risk subgroup. Results for the risk subgroups are also reported in the CS for time to response. Standard statistical methods, 2-sided unstratified log-rank test, two Cox regression model for heterogeneity, were applied. Sensitivity analyses were not performed for any subgroups. There were no subgroup analyses for the results of the patient-reported outcomes (PROs), EQ-5D-5 and FKSI-19. Hence results of the PROs are reported for the overall trial population in CS section B.2.6.4 but the economic base case is informed by EQ-5D-5L data for the favourable-risk subgroup (CS section B.3.4.1).

Handling of missing data: data was evaluated as observed, and no imputation method for missing values was used unless otherwise specified (CS Table 10 and confirmed in SAP section 5.3). The study protocol does not mention imputation except for the FKSI multi-item scales (section 9.3.2 page 140), however questionnaire completion rates for both EQ-5D and FKSI were high (CSR section 5.6 and Table 14.5.2.1.1.1). PFS was censored if the event was after two or more missing/inadequate post-baseline tumour assessments with sensitivity analysis for regardless of missing assessment or timing of the event (SAP 6.1.1.1); We did not find data on censoring reasons in the IMDC risk groups but in the full analysis set most reasons for censoring were [redacted] across both arms (CSR Table 14.2.5.3.1) and where there were differences, these were not unexpected (e.g. a [redacted] proportion of participants in the avelumab with axitinib arm were ongoing without an event whereas a [redacted] proportion of the sunitinib arm had started a new anti-cancer therapy). In the full analysis set [redacted]% in each arm were lost to follow up for OS (CSR Table 19).

EAG comment on study statistical methods

The statistical methods in the JAVELIN Renal 101 are appropriate. The decision problem focuses on two of the pre-specified subgroups within the trial due to the way in which the treatment pathway has changed since the original appraisal. The favourable- and intermediate-/poor-risk subgroups were not powered to detect statistical significance. The results for the subgroups are handled according to the trial protocol.

3.2.5 Efficacy results of the intervention studies

For the original TA645 appraisal efficacy data were presented for the full analysis set (FAS) population. Since then, subgroups by IMDC prognostic criteria, favourable-risk or intermediate-/poor-risk, have emerged as key subgroups when determining treatment choice in adults with untreated aRCC. The CS therefore presents results separately for these two subgroups and without selecting for PD-L1 expression status (as noted in section 3.2.3.1, the NICE committee for TA645 heard that clinical experts in the NHS do not measure PD-L1 in aRCC and the committee was satisfied that it could use the results for the total population in its decision making). It should be noted that the trial was not powered to detect statistical significance in IMDC subgroups (see section 3.2.4). A summary of PFS and OS results is also presented for the ITT population. We therefore present the results for the two subgroups by IMDC criteria and the ITT population separately below, focussing on the efficacy outcomes that inform the economic model which are OS and PFS and briefly summarising other outcomes. Data on treatment discontinuation is reported in section 3.2.5.7.2 and time to treatment discontinuation is considered in section 4.2.4.3 of this report.

3.2.5.1 JAVELIN RENAL 101 trial results for the favourable-risk subgroup by IMDC criteria

3.2.5.1.1 Overall Survival

CS Table 14 summarises the overall survival results from the final analysis for participants with favourable-risk disease. For participants in the avelumab with axitinib arm of the trial median OS was 14 months longer than in the sunitinib arm (79.4 months, 95% confidence interval [CI] 59.4, not evaluable [NE] versus 65.5 months, 95% CI 53.4, 78.6 respectively, Table 5). Of the 96 deaths that had occurred, 44 (46.8%) were in the avelumab with axitinib trial arm and 52 (54.2%) were in the sunitinib arm. The stratified hazard ratio was 0.73 (95% CI 0.48 to 1.10, p=0.1290) and the unstratified hazard ratio was 0.78 (95% CI 0.52 to 1.17, p=0.2281), values that correspond to a 27% and 22% reduction in the risk of death respectively for the avelumab with axitinib trial participants. CS Figure 6 displays the Kaplan-Meier plot of OS for the favourable-risk disease subgroup and shows that from 30 months onwards the survival curves for the two trial arms separate and remain separated for the remainder of the follow-up period.

3.2.5.1.2 Progression-free survival

BICR for PFS ended after the primary analysis for PFS (IA2, data cut-off 28 January 2019). Thereafter, PFS was assessed by the investigator and consequently PFS reported from the final analysis in the CS is by investigator assessment (CS Table 15 and CS Figure 7). For

favourable-risk disease participants in the avelumab with axitinib arm of the trial median PFS was 20.7 months (95% CI: 16.6, 26.2) in comparison to 13.8 months (95% CI: 11.1, 23.5) in the sunitinib arm (Table 5). The stratified hazard ratio was 0.75 (95% CI 0.53 to 1.07, p=0.1109). The same hazard ratio was obtained from the unstratified analysis with a similar 95% confidence interval (95% CI 0.54 to 1.04, p=0.0873). The hazard ratios correspond to a 25% reduction in the risk of disease progression or death for the avelumab with axitinib trial participants in comparison to those receiving sunitinib. CS Figure 7 displays the Kaplan-Meier plot of PFS for the favourable-risk disease subgroup which shows that the PFS curves for the two trial arms separate early (at the time of first tumour assessment which we believe to have been 6 weeks after randomisation[35]). Although the curves come close together or actually touch a few times thereafter (e.g. at 8 months and again at 24 months as shown in CS Figure 7) they are fully separated for the majority of the follow-up period.

3.2.5.1.3 Response outcomes

CS table 16 summarises objective response (investigator assessment) which is in favour of avelumab with axitinib. For example, a confirmed best overall response of complete response was observed in 9.6% of the avelumab with axitinib trial arm and 5.2% of the sunitinib arm and an objective response (sum of those with complete response and partial response) was observed in 75.5% and 45.8% in the avelumab with axitinib and sunitinib trial arms respectively. CS section B.2.6.1.4 summarises time to response and duration of response. Time to response was similar in both trial arms and duration of response was numerically in favour of the avelumab with axitinib trial arm by about 3 months.

3.2.5.2 JAVELIN RENAL 101 trial results for the intermediate-/poor-risk subgroup by IMDC criteria

3.2.5.2.1 Overall Survival

Overall survival results from the final analysis for participants with intermediate-/poor-risk disease are summarised in CS Table 17. Median OS was 37.8 months (95% CI 31.2, 42.6) for participants in the avelumab with axitinib arm of the trial and 29.5 months (95% CI 24.8, 36.1) in the sunitinib arm (Table 5). The proportions of deaths that had occurred among participants with intermediate-/poor-risk disease in each trial arm were similar (68.8% of the avelumab with axitinib trial arm and 69.8% of the sunitinib arm). The stratified hazard ratio was 0.90 (95% CI 0.75 to 1.08, p=0.2471) and the unstratified hazard ratio was 0.88 (95% CI 0.74 to 1.06, p=0.1739), values that correspond to a 10% and 12% reduction in the risk of death respectively for the avelumab with axitinib trial participants. CS Figure 8 displays the Kaplan-Meier plot of OS for the intermediate-/poor-risk disease subgroup. The curves

separate at 4 months and remain separate for the rest of the trial period. This is a much earlier separation of the curves than for the favourable-risk population (at 30 months).

3.2.5.2.2 Progression-free survival

As noted above (section 3.2.5.1.2) PFS reported from the final analysis in the CS is by investigator assessment (CS Table 18 and CS Figure 9 for the intermediate-/poor-risk disease subgroup). Participants with intermediate-/poor-risk disease in the avelumab with axitinib arm of the trial had a median PFS of 11.1 months (95% CI: 9.8, 14.6) in comparison to 8.1 months (95% CI: 6.9, 8.4) in the sunitinib arm (Table 5). The stratified hazard ratio was 0.64 (95% CI 0.54 to 0.76, p<0.0001). The same hazard ratio, confidence interval and p-value was obtained from the unstratified analysis. The hazard ratios correspond to a 36% reduction in the risk of disease progression or death for the avelumab with axitinib trial participants in comparison to those receiving sunitinib. CS Figure 9 displays the Kaplan-Meier plot of PFS by investigator assessment for the intermediate-/poor-risk disease subgroup which shows that the curves for the avelumab with axitinib treated patients and the sunitinib treated patients separate early and remain separate over the time period.

3.2.5.2.3 Response outcomes

CS section B.2.6.2.3 reports objective response and CS section B.2.6.2.4 time to response and duration of response. In the intermediate-/poor-risk patients the objective response outcomes from investigator assessment were in favour of the patients who received avelumab with axitinib. Median time to response (confirmed complete or partial response) was was [redacted] months [redacted] median duration of response was longer in the avelumab with axitinib treated patients (19.4 months versus 9.8 months among sunitinib treated intermediate-/poor-risk patients).

3.2.5.3 JAVELIN RENAL 101 trial subsequent treatment in the favourable-risk and intermediate-/poor-risk subgroups by IMDC criteria

In the IMDC favourable-risk subgroup, the proportion of patients in the sunitinib arm receiving a follow-up anticancer treatment was 79.2%, with 64.6% of these receiving a subsequent PD-1 or PD-L1 treatment. In the avelumab with axitinib arm the proportion of favourable-risk patients received a subsequent anticancer treatment was lower (67%) with just 29.8% of these receiving a subsequent PD-1 or PD-L1 treatment. The same pattern was observed among patients with intermediate-risk and poor-risk disease. CS Figure 10 shows subsequent PD-1 or PD-L1 inhibitor treatment in the IMDC risk groups and in the ITT population.

3.2.5.4 JAVELIN RENAL 101 trial results for the ITT trial population

The CS provides a brief summary of overall survival and progression-free survival results in the ITT trial population at the start of CS section B.2.6 which the company has provided for completeness. In current clinical practice, patients are categorised into risk groups for survival using the IMDC prognostic model and the risk group categorisation determines first-line treatment options. Therefore the results presented above, in sections 3.2.5.1 and 3.2.5.2 for the favourable-risk and intermediate-/poor-risk subgroups respectively, are the most relevant to clinical practice. We note that both PFS (by BICR assessment and by investigator assessment) and OS in the ITT population were secondary outcomes, the primary outcomes for the trial were PFS (by BICR assessment) and OS in patients with PD-L1-postive tumours (see section 3.2.5.6.2).

Table 5 summarises the PFS and OS outcomes for the ITT population alongside those of the favourable-risk and intermediate-/poor-risk subgroups. As previously noted, the majority of participants had intermediate-/poor-risk aRCC, only 21.4% had favourable-risk disease. Consequently, the PFS and OS results for the ITT population are most aligned with those of the intermediate-poor-risk subgroup. Median OS was longest (79.4 months and 65.5 months in the avelumab with axitinib and sunitinib arms respectively) and the reduction in the risk of death was greatest in the favourable-risk subgroup (27% from stratified hazard ratio). However, the favourable-risk subgroup PFS and OS confidence intervals are wider than the ITT and intermediate-/poor-risk subgroup confidence intervals which reflects the small size of the favourable-risk subgroup and the greater uncertainty around the central estimates of PFS and OS in this subgroup.

Table 5 Summary of PFS (by investigator assessment) and OS results in the ITT population, favourable-risk and intermediate-/poor-risk subgroups. Final analysis (DCO 31 August 2023)

	ITT population		Favourable-risk subgroup		Intermediate-/poor-risk subgroup	
	Avelumab + axitinib (n=442)	Sunitinib (n=444)	Avelumab + axitinib (n=94)	Sunitinib (n=96)	Avelumab + axitinib (n=343)	Sunitinib (n=348)
PFS						
Median follow up, months (95% CI)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Median PFS, months (95% CI)	13.9 (11.1, 16.6)	8.5 (8.2, 9.7)	20.7 (16.6, 26.2)	13.8 (11.1, 23.5)	11.1 (9.8, 14.6)	8.1 (6.9, 8.4)
HR (95% CI), 1 sided p-value	0.66 (0.565, 0.768) <0.0001		0.75 (0.53, 1.07) 0.1109		0.64 (0.54, 0.76) <0.0001	
OS						
Median follow up, months (95% CI)	73.7 (72.3, 74.6)	73.6 (72.0, 75.5)	Not reported	Not reported	Not reported	Not reported
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	44.8 (39.7, 51.1)	38.9 (31.4, 45.2)	79.4 (59.4, NE)	65.5 (53.4, 78.6)	37.8 (31.2, 42.6)	29.5 (24.8, 36.1)
HR (95% CI), 1 sided p-value	0.88 (0.749, 1.039) 0.0669		0.73 (0.48, 1.10)[a] 0.1290		0.90 (0.75, 1.08)[a] 0.2471	

Source: CS Tables 13, 14, 15, 17 and 18
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NE, not evaluable; OS, overall survival. PFS, progression-free survival
[a] Stratified hazard ratio

3.2.5.5 HRQoL outcomes

3.2.5.5.1 EQ-5D-5L score change from baseline

We agree that the EQ-5D-5L index scores were "*relatively stable over time*" for both treatment arms (CS section B.2.6.4.1). CS Figure 11 shows the sunitinib arm started with a slightly higher baseline score and generally maintained a higher score than the avelumab with axitinib arm; and both arms' scores decreased approaching the end of treatment. The confidence intervals for the scores of the treatment arms frequently overlap indicating uncertainty in any difference between the two arms. Additionally, the assessment schedule potentially favours the sunitinib arm as they were assessed at the point of lowest symptom burden (see section 3.2.3.2 above) so the results may not reliably reflect EQ-5D-5L at other points in the sunitinib treatment schedule.

CS Figure 12 shows that both treatment arms started the trial with almost identical EQ-5D-5L VAS scores and made small score increases for the duration of the trial. However, the mean scores for change from baseline, -5.0 for avelumab with axitinib and -4.3 for sunitinib, are not described as clinically meaningful, and there is little difference between the two treatment arms as the line plots frequently cross and the confidence intervals of the treatment groups consistently overlap up to the end of treatment.

3.2.5.5.2 FKSI-19 score change from baseline

CS Figure 13 shows that both treatment arms started the trial with almost identical FKSI-19 total scores, and that up to Cycle 21 there were small differences between the treatment groups but the plot lines frequently cross and the confidence intervals frequently overlap showing no significant differences between groups. After Cycle 21, up to Cycle 32 just before the end of the trial, the sunitinib group shows a slightly greater increase in score (i.e. better HRQoL) than the avelumab with axitinib group and the degree of overlap in the confidence intervals for the two groups reduces. The sunitinib group was assessed at the point of lowest symptom burden in a treatment cycle (week 6 being the off-treatment period) but this was the case throughout the trial, not just after Cycle 21, so the reason for this apparent slight increase in sunitinib HRQoL is unclear. However, sunitinib's apparent better performance in FKSI-19 results is not clinically meaningful, as the MCID should be about a 3-point difference (see section 3.2.3.2 above).

The results for the prespecified PROs do not show any clear or meaningful difference between treatments and may be biased in favour of sunitinib due to the assessment scheduling.

3.2.5.5.3 Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST)

Results for the post-hoc Q-TWiST analysis are reported in CS Appendix M.2 and are supportive of a 3.20-month gain in quality-adjusted time without symptoms or toxicity for avelumab with axitinib compared to sunitinib. The CS states this is a 10.9% relative improvement, thus achieving an established 10% MCID.[36] The company have not explained the reason for this post-hoc analysis.

3.2.5.6 Subgroup analyses

Subgroups specified in the NICE scope and company decision problem are the IMDC favourable-risk subgroup, the IMDC intermediate-/poor-risk subgroup and PD-L1 status (CS Table 1). Subgroup analyses in JAVELIN Renal 101 were pre-specified for the OS, PFS, OR and duration of response outcomes.

Subgroup analyses were not planned for the EQ-5D-5L, FKSI-19 and FKSI-DRS outcomes according to the study SAP, however, the Nolla et al. 2023 publication[33] refers to PRO results according to risk subgroups albeit for an earlier data cut-off. The authors note that the poor risk disease category had significantly better FKSI-19, FKSI-DRS, and EQ-5D VAS scores for avelumab with axitinib treated patients compared to those treated with sunitinib, however the effect sizes were considered too small to be conclusive, [33] and the poor-risk subgroup alone is not a subgroup of interest in the NICE scope. We do not believe that any (post-hoc) subgroup analyses of PROs for the final analysis would add anything meaningful mainly due to assessment scheduling.

3.2.5.6.1 IMDC risk status

The IMDC risk subgroups were among the prespecified trial subgroups in JAVELIN Renal 101 for further analysis of OS, PFS and OR outcomes. These results for the IMDC risk subgroups have been discussed in sections 3.2.5.1 and 3.2.5.2 above and the time to treatment discontinuation results by subgroup inform the economic model (section 4.2.4.3).

3.2.5.6.2 PD-L1 status

PD-L1 status was originally a pre-specified subgroup in the JAVELIN Renal 101 trial and a data-driven protocol amendment made the PD-L1 positive subgroup the subject of the co-primary outcomes, discussed in the previous appraisal's EAG report section 4.5.[25] Results for the subgroup of patients with PD-L1 positive tumours, subdivided by IMDC favourable- and intermediate-/poor-risk status, are reported in CS Table 20 and are described by the company as "*generally similar*" to the ITT population in both IMDC risk groups (CS section B.2.7).

Overall survival. In the favourable-risk subgroup, participants with PD-L1 positive tumours had a [redacted]% reduction in risk of death for avelumab with axitinib compared to sunitinib (stratified analysis, CS Table 14) which was [redacted] than the 27% risk reduction reported for the favourable-risk subgroup overall (CS Table 20). Median OS was [redacted] in the PD-L1 positive subgroup of favourable-risk participants for both the avelumab with axitinib and sunitinib arms: in the avelumab with axitinib arm the PD-L1 positive subgroup median OS was [redacted] (95% CI [redacted]) months, compared to 79.4 months (95% CI 59.4 – not estimable) in the favourable-risk subgroup overall in the sunitinib arm the PD-L1 positive subgroup median OS was [redacted] months (95% CI [redacted]) compared to 65.5 months (95% CI 53.4 – 78.6) in the favourable-risk subgroup overall (CS Tables 14 and 20 respectively). Results for the PD-L1 positive patients in the intermediate-/poor-risk subgroup were very similar to the results for the intermediate-/poor-risk as a whole (CS Tables 17 and 20).

Progression free survival. In the favourable-risk subgroup for participants with PD-L1 positive tumours there was a [redacted] reduction of risk of progression or death for avelumab with axitinib compared to sunitinib ([redacted]%, CS Table 20) in comparison to the total subgroup of participants with favourable-risk disease (25% risk reduction, (CS Table 15). In both trial arms, median PFS was slightly shorter in the PD-L1 positive subgroup than in the overall subgroup of favourable-risk participants: in the avelumab with axitinib arm [redacted] months (95% CI [redacted]) compared to 20.7 months (95% CI 16.6- 26.2) for all favourable-risk participants; in the sunitinib arm [redacted] months (95% CI [redacted]) compared to 13.8 months (95% CI 11.1 to 23.5) for all favourable-risk participants (CS Tables 15 and 20). In the intermediate-/poor-risk subgroup avelumab with axitinib treatment in comparison to sunitinib treatment led to a [redacted] reduction of risk of progression or death for participants with PD-L1 positive tumours than for the intermediate-/poor-risk subgroup as a whole: [redacted]% risk reduction (CS Table 20) compared to a 36% risk reduction (CS Table 18). Median PFS for the PD-L1 positive subgroup was similar to the intermediate-/poor-risk subgroup as a whole (CS Tables 18 and 20).

Objective response. In the favourable-risk subgroup patients with PD-L1 positive status do marginally better than the favourable-risk subgroup as a whole receiving avelumab with axitinib, but results are mostly similar (CS Tables 16 and 20). A similar pattern was observed in the intermediate-/poor-risk subgroup patients (CS Tables 19 and 20).

3.2.5.6.3 Other JAVELIN Renal 101 pre-specified subgroup analyses

Further pre-specified subgroup analyses were undertaken within the JAVELIN Renal 101 trial as described in the CS and EAG report for the previous appraisal of this topic (TA645[1]

[37]). Results for these subgroups are not reported in the CS but they are available for the outcome of overall survival in the CSR[38] The result for most of the subgroups is consistent with the overall survival for the full trial population (i.e. all participants regardless of disease risk category) being numerically in favour of avelumab with axitinib but with confidence intervals that cross 1.0. Confidence intervals do not cross 1.0 for the Heng (IMDC) poor risk subgroup, the Caucasian/White race subgroup and the male gender subgroup, (CSR Figure 14.2.3.1.5[38]). With the exception of the PD-L1 subgroup, the study was not powered to detect treatment effects in subgroups and the results should be interpreted cautiously.

3.2.5.7 Safety outcomes

The company report safety outcomes from the final analysis of JAVELIN Renal 101, and for completeness, they additionally provide a confidential summary of clinical safety report of pooled safety results from an earlier interim analysis of JAVELIN Renal 101, JAVELIN Renal 100, and two other clinical studies of monotherapy avelumab and axitinib.[34] We focus on the evidence from the final analysis of JAVELIN Renal 101 because it has a comparator arm and is the most up-to-date.

Results are reported for the safety set which is for the overall trial population, not according to IMDC risk subgroup, as this provides the most comprehensive information. An overarching summary for the on-treatment period is provided in CS Table 31.

The extent of exposure to each study drug is reported in section 4.6 of the CSR: avelumab was [redacted] weeks, axitinib was [redacted] weeks, and sunitinib was [redacted] weeks.[38] The extent of exposure to avelumab and axitinib is [redacted] as the extent of exposure to sunitinib. Similar to the EAG opinion in the previous appraisal (TA645 EAG report 4.9.1[25]), this reflects the improved PFS for patients receiving avelumab with axitinib versus sunitinib and the increase in follow-up time since TA645 when the difference in extent of exposure was described as marginally longer for avelumab with axitinib.

3.2.5.7.1 Adverse events

Treatment-emergent adverse events: The most common treatment-emergent adverse events (TEAEs) are summarised in CS Table 32. In the avelumab with axitinib arm the most common TEAEs were diarrhoea [redacted], hypertension ([redacted]), fatigue ([redacted] and nausea ([redacted] These were the most common TEAEs in the sunitinib arm too, though experienced by a smaller proportion of participants than in the avelumab with axitinib arm, at [redacted] respectively. The most common Grade $\geq$3 TEAE was hypertension for both study arms: [redacted] for avelumab with axitinib and [redacted] for sunitinib. This is consistent with earlier analyses.

Treatment-related TEAEs: The most common treatment-related TEAEs are reported in CS Table 33 and similarly show that diarrhoea and hypertension are the most common for both arms, with higher frequency in the avelumab with axitinib arm. The comparison made in CS section B.2.11.1.2 between avelumab with axitinib as a combination therapy and each agent as a monotherapy is between the JAVELIN Renal 101 final analysis and the two clinical trials of avelumab and axitinib as monotherapies that were included in the aforementioned company confidential summary of clinical safety report.[34] It shows that diarrhoea, hypertension, hypothyroidism and increased alanine aminotransferase were all reported at higher frequencies for the avelumab with axitinib combination than for either single agent alone, though these are all known adverse events for these treatments.

Serious TEAEs: More patients reported serious TEAEs in the avelumab with axitinib arm ([redacted]%) than in the sunitinib arm ([redacted]%) (CS Table 35). The most common serious TEAEs differed between treatment arms: in the avelumab with axitinib arm they were diarrhoea ([redacted]), acute myocardial infarction ([redacted]), disease progression ([redacted]) and acute kidney injury ([redacted]), whereas in the sunitinib arm they were abdominal pain ([redacted]), anaemia ([redacted]) and acute kidney injury ([redacted]) (CS Table 35). There were no serious treatment-related TEAEs reported for ≥2% of patients in either treatment arm (CS section B.2.11.2.2).

Deaths: During the trial, [redacted]) of patients in the avelumab with axitinib arm and [redacted]) of patients in the sunitinib arm died. The most common cause of death was disease progression for both arms, [redacted]) in the avelumab with axitinib arm and [redacted]) in the sunitinib arm (CS section B.2.11.2.1). Similarly, the most common TEAE leading to death was disease progression: [redacted]) in the avelumab with axitinib arm and [redacted]) in the sunitinib arm (CS Appendix Table 38).

Adverse events of special interest: The EAG for the previous appraisal noted areas of uncertainty around potential cardiovascular adverse events associated with VEGF TKIs (here, axitinib and sunitinib) and risk of myocarditis associated with avelumab and other checkpoint inhibitors, and immune-related adverse events associated with the mechanism of action of avelumab.[25] These, and infusion-related adverse events relating only to avelumab due to method of administration, are of special interest and are reported in CS section B.2.11.4.

Cardiac disorders were reported for [redacted]% of patients in the avelumab with axitinib arm compared to [redacted]% of patients in the sunitinib arm, of which [redacted]% and [redacted]% of events respectively were Grade ≥3 (CS section B.2.11.4.3). Additionally, cardiac-related adverse events were reported for decreased ejection fraction, increased troponin T, and increased

myocardial necrosis marker: these events were [redacted] in the avelumab with axitinib arm (CS section B.2.11.4.3). As mentioned above, acute myocardial infarction was the second most common serious TEAE in the avelumab with axitinib arm ([redacted]), [redacted] Grade ≥3, compared to [redacted] in the sunitinib arm. Cardiac-related adverse events are not reported as leading to dose interruption, dose reduction or discontinuation of any study drug (CS section B.2.11.3). There were [redacted] deaths due to cardiac disorders in the avelumab with axitinib arm compared to [redacted] in the sunitinib arm (CS Appendix Table 38).

Immune-related adverse events were reported for 50.7% of patients in the avelumab with axitinib arm compared to 4.8% of patients in the sunitinib arm reflecting avelumab's mechanism of action; 14.7% and 0.2% respectively were Grade ≥3 events (CS section B.2.11.4.1). Thyroid disorders were the most common immune-related adverse events ([redacted]%) in the avelumab with axitinib arm (CS section B.2.11.4.1). No immune-related adverse events were reported as leading to death (CS Appendix Table 38) or to changes in treatment (CS section B.2.11.3).

CS section B.2.11.4.2 and CS Table 31 report that infusion-related reactions were experienced by [redacted]% of participants. CS Table 32 reports TEAEs which included 57 (13.1%) infusion-related reactions of all grades of which [redacted]% were Grade ≥3 infusion-related reactions. It is not clear to us why the proportion of patients with infusion-related reactions differs between CS Table 31 and CS Table 32. Treatment-related infusion-related reactions at any grade in ≥10% of participants were reported in 12.9% of patients, and Grade ≥3 infusion-related reactions in ≥5 participants were reported for 1.6% of patients (CS Table 33).

Final summary: The safety results from the final analysis show no new concerns and they are consistent with previous analyses. The additional evidence from greater extent of exposure may provide more certainty around cardiovascular and immune-related adverse events which do not appear to affect dose changes or treatment discontinuation. Cardiac events have led to death, but the numbers of events are low and the proportions are low and similar in both arms.

3.2.5.7.2 Treatment discontinuation

The proportions of patients with permanent discontinuations due to adverse events are similar for both study arms: discontinuing either avelumab or axitinib (34.3%) compared to sunitinib (17.5%), and discontinuing both avelumab and axitinib (13.1%) compared to sunitinib (17.5%) (CS section B.2.11.3.1).

Time to treatment discontinuation is used in the economic model (CS Table 6; CS section B.3.3.3) and was derived from the JAVELIN Renal 101 trial data. The CS does not report time to treatment discontinuation in the clinical effectiveness or safety results sections of the CS.

3.2.6 Real-world evidence on avelumab with sunitinib

In this section our principal focus is on data from the SACT database because, as noted above (section 3.2) and confirmed in clarification response A6, some or all of the patients whose data contributes to the analyses in Nathan et al.[26 39 40] and McGrane et al. [5] may also be included in the SACT cohort. McGrane et al.[5] is considered in section 3.2.8 because data from this source provides information for real-world outcomes from TKIs as first-line therapy for aRCC as well as real-world outcomes following IO+TKI combination treatment.

3.2.6.1 Overview of the SACT dataset

The National Disease Registration Service (NDRS) collected SACT data for [redacted] unique patients who received avelumab with axitinib within the CDF and an additional [redacted] patients who received avelumab with axitinib within the EAMS. Of these patients, [redacted]% of the CDF cohort and [redacted]% of the EAMS cohort were identified has having completed treatment. The median treatment duration was [redacted] months (95% CI [redacted]) for all patients in the CDF cohort and [redacted] months (95% CI [redacted]) for all patients in the EAMS cohort. The median follow-up times for the CDF and EAMS cohorts (measured from initiation of treatment to last treatment data in the SACT dataset plus the length of prescription) were [redacted]months and [redacted] months respectively.

3.2.6.2 Characteristics of patients in the SACT dataset

The baseline demographics and clinical characteristics of patients in the SACT dataset are provided side-by side for the CDF and EAMS cohorts in CS Table 22. In the CDF cohort the proportion of patients with favourable-risk aRCC was [redacted] than in the JAVELIN Renal 101 trial and [redacted] than the estimate by Esterberg et al.[41] cited by the company in section CS B.1.3.2 on epidemiology of kidney cancer ([redacted]% in the CDF cohort versus 21% in the FAS for the overall JAVELIN Renal 101 trial and 16% estimated by Esterberg et al.[41]. Data on IMDC risk group status was not recorded in the EAMS cohort. In comparison to the JAVELIN Renal 101 RCT, the median age of the patients in the SACT dataset is [redacted] (median [redacted] years in the CDF cohort which makes up 89% of the SACT dataset and [redacted] in the EAMS cohort in comparison to 62 years and 61 years in the avelumab with axitinib and sunitinib FAS trial arms respectively) and a [redacted] proportion had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 at treatment initiation than was observed for

the JAVELIN Renal 101 trial arms at baseline ([redacted]% in the CDF cohort and [redacted]% in the EAMS cohort in comparison to [redacted]% and [redacted]% in the avelumab with axitinib and sunitinib FAS trial arms respectively). The ECOG PS status of the patients in the SACT dataset suggest that they would likely have a poorer prognosis than participants in the JAVELIN Renal 101 trial. Our clinical expert confirmed that fitter patients (i.e. ECOG PS of 0) tolerate treatment side-effects better so therefore have a lower dose reduction or treatment cessation rate and consequently achieve better response rates. They also noted that patients with ECOG PS of 0 are not clinically affected by their metastatic disease, suggesting that either their disease is being treated more promptly or is having less physiological effect than in those patients who have a PS greater than 0.

It was an inclusion criterion for the JAVELIN Renal 101 trial that participants had aRCC with a clear cell component whereas this restriction on histological subtype did not apply to the SACT dataset. Therefore [redacted]% of the CDF cohort had RCC with a clear cell component and the remaining patients either had unclassified RCC ([redacted]%) or RCC of another histological subtype, [redacted] papillary RCC ([redacted]%) or chromophobe RCC ([redacted]%) with a further four histological subtypes recorded in CS Table 22. The histological subtype was not recorded for [redacted] ([redacted]%) of the CDF cohort and [redacted] for the EAMS cohort.

3.2.7 Results from the SACT dataset

3.2.7.1 Overall survival in the SACT dataset

Overall survival results for the SACT dataset are presented in CS section B.2.8.2.2 and summarised below in Table 6.

Table 6 Summary of overall survival results in the CDF and EAMS cohorts in comparison to the JAVELIN Renal 101 avelumab with axitinib trial arm.

	CDF cohort (n=[redacted])	EAMS cohort (n=[redacted])	JAVELIN Renal 101 Avelumab + axitinib (n=442)
Median follow-up time	[redacted] months [redacted]	[redacted] months [redacted]	73.7 months (95% CI 72.3, 74.6)
Maximum follow-up period for survival	[redacted] months	[redacted] months	Not reported
Number of deaths [a]	[redacted] [b]	[redacted] [b]	[redacted]

	CDF cohort (n=[redacted])	EAMS cohort (n=[redacted])	JAVELIN Renal 101 Avelumab + axitinib (n=442)
Median OS (95% CI)	[redacted] months (95% CI [redacted])	[redacted] months (95% CI [redacted])	44.8 months (39.7, 51.1)
Clear-cell histology subgroup, Median OS	[redacted] months (95% CI [redacted]) [n=[redacted]]	RCC histology not recorded	
Non clear-cell histology subgroup, Median OS	[redacted] months (95% CI [redacted]) [[redacted]][c]		Non clear-cell aRCC excluded from trial.
Favourable-risk subgroup OS (95% CI)	[redacted]	IMDC risk group status not recorded	79.4 months (59.4, NE) [n=94]
Intermediate-risk subgroup OS (95% CI)	[redacted]		37.8 months (31.2, 42.6) [n=343]
Poor-risk subgroup OS (95% CI)	[redacted]		

Source: EAG Table compiled from data presented in CS section B.2.8.2.2, CS Table 13, CS Table 14, CS Table 17 and the source reference for the SACT data.[4]
aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; CI, confidence interval; EAMS, Early Access to Medicines Scheme; IMDC, International Metastatic RCC Database Consortium; NE, not evaluable; OS, overall survival; RCC, renal cell carcinoma
[a] For the total population (i.e. all risk groups combined). In the CDF and EAMS cohorts this was at the end of follow-up period (2nd July 2024) for the JAVELIN Renal 101 trial this was at final analysis.
[b] Percentage calculated by EAG
[c] n calculated by EAG

3.2.7.1.1 People with clear cell aRCC

As the JAVELIN Renal 101 trial only included participants with clear cell aRCC the analogous real-world evidence is the clear-cell histology subgroup in the CDF cohort (n=[redacted]). This subgroup had a median overall survival of [redacted] months (95% CI [redacted]) which is [redacted] than the 44.8 months (95% CI 39.7, 51.1) median survival observed in the avelumab with axitinib arm of the JAVELIN Renal 101 trial. We do not know the IMDC risk group profile for the clear-cell histology subgroup in the CDF cohort but we know that across all the patients in CDF cohort the proportion with favourable-risk aRCC was [redacted] than in the JAVELIN Renal 101 trial as noted above (section 3.2.6.2). Histology subgroups were not reported for the EAMS cohort but median survival was [redacted] than in the avelumab with

axitinib arm of the JAVELIN Renal 101 trial ([redacted] months versus 44.8 months). OS was longer in the EAMS cohort over time and the NHS England SACT report states that the difference was statistically significant at 18, 24 and 36 months (CS Table 23). The company do not comment on possible reasons for this, but we note from CS Table 22 that the EAMS cohort was [redacted] and a [redacted] proportion had ECOG PS 0 at treatment initiation.

3.2.7.1.2 People with non-clear cell aRCC

As stated in section 2.1 one of the key areas of clinical uncertainty identified by the appraisal committee during TA645 and listed in the managed access agreement was the lack of data on whether the treatment is effective for non-clear-cell disease. Patients with non-clear cell disease made up approximately [redacted]% of the SACT dataset. The median OS among these patients was [redacted] months (95% CI: [redacted]). This [redacted] OS was statistically significantly different to that of the patients with clear-cell disease (Figure 2).

Figure 2 Kaplan-Meier survival plot by RCC histology in the CDF cohort (N=1,294)

Source: Reproduction of Figure 9 from the NHS England report[4]
CDF, Cancer Drugs Fund; RCC, renal cell carcinoma

3.2.7.1.3 Subgroups by IMDC risk category

When considering overall survival for subgroups by IMDC risk category, median overall survival was [redacted] for the favourable-risk category subgroup in the CDF cohort. Overall survival for both the intermediate-risk and poor-risk category subgroups from the CDF cohort were [redacted] than in the combined intermediate-/poor-risk category subgroup for the avelumab with axitinib arm of the JAVELIN Renal 101 trial. The source reference for the CDF data[4] presents Kaplan-Meier plots by IMDC factor and we reproduce this below in Figure 3. The SACT dataset does not provide evidence for overall survival for patients who receive sunitinib so this source does not provide an estimate for the treatment difference between avelumab with axitinib and sunitinib in real world NHS practice.

Figure 3 Kaplan-Meier survival plot by IMDC factor for the CDF cohort (n=1,294)

Source: Reproduction of Figure 8 from the NHS England report[4]
IMDC, International Metastatic RCC Database Consortium

3.2.7.2 Treatment duration

The company presents results on treatment duration for the CDF and EAMS cohorts in CS section B.2.8.2.3 and the results are summarised in Table 7. There were statistically

significant differences in treatment duration [redacted] and [redacted] and treatment duration was longer in the EAMS cohort than in the CDF cohort with the differences at 24 and 36 months being statistically significant (CS Table 24).

Table 7 Treatment duration in the CDF and EAMS cohorts

	CDF cohort (n=[redacted])	EAMS cohort (n=[redacted])
Completed treatment by 29 February 2024	[redacted]	[redacted]
Median follow-up time[a]	[redacted]	[redacted]
Median treatment duration	[redacted]	[redacted]
Clear-cell histology subgroup, median treatment duration	[redacted]	RCC histology not recorded
Non clear-cell histology subgroup, median treatment duration	[redacted]	
Favourable-risk subgroup median treatment duration (95% CI)	[redacted]	IMDC risk group status not recorded
Intermediate-risk subgroup median treatment duration (95% CI)	[redacted]	
Poor-risk subgroup median treatment duration(95% CI)	[redacted]	

Source: Compiled by EAG from data presented in CS section B.2.8.2.3.
CDF, Cancer Drugs Fund; CI, confidence interval; EAMS, Early Access to Medicines Scheme; IMDC, International Metastatic RCC Database Consortium; RCC, renal cell carcinoma.
[a] Median observed time from initiation of treatment to last treatment date in the SACT dataset plus the length of prescription.

3.2.8 Real-world evidence on TKIs as first-line therapy

The SACT dataset provides evidence on the real-world effectiveness of avelumab with axitinib as a first-line therapy for aRCC but it does not provide any data for patients who receive sunitinib or other TKI therapies first-line. We therefore looked to the analyses by two of the other real-world evidence sources identified by the company, Nathan et al. 2024[26 27] and McGrane et al. 2024,[5]. Nathan et. al 2024[26 27] only reports on aRCC patients who received avelumab with axitinib via the EAMS at 10 UK sites. McGrane et al. 2024[5] retrospectively reviewed patients from 17 UK NHS trusts who started systemic anti-cancer therapy for first-line metastatic RCC between 01 January 2018 and 30 June 2021, including an analysis of data from patients in the IMDC favourable-risk group. We focus on the favourable-risk patients here because the company's focus in the CS is the favourable-risk subgroup.

McGrane et al. 2024[5] included 1,286 patients in their analysis (a total of 1,319 met the inclusion criteria but the 33 patients who received treatments described as Misc/Other were

omitted from the analysis). Patient demographics and clinical characteristics at baseline for the whole cohort, 294 of whom had favourable-risk disease, are shown in CS Table 29. First-line treatments were grouped by drug class. In the IO+TKI group there were 66 patients with favourable-risk disease and 95.5% received avelumab with axitinib. Patients with favourable-risk disease in the TKI group (n=206) received sunitinib (50.5%), pazopanib (31.6%) or tivozanib (15%) with only 2.9% receiving cabozantinib. As shown earlier in Figure 1 patients with favourable-risk disease are not eligible to receive cabozantinib as a first-line therapy. We report outcomes from McGrane et al. 2024[5] in Table 8. For both progression-free survival and overall survival McGrane et al.[5] report that a log-rank test suggested a statistically significant difference between the IO+TKI and TKI groups with IO+TKI therapy delaying the time to death or progression (hazard ratio (HR) =0.60, 95% CI 0.39, 0.91) and delaying the time to death (HR=0.42, 95% CI 0.18, 0.99) versus TKI therapy. Despite the limitations of this real-world study which is based on retrospective data collection, it does provide data from UK NHS centres showing an overall survival benefit for favourable-risk patients receiving IO/TKI (predominantly avelumab with axitinib) in comparison to favourable-risk patients who received a TKI (predominantly either sunitinib, pazopanib or tivozanib). However, these difference in outcome may have been due to factors other than the first-line treatment received because the patients receiving different treatment types may have differed in one or more characteristics that could affect outcomes.

Table 8 Summary of PFS and OS results in real-world favourable-risk patients

	McGrane real-world evidence[5] Favourable-risk patients	
	IO+TKI (n=66), avelumab+axitinib (95.5%)	**TKI (n=206), sunitinib (50.5%), pazopanib (31.6%), tivozanib (15%) or cabozantinib (2.9%)[a]**
PFS		
Median PFS, months (95% CI)	25 months (95% CI not reported)	14.6 months (95% CI 34.4 months, NE)
HR (95% CI)	0.60 (95% CI 0.39, 0.91)	
OS		
Median OS, months (95% CI)	Not reached	41.1 months (95% CI 34.4 months, NE)
HR (95% CI)	0.42 (95% CI 0.18 to 0.99)	

Source: CS section B.2.8.4 and McGrane et al.[5]
CI, confidence interval; HR, hazard ratio; IO, immunotherapy; NE, not evaluable; OS, overall survival. PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a] As per Figure 1 favourable-risk patients are not eligible to receive cabozantinib as a first-line treatment.

3.2.9 Pairwise meta-analysis of intervention studies

Pairwise meta-analysis was not conducted because the JAVELIN Renal 101 trial is the only trial included in the CS that directly evaluates avelumab with axitinib with a relevant comparative treatment option.

3.3 Critique of studies included in the indirect comparison

3.3.1 Rationale for ITC

There are no head-to-head trials comparing avelumab with axitinib to treatment options other than sunitinib, and as noted in Table 4 treatment choice in adults with untreated aRCC is now determined by considering IMDC risk category alongside individual patient characteristics. The range of comparator treatments available differs according to the population being considered: ITT population, favourable-risk subgroup or intermediate-/poor-risk subgroup.

For the ITT population and favourable-risk subgroup the relevant comparators for decision-making are the single-agent TKIs (sunitinib, pazopanib and tivozanib). In previous NICE appraisals it has been considered reasonable to assume that sunitinib and pazopanib have broadly equivalent efficacy and that tivozanib may have a similar effect to sunitinib or pazopanib.[1 12-14 16 17 42] Therefore, the relative effects from the JAVELIN Renal 101 trial, where the comparator is sunitinib, are taken to represent the effects that would be obtained if pazopanib and tivozanib were the comparators. Consequently, an ITC is not necessary for the ITT or favourable-risk populations.

For the subgroup of people with intermediate-/poor-risk aRCC the comparators include the three single-agent TKIs listed above and four additional options: cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib and nivolumab + cabozantinib. There is no head-to-head evidence comparing avelumab with axitinib with these four additional comparators so the company have conducted an ITC in the form of a network meta-analysis (NMA) to enable a comparison for the intermediate-/poor-risk subgroup.

As already noted, the company's focus in their submission is the favourable-risk subgroup; consequently we have taken a light-touch approach to our critique of the company's NMA for the intermediate-/poor-risk subgroup.

3.3.2 Identification, selection and feasibility assessment of studies for NMA

The company identified evidence from the most recent update of their clinical SLR (originally conducted in 2018 to inform TA645) which is described in CS Appendix D and critiqued by us in section 3.1.1. Five studies were identified that included data for the intermediate-/poor-risk subgroup for two or more treatments relevant to this appraisal. One of these is the JAVELIN Renal 101 trial. All the studies are listed in CS Table 30. The company were able to construct a network connecting the five trials though sunitinib which was a common comparator between them. The company's network diagram is provided in CS Figure 15. The company focussed on the PFS and OS outcomes as these were the key clinical outcomes used to inform the economic model and these outcomes were available for each trial. As the company point out in CS B.2.10.6 the evidence comes from a subgroup of patients in each trial and it is therefore likely to be more uncertain, particularly as the RCTs were not powered for subgroup analyses.

The company also assessed the Kaplan-Meier estimates for OS and PFS from each study to see if the proportional hazards assumption held. These assessments are provided in CS Appendix N. The company concluded that for the purpose of estimating relative effects to use in the economic model the proportional hazards assumption was reasonable. We note that in the NICE appraisal for lenvatinib with pembrolizumab (TA858)[16] the committee concluded that the proportional hazards approach could be used for decision-making even though they agreed with the EAG that the proportional hazards assumption was violated for PFS in the intermediate-/poor-risk subgroup. The committee agreed that results should be interpreted cautiously and they took the uncertainty into consideration.

3.3.3 Clinical heterogeneity assessment

The company do not discuss treatment effect modifiers that could influence the relative treatment effects. As part of clarification question A9 we asked the company to provide further information on the baseline characteristics for the participants from the studies that were included for the intermediate-/poor-risk subgroup. The company provided this (Table 3 in the company response to clarification questions) but it is only possible to compare median age, gender, prior nephrectomy and disease-risk status across four of the five trials because for other characteristics there are missing data for one or more for the trials and no baseline characteristics were available for the CLEAR trial. The company raise the heterogeneity of

the studies in CS section B.2.10.6 where they discuss the limitations and uncertainties in the ITC and indicate that there is some uncertainty about the heterogeneity of the studies because data were not available for all studies to enable comparisons of characteristics, particularly for the intermediate-/poor-risk subgroup. However, the company also state that the design and patient baseline characteristics of the studies are generally similar. We agree that this is likely to be the case.

3.3.4 Similarity of treatment effects and consistency in the network

None of the connections in the network included data from more than one study and there were no loops in the network. Therefore, similarity of treatment effects and consistency could not be investigated.

3.3.5 Risk of bias assessment for studies included in the NMA

The company did not provide risk of bias assessments in the CS for the five trials included in the NMA. We requested these (Clarification question A9) and in the response the company provided their assessments, but these had not all been done using the same tool because of the time period over which the company had conducted their original SLR and then updated this. For three trials (CABOSUN, CheckMate 214 and JAVELIN renal 101) the NICE checklist was used, for the remaining two trials (CLEAR and CheckMate 9ER) the response to clarification question A9 Table 5 states that the assessment has used the Cochrane ROB 2.0 checklist. However, when used correctly, the ROB 2.0 checklist should provide risk of bias judgements of 'low', 'high' or 'some concerns' for the five domains assessed whereas the company has reported judgements as Y or N (presumably signifying 'Yes' or 'No') and has not provided the underlying answers from the signalling questions. The company's assessment is therefore flawed and of very limited use. We note that risk of bias assessments for the trials have also been previously reported during other NICE appraisals as shown in Appendix 4. These assessments have shown that none of the trials would be considered at an overall low risk of bias because all are open label trials and a variety of other risks of bias have been raised (Appendix 4).

EAG comment on the studies included in the NMA

The studies included in the company's NMAs are those that have been included in previous NICE appraisals in this topic area. None of the studies were blinded and therefore they are at risk of performance and detection bias. Even though overall survival is an objective outcome, this might still be affected if the choice of second-line therapies differed between study arms outcome due to the lack of blinding. The extent to which the PFS outcome may be affected by the lack of blinding is less certain.

Independent central review (ICR) PFS or BICR PFS was available for all studies which may have helped to minimise bias but we know that for the JAVELIN Renal 101 trial data presented in the CS, only investigator assessments of PFS are available beyond the second interim analysis.

3.4 Critique of the NMA

The company report the methodology used for the NMA in CS B.2.10.4 and in the ITC report update document supplied in the clarification response.[43]

3.4.1 Data inputs to the NMA

The OS and PFS data inputs to the NMA were not provided in the CS but were provided in response to clarification question A9, Table 2. The company does not indicate what time-points the data comes from in the different trials. CS Table 30 indicates that ICR or BICR data were available for all studies and which data cut the evidence comes from for the CheckMate 9ER, CheckMate 214 and CLEAR studies.

3.4.2 Statistical methods for the NMA

The CS states that their proportional hazard NMA methods followed the guidance provided in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2-4.[44-46] The treatment effect model used was that described in NICE DSU TSD 2[45] and the models were implemented using the *gemtc* package in R software. Markov chain Monte Carlo (MCMC) methods were used to estimate relative treatment effects and 95% credible intervals using a minimum of 50,000 samples after convergence was achieved. The company state that autocorrelation plots were used to assess autocorrelation and that, if needed, a thinning interval was applied. The company does not report if thinning was actually necessary.

3.4.2.1 Choice between random effects and fixed-effect model

Fixed- and random-effects models were fitted to the data and goodness of fit was then compared using the deviance information criteria (DIC) and/or the total residual deviance and model choice was also guided by clinical plausibility of the estimated relative treatment effects.

3.4.3 Summary of EAG critique of the NMA

The company have provided very brief details of their NMA in the CS but this may be because it enables a comparison for the intermediate-/poor-risk subgroup of patients which is not the focus of the CS. From the information provided in the CS it seems that appropriate NMA methods have been chosen and implemented.

3.5 Results from the NMA

3.5.1 Overall survival in the intermediate-/poor-risk population

The CS presents results from the fixed-effects model only (results for the random effects model are presented in the ITC report provided with the clarification response). CS section B.2.10.6 states that the point estimates for the fixed- and random-effects models were similar but the credible intervals were substantially wider for the random-effects model. DIC was also similar between models. The company conclude that the relatively low number of studies (both in the network and with only a single study informing each treatment comparison), is the likely cause of the wide credible intervals for the random-effects model. The EAG concurs.

Figure 4 reproduces the forest plot for overall survival from the CS for the results from the fixed effect model in which avelumab with axitinib is the reference treatment. The credible intervals for the comparators all reach or cross the line for hazard ratio = 1 indicating that the results are not statistically significant. The point estimates suggest that in comparison to sunitinib, avelumab with axitinib and the other four comparator treatments lead to a reduction in the hazard of death but the reduction is greater for the other four comparator treatments. However, given the uncertainties associated with the NMA and because the results come from the fixed effect model which does not account for any heterogeneity between trials our view is that the results are very uncertain.

Figure 4 OS forest plot for intermediate-/poor-risk population comparing avelumab with axitinib to all other treatments – fixed-effects model

Source: Reproduction of CS Figure 16
CrI, credible interval; HR, hazard ratio

3.5.2 Progression-free survival in the intermediate-/poor-risk population

Similarly to the overall survival results, the CS only presents progression-free survival results from the fixed-effects model (results for the random effects model are presented in the ITC report provided with the clarification response). DIC was again similar between fixed and random effects models.

Figure 5 reproduces the forest plot from the CS showing avelumab with axitinib as the reference treatment. For two comparators, sunitinib and pembrolizumab + lenvatinib, the credible intervals do not cross the line for hazard ratio = 1 indicating that there is a statistically significant difference in the results. In comparison to sunitinib, avelumab with axitinib is associated with a lower hazard of progression or death whereas in comparison to pembrolizumab + lenvatinib, avelumab with axitinib is associated with a higher hazard of progression or death. For the other comparators where the 95% credible interval crosses the hazard ratio = 1 line, compared to nivolumab + ipilimumab, the point estimate for avelumab with axitinib suggests a lower hazard of progression or death. For the remaining 3 comparators (cabozantinib, nivolumab + cabozantinib and pembrolizumab + lenvatinib) there is a numerical increase in the hazard of progression or death for avelumab + axitinib treatment. Again, we view that these fixed effect results fail to take into account heterogeneity and are thus very uncertain.

Figure 5 PFS forest plot for intermediate-/poor-risk population comparing avelumab with axitinib to all other treatments – fixed-effects model

Source: Source: Reproduction of CS Figure 17
CrI, credible interval; HR, hazard ratio

3.6 Conclusions on the clinical effectiveness evidence

The appraisal committee during TA645 concluded that further data collection within the CDF could resolve the uncertainty by allowing for more mature survival data to be collected and providing evidence for the effectiveness of avelumab with axitinib in non-clear-cell aRCC.

The updated comparative evidence in the CS is from the final analysis of JAVELIN Renal 101 (data cut-off 31 August 2023) with median follow-up in the avelumab with axitinib arm of 73.2 months and 73.0 months in the sunitinib arm. As noted during TA645, the JAVELIN Renal 101 trial only enrolled patients with clear-cell aRCC. In our opinion the evidence from JAVELIN Renal 101 is at moderate risk of bias due to the open-label study design and use of investigator assessment for PFS. PFS and OS are both used in the economic model. All outcomes from JAVELIN Renal 101 were updated from the final analysis for this appraisal.

Since avelumab with axitinib entered the CDF in 2020, the treatment pathway for people with aRCC has evolved and decisions about first-line treatment now consider a person's prognostic risk status. The company have focussed their submission for this appraisal on the IMDC favourable-risk group (which is the population in the economic model base case) but also present evidence for the intermediate-/poor-risk subgroup as well as the full ITT population.

Has the uncertainty arising from the immature survival data presented for TA645 been resolved?

Overall survival data from the company pivotal trial, JAVELIN Renal 101, is now mature and median survival time was reached for the ITT population and for both the favourable-risk and intermediate-/poor-risk subgroups. Therefore, we have more certainty in the OS results than in the previous appraisal. In the ITT population, although OS was numerically in favour of avelumab with axitinib in comparison to sunitinib, the difference between groups was not statistically significant (see section 3.2.5.4 above). PFS in the ITT population was statistically significantly in favour of avelumab with axitinib.

The pre-specified IMDC risk subgroups in the JAVELIN Renal 101 trial provide direct comparative evidence for the IMDC risk subgroups in the NICE scope, albeit the favourable-risk subgroup is small at 21.4% (n=190) of the ITT population. OS and PFS outcomes from the favourable-risk subgroup both inform the base case economic model, these were numerically better for avelumab with axitinib compared to sunitinib (section 3.2.5.1 above). OS and PFS were also in favour of avelumab with axitinib in comparison to sunitinib in the

intermediate-/poor-risk subgroup (section 3.2.5.2 above). The trial was not powered to detect statistical significance in IMDC subgroups.

RWE for OS that is directly generalisable to NHS practice is derived from the CDF (n=[redacted] patients) and EAMS (n=[redacted]) cohorts presented in the NDRS SACT report. Patients had aRCC of a variety of histological subtypes (i.e. not limited to clear-cell aRCC) and IMDC status at treatment initiation but information on disease risk status and RCC histological type was not recorded for the EAMS cohort. The CDF cohort had a [redacted] median OS than the JAVELIN Renal 101 trial ITT population, and the EAMS cohort had a [redacted] median OS than the JAVELIN Renal 101 ITT population.

For the subgroup of patients with IMDC favourable-risk disease (n=[redacted] and with aRCC of any histological type in the CDF cohort, median OS was [redacted] so therefore RWE is less certain for this subgroup. For the subgroup with clear-cell histology and any IMDC risk category (n=[redacted]) median OS was [redacted] than in the JAVELIN Renal 101 ITT population.

The RWE from the SACT report is not comparative, however, further UK RWE from McGrane et al. 2024,[47] compares drug treatments by class. In the group of 294 favourable-risk patients, 66 received combination therapy of IO + TKI and avelumab with axitinib treatment accounted for 95.5% of this group. The remaining 206 favourable-risk patients had received a TKI with 97.1% of these receiving either sunitinib, pazopanib, or tivozanib (the remaining 2.9% received cabozantinib). The patients who received a TKI had a shorter median PFS and OS than reported for the favourable-risk patients in this real-world study who received a combination therapy with IO + TKI. However, great caution is needed in interpreting these data because the patients who received a TKI only and those who received combination therapy with IO + TKI were not randomised or matched in anyway and therefore the differences observed in outcome may have been due to factors other than the first-line treatment received.

Has the uncertainty around clinical effectiveness in the non-clear cell aRCC population been resolved?

Evidence for the non-clear cell aRCC population is provided from the CDF via the NDRS SACT Report provided with the CS. It shows that median OS in the non-clear cell population (n=[redacted]) is [redacted] than for the clear cell aRCC population (n=[redacted]) (section 3.2.7.1.2 above). However, as there is no comparator group in the SACT data we cannot observe any differences between treatments. Similarly, the Nathan et al. UK RWE study included analysis of participants with non-clear cell aRCC, but there was no

comparator treatment. The McGrane study (which reported comparative treatment data by drug class) included participants with both clear and non-clear cell aRCC but did not report results for these participants by aRCC histology subgroups. As noted above in section 3.1.2 the RWE SLR did not seek to identify comparative RWE evidence, and the JAVELIN Renal 101 trial excluded people with non-clear cell aRCC. Therefore, we can observe a greater disease burden in people with a non-clear cell disease component, but uncertainty remains around the comparative effectiveness of avelumab with axitinib in people with non-clear cell aRCC.

4 COST EFFECTIVENESS

This section presents a summary and critique of the cost effectiveness evidence included in the company's submission. Section 5 reports results from the company's economic analyses and the EAG's validation of the model. Additional analyses conducted by the EAG are presented in section 6.

The results in sections 4 to 6 all relate to the favourable-risk subgroup, which is the focus of the company's submission. We report results for the intermediate/poor-risk subgroup and the ITT population in Appendix 5.

4.1 EAG comment on company's review of cost-effectiveness evidence

The company summarise the results of their systematic review of cost-effectiveness evidence in CS section B.3.1, which updates their review for TA645. The methods and results of the original and updated economic reviews are described in a report provided with the CS references.[48] A single search was used to identify cost-effectiveness studies and sources of evidence for utilities and for resource use and costs. The searches for TA645 were conducted in September 2017 and March 2019, and the new update search in June 2024. The EAG considers that the search methods are appropriate.

The searches for TA645 did not find any cost-effectiveness studies for avelumab with axitinib. The company state that the updated search identified five studies that presented cost-effectiveness results for avelumab with axitinib, all relating to the aRCC population (CS section B.3.1). Tables 7 and 8 of the economic systematic review report (2024)[48] summarise methods and results for seven studies including avelumab with axitinib and sunitinib and/or nivolumab + ipilimumab: [1 49-54] The company do not discuss these papers, but we do not consider that they add relevant additional information.

See sections 4.2.5 and 4.2.6.1, respectively, for discussion of the reviews of sources of evidence for quality of life ('utility') and for resource use and costs.

4.2 Critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 9 summarises the EAG view's on whether the company's economic analysis complies with methodological criteria specified in the NICE reference case checklist.[55] We consider that the company's approach is reasonable.

Table 9 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, for patients (carer outcomes are not included)
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes, cost-utility analysis. The company report pairwise ICERs, not fully incremental results. This is reasonable as two of the comparators are dominated (see section 5.1)
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, the time horizon is lifetime in the base case
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, EQ-5D-5L data collected from patients in the clinical trial (4.2.5.2)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, utilities are mapped UK population values using the Hernández-Alava et al. (2017) function.[56]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of	Yes. The severity modifier is not applicable for the

Element of health technology assessment	Reference case	EAG comment on company's submission
	individuals receiving the health benefit	favourable-risk population (see section 4.3)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: Produced by the EAG based on information from the company's submission and model
EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life year.

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model structure is described in CS section B.3.2.2. It is a partitioned survival structure model, programmed in Microsoft Excel with a time horizon of 40 years and a cycle length of one week. The model structure comprises three health states: progression-free, progressed disease, and death. The company divide the progression-free health state into on- and off- treatment periods to reflect costs and health outcomes as patients may discontinue treatment prior to documented disease progression. The structure is illustrated in CS Figure 18 (reproduced in Figure 6 below).

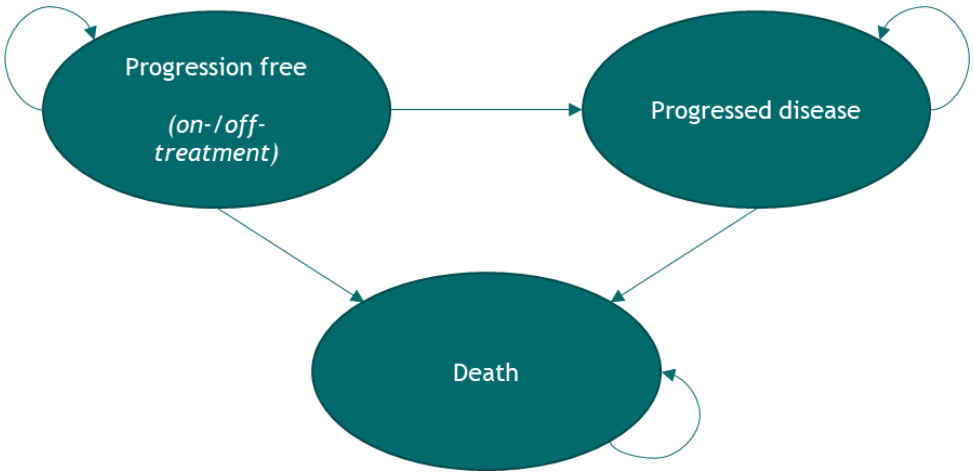

Figure 6 Company's economic model structure

Source: Reproduced from CS Figure 18.

Patients enter the model in the progression-free health state and can transition to the progressed disease or death health states. Patients in the progressed disease health state are only able to remain in the progressed disease state or transition to the death state. The proportion of patients in the progression-free state is estimated directly from the modelled PFS curves, whilst the proportion of patients in the death state is calculated from the inverse probability of the OS curve at that time. The proportion of patients in neither the progression-free nor death health states make up the progressed disease health state. The company assume that initial treatment ceases upon disease progression.

EAG comment on model structure

The model structure is appropriate. It is the same as that used in the original company submission and accepted by the NICE committee for TA645.

4.2.3 Decision problem for the model

4.2.3.1 Population

The base case population for the company's economic analysis is the subgroup of patients with favourable-risk disease (CS section B.3.2.1). The main economic sections of the CS (3.2 to 3.9) focus on the model inputs and results for this population. The company also report results for the intermediate/poor-risk subgroup (CS B.3.10) and for the ITT population (Appendix O).

The base case favourable-risk population is narrower than the population of all adults with untreated aRCC included in TA645 and in the NICE scope for the current managed access review. The company give two reasons for this change: 1) that there is a greater unmet need for the favourable-risk subgroup, as additional treatment options are now available for people with intermediate/poor-risk disease; and 2) that the JAVELIN Renal 101 study "*showed avelumab + axitinib to be clinically effective vs. sunitinib*" (CS B.3.2.1 page 105). The latter statement is true for the ITT population, as there was a significant effect on PFS, but we note that the trial was not powered for statistical significance in the IMDC subgroups, and numerical improvements in PFS and OS in these subgroups were not statistically significant (Table 5). Nevertheless, based on the assumption that pazopanib and tivozanib have similar efficacy to sunitinib (3.3.1), indirect evidence is not required to model cost-effectiveness in the favourable-risk subgroup. In contrast, indirect evidence is required to model the effect of other comparators in the intermediate-/poor-risk subgroup.

The modelled cohort for the base case reflect the characteristics of the favourable-risk subgroup in the JAVELIN Renal 101 trial: [redacted]% female with a mean age of [redacted] years (CS Table 40).

4.2.3.2 Interventions and comparators

The modelled intervention is avelumab at a fixed dose of 800mg administered by intravenous infusion once every two weeks with oral axitinib at 8mg twice daily. The comparators match those specified in the NICE scope. For the base case favourable-risk population, the comparators are sunitinib, tivozanib and pazopanib. The company cite SACT data which indicates that sunitinib is the most prescribed TKI monotherapy for people with favourable-risk untreated aRCC in UK practice, followed by pazopanib and then tivozanib (see CS section B.3.2.3). We discuss dosing assumptions for the comparators and subsequent treatments for the base case analysis in section 4.2.6.2 below.

For the intermediate/poor-risk subgroup analysis, the model includes NICE scope includes four additional comparators: cabozantinib monotherapy, nivolumab + ipilimumab, lenvatinib + pembrolizumab and cabozantinib + nivolumab. Information about dosing for comparators in the intermediate/poor-risk subgroup is provided in CS Appendix section O.1.

EAG conclusion on the decision problem for economic analysis

The EAG considers that the company's focus on the favourable-risk population in their base case for economic modelling is reasonable. Given that different comparators are indicated for the favourable-risk and intermediate/poor-risk subgroups, and that they have very different prognoses, it would not be appropriate to model these subgroups together in the ITT population. We agree with the company's rationale for selecting the favourable-risk subgroup for their base case, based on unmet need in this population and reduced uncertainty over clinical effectiveness relative to the intermediate/poor-risk subgroup.

4.2.4 Treatment effectiveness and extrapolation

The economic model uses parametric curves fitted to data for OS, PFS and TTD from the JAVELIN Renal 101 trial for avelumab, axitinib and sunitinib. The company assume that estimates for tivozanib and pazopanib are equivalent to sunitinib. We discuss results for the favourable-risk population in this section. The company report survival curves for the intermediate/poor-risk subgroup and the ITT population in CS Appendix O.

Although treatment waning was originally applied in TA645, this was removed following technical engagement. Therefore, in line with this decision, the company have not

implemented treatment waning in this appraisal. Similarly, a two-year stopping rule that was initially applied for avelumab with axitinib in TA645 has also been removed from the current appraisal. Patients cease first-line treatment prior to or at disease progression only.

4.2.4.1 Overall survival

KM estimates of OS for patients with favourable-risk disease from the JAVELIN Renal 101 trial are provided in CS Figure 6. CS section B.3.3.2 reports how parametric survival models were fitted to these data to produce extrapolations for use in the economic model. Six standard parametric survival distributions were used, including the exponential, as requested by NICE in the Managed Access Agreement. The fitted curves for avelumab with axitinib and sunitinib are shown in CS Figures 20 and 21, respectively. Goodness-of-fit statistics (AIC and BIC) and landmark survival estimates (at 1, 2, 5 and 10 years) are reported in CS Tables 41 and 42 for avelumab with axitinib, and in CS Tables 43 and 44 for sunitinib. The cost-effectiveness model includes an adjustment of the fitted extrapolations to ensure that the mortality risk for the modelled population cannot be lower than that expected for members of the general population of the same age and sex.

The hazard plots for the outcomes of OS were provided in Figure 3 of the company's clarification response. The company state that the evidence does not clearly support the proportional hazards assumption, and therefore that they chose to fit parametric curves to each treatment arm independently. Figure 7 and Figure 8 below show the fitted extrapolations for avelumab with axitinib and sunitinib, respectively. Table 10 reports overall survival estimates for patients with favourable-risk disease based on extrapolated results from the JAVELIN Renal 101 trial, including adjustment for general population mortality.

Table 10 OS adjusted for general population mortality (favourable-risk population)

Parametric function	Estimated survival				
	5 years	10 years	20 years	30 years	40 years
Avelumab with axitnib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parametric function	Estimated survival				
	5 years	10 years	20 years	30 years	40 years
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's model

Figure 7 Avelumab with axitinib OS extrapolations (favourable-risk population)

Source: Produced by the EAG from the company's economic model

Figure 8 Sunitinib OS extrapolations (favourable-risk population)

Source: Produced by the EAG from the company's economic model

The company used visual inspection, statistical goodness-of-fit and expert opinion on the plausibility of the long-term survival estimates from three clinicians to choose the parametric distribution for their base case and alternatives for scenario analysis (CS Table 78).

- For avelumab with axitinib, the company chose the log-normal distribution for the base case and generalised gamma and log-logistic distributions for scenario analysis.
- For sunitinib (and by assumption, for tivozanib and pazopanib) the company chose the generalised gamma for their base case, with log-logistic and Weibull distributions as scenarios.

The EAG notes that according to AIC/BIC scores the log-logistic, Weibull and log-normal OS distributions have a very similar fit for the avelumab + axitinib arm. And for sunitinib, the Weibull, log-logistic and log-normal have a similar statistical fit.

For comparison, the RCC Pathways Pilot model (Lee et al. 2023)[15 57], the exponential distribution was selected for sunitinib for the favourable-risk population, with the Weibull curve explored as a scenario. The exponential gives a very poor fit to the KM with the updated final analysis of JAVELIN Renal 101 data, but the Weibull still provides a good fit.

For the EAG's preferred analysis, we retain the company's base case OS extrapolations, and we report scenarios with the generalised gamma for avelumab + axitinib, and with the Weibull for sunitinib. In addition, we report results using the exponential distribution, as this was requested by the committee in TA645. The exponential provides a comparison against an assumption of a constant hazard, but it does not provide a good fit to the updated trial data in either arm.

4.2.4.2 Progression free survival

The KM estimates of PFS for avelumab with axitinib and sunitinib from the JAVELIN Renal 101 study are presented in CS Figure 7. The parametric curves, including the exponential, fitted to each arm are provided in CS Figure 22 and CS Figure 23. The hazard plots for the outcomes of PFS are given in clarification response Figure 4. As with OS, the company assume that proportional hazards do not hold and fit models independently for each arm. The company selected the log-normal curve for avelumab with axitinib, and the generalised gamma model for sunitinib (and therefore also tivozanib and pazopanib). We note that the model includes an adjustment to prevent PFS exceeding OS.

Table 11 PFS adjusted for general population mortality (favourable-risk population)

Model	Estimated survival (years)				
	5	10	20	30	40
Avelumab + axitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's model

The EAG notes that the best fitting curves according to AIC/BIC scores are the log-normal model for avelumab with axitinib and the log-normal and exponential models for sunitinib. However, as the PFS data is now very mature all of the survival distributions have a similarly good fit to the KM data and provide similar long-term extrapolations and cost-effectiveness results. We report selected PFS scenarios in section 6 of this report (see Table 20).

4.2.4.3 Time to treatment discontinuation

The parametric curves were fitted to avelumab and axitinib individually, as patients may discontinue the drugs independently and TTD data is available by medication from the JAVELIN Renal 101 trial. The KM estimates for avelumab, axitinib, and sunitinib are provided in CS Figure 24, and the log-cumulative hazard plots are presented in clarification response Figure 5. CS Figures 25, 26 and 27 show the parametric survival model fits for avelumab, axitinib, and sunitinib, respectively (including the exponential model). As with OS and PFS, the company argue that the proportional hazards assumption does not hold and fits parametric curves independently for each treatment. The company selects the generalised gamma model for avelumab, axitinib, and sunitinib (and therefore tivozanib and pazopanib). We note that the model includes an assumption that patients discontinue avelumab + axitinib on disease progression.

The EAG notes that the best fitting curves according to AIC/BIC scores are the Gompertz and exponential models for both avelumab and axitinib (independently) and the exponential model for sunitinib. As with PFS, TTD data is very mature and all of the parametric

distributions provide a similar and very good fit to the KM data. We report selected scenarios for the TTD in EAG analysis (see Table 20).

Table 12 TTD (favourable-risk population)

Model	Estimated survival (years)				
	5	10	20	30	40
Avelumab					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's economic model

EAG comment on treatment effectiveness and extrapolation

The EAG agrees with the company's methods and selection of base case extrapolations for OS, PFS, and TTD. We note that there is still high uncertainty over long-term survival, as there are several alternative parametric survival distributions with a good fit to the KM data that give very different projections of survival at 10 years and beyond. Thus, cost-effectiveness estimates are sensitive to the choice of OS extrapolation.

4.2.5 Health related quality of life

The company describe their approach to estimating health-related quality of life (utility) for the cost-effectiveness analysis in CS section B.3.4.

Base case utilities for the progression-free and progressed disease health states are estimated from EQ-5D-5L data for patients with IMDC favourable-risk disease in the

JAVELIN Renal 101 trial. Results are also reported for a scenario with an alternative specification of the utility analysis, and for scenarios with utilities from previous NICE appraisals. Age-adjustment of utilities is applied (see section 4.2.5.3 below). Specific disutilities for adverse events are not used, as it is assumed that the effects of such events are already reflected in the trial data.

The approach to utility estimation is consistent with that accepted in TA645, although the utility values differ due to changes in the target population (favourable-risk only rather than ITT), the availability of longer trial follow-up and a change in the NICE-preferred method for valuing EQ-5D-5L data.[55] See the subsections below for further discussion.

4.2.5.1 Systematic literature review for utilities

The updated review of utility studies identified 17 UK studies, of which 8 were NICE TAs.[48] The company do not discuss these results, but instead compare the utility estimates from the updated analysis of JAVELIN Renal 101 trial data with estimates from previous NICE appraisals (CS section B.3.4.3 and Table 59), as in the submission for the original appraisal TA645. The previous appraisals all relate to an ITT population, rather than the favourable-risk subgroup considered in the current appraisal, see discussion in section 4.2.5.4 below.

4.2.5.2 Utility estimates from trial data

The methods used to analyse the EQ-5D-5L data from the JAVELIN Renal 101 trial are described in CS sections B.3.4.1 and B.3.4.2, with further information in the company's response to clarification question B7.

EQ-5D-5L data were collected at the beginning of each 6-week treatment cycle, and after treatment discontinuation at day 30, 60 and 90 and then every 3 months.[58] The questionnaire data was mapped to EQ-5D-3L 'UK tariff' utility values using the Hernández-Alava et al. (2017) function, as recommended by NICE.[55 56] The company report that as the number of missing utility observations is low ([redacted]), imputation is not necessary (clarification response B7). We note that it is not clear from the description in the clarification response whether this cited proportion of missing data accounts for all observations that would have been due in follow-up for non-censored participants, or whether it only applies to submitted EQ-5D-5L questionnaires.

Utility values were estimated using pooled data for both treatment arms in the favourable-risk subgroup and analysed with a linear mixed-effects regression to account for repeated measurement. The base case utility model included progression status as the only fixed effect covariate (Model 1). A scenario with treatment status (on/off treatment) as an

additional covariate (Model 2) is reported, but not used in the base case as the treatment status coefficient was not statistically significant.

We noted a discrepancy in the reporting of the Model 2 'On treatment' status coefficient as a positive value ([redacted]) in CS Table 57, and the way that it is applied in the company's model as a decrement (due to an adjustment in cells X160-X162 on the Parameters sheet). The company clarified in their factual accuracy check that there was an error in CS Table 57 and that the on-treatment coefficient should have a negative value ([redacted]), as in their economic model. The on-treatment utilities reported in CS Table 58 are also incorrect, see Table 13 below for the correct values.

The company do not report any other tests of alternative model specifications (clarification response B7), but we note that the simple base case utility model is consistent with that accepted in the TA645, and in NICE appraisals of the comparators (TA178, TA215 and TA512).[12 13 59] The company submission for TA645 reported that the coefficient for the treatment arm was not significant and that clinical expert opinion supported the assumption of equal health state utilities for avelumab with axitinib and sunitinib.

Results for the favourable-risk subgroup are reported in CS Tables 57 and 58. Equivalent results for the intermediate/poor risk subgroup and the ITT population are reported in CS Appendix O.5.1, Tables 86 and 87.

4.2.5.3 General population utilities and age adjustment

The model includes an adjustment to reflect declining quality of life with age in the general population based, on the Ara and Brazier (2010) formula (see CS section B.3.4.5).[60] This adjustment is correctly applied and in accordance with NICE guidance.[55] We confirm that the modelled utility in the progression-free health state remains lower than expected utility for people of the same age and gender in the general population, based on both the Ara and Brazier formula and more recent estimates of general population utility in England reported by McNamara et al. (2023).[61]

4.2.5.4 Summary of utility estimates

Table 13 shows the utility estimates for the progression free (PF) and progressed disease (PD) health states from the company's updated analysis of JAVELIN Renal 101 data (favourable-risk and ITT populations), together with values from the previous analysis of JAVELIN Renal 101 data for TA645, and from NICE appraisals for the comparators sunitinib, pazopanib and tivozanib (TA178, TA215, TA512) and the sunitinib arm in TA581. [12 13 59 62 63]

The utilities from previous appraisals are all derived from ITT trial populations with untreated aRCC, including people with poor, intermediate and favourable-risk disease. As might be expected, utilities for the favourable-risk subgroup in the updated JAVELIN Renal 101 analysis are higher than the equivalent analysis in the ITT population and ITT estimates from previous appraisals. We also note that the loss of utility associated with disease progression in the updated JAVELIN Renal 101 trial analysis is somewhat lower for the favourable-risk subgroup than for the ITT population: [redacted] versus [redacted] in Model 1. The progression disutility is also much higher in the TA645 analysis of the JAVELIN Renal 101 trial data (0.070), which may be related to the shorter duration of follow up.

Table 13 Comparison of utility values from the trial and other NICE appraisals

Population	Analysis	Treatment arm	Treatment status	Health state utilities		
				PF	PD	Decrement
Updated analysis of JAVELIN Renal 101 utility data						
Favourable risk (CS Table 58)	Model 1	Pooled [a]	-	[redacted]	[redacted]	[redacted]
	Model 2	Pooled [a]	On [c] Off	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
ITT population (CS Table 87)	Model 1	Pooled [a]	-	[redacted]	[redacted]	[redacted]
	Model 2	Pooled [a]	On [c] Off	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
Utilities from TA645 and previous NICE appraisals for comparators						
ITT population	TA645	Pooled [a]		0.753	0.683	0.070
	TA178	Sunitinib [b]	-	0.780	0.700	0.080
	TA215	Pazopanib	-	0.700	0.590	0.110
	TA512	Tivozanib	-	0.726	0.649	0.077
	TA581	Sunitinib	-	0.719	0.699	0.020

Source: Adapted by the EAG from CS Tables 58, 59, Appendix Table 87 and from the model
aRCC, advanced renal cell carcinoma; CS, company submission; ITT, intention-to-treat; PF, progression free; PD, progressed disease; TA, technology appraisal.
[a] Pooled data for both treatment arms: avelumab with axitinib and sunitinib.
[b] Values from TA178 Assessment Group model for first-line treatments, same as in TA169.
[C] Values differ from those in CS Table 58 because the 'on treatment' coefficient in the Model 2 regression is applied as a negative value, as in the company's submitted model.

EAG comment on utilities

The methods used to estimate health state utilities in the JAVELIN Renal 101 trial are consistent with NICE's preferred methods,[55] and with the approach used in the original analysis of the trial data for TA645.[1] The base case utility values for the favourable-risk subgroup in the current appraisal are higher than those in TA645, which were estimated for the ITT trial population and with shorter follow-up. To investigate the impact of this change, we report an additional EAG scenario analysis with the TA645 utilities. For comparison, we also report an

exploratory scenario analysis with utilities from updated trial data for the ITT population (as reported in CS Table 87). The approach to utility analysis is also consistent with approaches in NICE appraisals for comparators, but values from comparator appraisals are also related to ITT populations and are of less relevance than those from TA645. We therefore do not report scenario results with utilities from other appraisals.

4.2.6 Resources and costs

4.2.6.1 Systematic literature review for costs and resource use

Results from the systematic review of evidence for cost and resource use are reported in section 4 of the updated economic systematic review report (2024).[48] The review included 18 studies, of which 10 were NICE appraisals.[1 11-17 59 63]

In the following sections, we compare the company's resource use and cost assumptions with those in the original appraisal TA645 and with reference assumptions from the PenTAG RCC Pathways pilot assessment report (Lee et al. 2023).[15 57]

4.2.6.2 Drug costs

4.2.6.2.1 Unit costs

Unit costs for intervention and comparator drugs are reported in CS Table 61 and unit costs for other drugs used in subsequent treatment are reported in CS Table 70 (also listed in Tables 45 and 46 in CS Appendix K). Costs for premedication with an antihistamine and paracetamol are added to the intervention costs (CS Table 62).

The company used list prices sourced from the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT), cited access date 13/04/23. We checked updates of the BNF and eMIT (access date 13/01/25). [64 65] The latest edition of eMIT (July 2023 to June 2024) reports lower weighted average prices for sunitinib and everolimus, which we use in EAG analyses (see section 6).

The company apply an existing simple PAS price discount of [redacted]% for avelumab and a published discount of 12.5% for pazopanib (NICE TA215).[12] Price discounts are also available for axitinib, tivozanib and for other drugs used in subsequent treatment, but these are confidential. We provide cost-effectiveness results including all available NHS price discounts in a confidential addendum to this report. The company use scenario analysis to illustrate the impact of potential price reductions for axitinib (CS Table 78),

[redacted]. We do not report these scenarios as this is not usual practice.

Table 14 summarises unit costs for all drugs in the company's model, updated prices used in the EAG base case and sources for drug costs in the confidential EAR Addendum.

4.2.6.2.2 Dosing assumptions

We summarise dosing assumptions and total drug acquisition and administration costs used in the company's base case model in Table 15. Dosing assumptions are reported in CS section B.3.2.3 for the intervention and comparators, and in CS Table 71 for subsequent treatments. Other information is obtained by the EAG from the company's model.

Adjustment for wastage is not necessary for avelumab, as it is available in 200 mg vials for infusion, with a recommended dose of 800 mg every 2 weeks. For simplicity, the company assume a fixed infusion dose of 240 mg for nivolumab in subsequent treatment (3 mg/kg, with an assumed mean body weight of 80 kg). Other drugs are administered orally, with an assumption of no wastage.

4.2.6.2.3 Relative dose intensity

The company apply relative dose intensity (RDI) adjustments to costs of the intervention and comparator drugs, see CS Table 63. RDIs for avelumab, axitinib and sunitinib are derived from JAVELIN Renal 101 trial data (ITT population, final analysis); and estimates for tivozanib and pazopanib are derived from trial data, as used in the NICE appraisals TA512 and TA215 respectively.[12 13 66]

The model includes some RDI estimates for subsequent treatments (Costs!U44-U55), but these do not inform the company's cost-effectiveness results. We note that the RCC Pilot Pathway reports RDI estimates from trial and real-world evidence (Table 87 in Lee et al. 2023)[57]. The real-world figures are redacted but we list the RDI values for subsequent treatments from clinical trials in Table 15. A scenario using these RDIs is performed in section 6.

4.2.6.2.4 Drug administration costs

The model includes a cost of £217 for administration of drugs by intravenous infusion (NHS National Cost Collection 2022/23, SB12Z Outpatient).[67] No cost is applied for administration of oral medications, which differs from the approach in TA645 which included a one-off cost for initiation of exclusively oral medication (HRG code SB11Z), and ongoing pharmacist costs for continuing use (TA645 company submission Table B.3.46). The RCC Pathway Pilot

Assessment Report follows this approach, with a cost of £197.25 for initiation of oral therapy and £11 per new pack of medication required (Table 88, Lee et al. 2023).[1 57] It is likely that the company's exclusion of costs for delivery of oral drugs is conservative because the one-off cost for initiation of oral therapy is incurred for the comparators but not for the intervention (as the cost for initiation of axitinib is already covered in the administration cost for avelumab).

Table 14 Unit costs for drugs used in the base case model (favourable-risk population)

Drug	Form	Unit	Pack size	Company base case		EAG analysis - if different		cPAS Addendum
				Cost	Source	Cost	Source	Source
Intervention								
Avelumab	Infusion vial	200 mg	1	[redacted]	CS, PAS price			CS, PAS price
Axitinib	Tablet (oral)	5 mg	56	£3,517	BNF 2024			Confidential PAS price
Comparator								
Sunitinib	Capsule (oral)	50 mg	28	£348.78	eMIT 2023	£89.07	eMIT Jul 23-June 24	eMIT July 23-June 24
Tivozanib	Capsule (oral)	1.34 mg	21	£2,052	BNF 2024			Confidential PAS price
Pazopanib	Tablet (oral)	400 mg	30	£980.88	Public PAS price [a]			Public PAS price [a]
Subsequent treatments								
Cabozantinib	Tablet (oral)	40 mg	30	£5,143	BNF 2024			Confidential PAS price
		60 mg	30	£5,143	BNF 2024			
Everolimus	Tablet (oral)	5 mg	30	£429.75	eMIT 2023	£252.29	eMIT Jul 23-June 24	eMIT July 23-June 24
		10 mg	30	£488.32	eMIT 2023	£283.71	eMIT Jul 23-June 24	
Lenvatinib	Capsule (oral)	4 mg	30	£1,437	BNF 2024			Confidential PAS price
		10 mg	30	£1,437	BNF 2024			
Nivolumab	Infusion vial	240mg	1	£2,633	BNF 2024			Confidential PAS price

Source: Produced by the EAG using information from CS Appendix K, BNF 2024 and eMIT (accessed 13 Jan 2025)[64 65] and NICE Pricing tracker form (received 14 Jan 2025)

BNF, British National Formulary; CAA, commercial access arrangement; CS, company submission; eMIT, drugs and pharmaceutical electronic market information tool; PAS patient access scheme.

[a] Unit cost for pazopanib includes publicly available simple price discount of 12.5% (NICE TA215) applied to the list price £1,121 (BNF 2024)

Table 15 Dosing assumptions used in the base case model (favourable-risk population)

Regimen	Drug	Route	Dose	Frequency	Admin cost [a]	Relative dose intensity		Time on treatment (days) [d]
						Company base case [b]	Subsequent treatment [c]	
Intervention								
Ave + axi	Avelumab	IV	800 mg	Every 2 weeks	£217.22	91.7%		TTD
	Axitinib	Oral	5 mg	Twice daily		83.7%		TTD
Comparators								
Sunitinib	Sunitinib	Oral	50 mg	Once daily 4/6 weeks		81.9%		TTD
Tivozanib	Tivozanib	Oral	1.34 mg	Once daily 3/4 weeks		94.0%	94.0%	TTD
Pazopanib	Pazopanib	Oral	800 mg	Once daily		86.0%	86.0%	TTD
Subsequent treatments								
Cabozantinib	Cabozantinib	Oral	60 mg	Once daily		100%	93.3%	231.7
Everolimus	Everolimus	Oral	10 mg	Once daily		100%	84.0%	167.3
Axitinib	Axitinib	Oral	5 mg	Once daily		100%	99.0%	220.5
Sunitinib	Sunitinib	Oral	50 mg	Once daily 4/6 weeks		100%	81.9%	172.9
Nivolumab	Nivolumab	IV	240 mg	Every 2 weeks	£217.22	100%	97.5%	294.0
Len + Eve	Lenvatinib	Oral	18 mg	Once daily		100%	70.4%	243.5
	Everolimus	Oral	5 mg	Once daily		100%	89.3%	243.5
Pazopanib	Pazopanib	Oral	800 mg	Once daily		100%	86.0%	348.6

Source: Produced by the EAG using information from CS sections B.3.2.3 and B.3.5.1 and from the company's model.
Admin, administration; Ave + axi, avelumab with axitinib; IV intravenous infusion; Len + Eve, lenvatinib with everolimus; RDI, relative dose intensity; TTD, time to treatment discontinuation.
[a] NHS National Cost Collection 2022/23 (SB12Z Outpatient). No costs are applied for oral medications.
[b] RDIs for intervention and comparators from CS Table 63. RDI not applied in costings for subsequent treatments in the company's model.
[c] RDIs based on trial data from Table 87 RCC Pilot Pathways Assessment Report (2023).[57]
[d] TTD distribution for intervention and comparators based on JAVELIN Renal 101 TTD favourable-risk data, assuming TTD for tivozanib and pazopanib is the same as for sunitinib (see 4.2.4.3).

Table 16 Subsequent treatment assumptions for the favourable-risk subgroup

Subsequent treatments	**Company base case** (JR101, rescaled to remove nivolumab after Ave + axi)		**No rescaling for nivolumab**		**TA645**[1]		**100% nivolumab or cabozantinib**		**UK ROC study (McGrane 2024)**[5]	
	Ave + axi	Sunitinib	Ave + axi	Sunitinib	Ave + axi	Sunitinib	Ave + axi	Sunitinib	Ave + axi	Sunitinib
Cabozantinib	59.45%	30.56%	42.91%	30.56%	25.40%	15.80%	100.00%	-	70.61%	59.29%
Everolimus	24.10%	12.01%	17.40%	12.01%	4.90%	1.70%	-	-	-	-
Axitinib	22.50%	13.10%	16.24%	13.10%	9.10%	9.60%	-	-	-	13.27%
Sunitinib	20.89%	15.28%	15.08%	15.28%	9.10%	13.00%	-	-	-	1.77%
Nivolumab	-	86.23%	42.91%	86.23%	8.50%	60.50%	-	100.00%	-	67.26%
Len + eve	19.28%	14.19%	13.92%	14.19%	6.70%	9.00%	-	-	45.39%	6.19%
Pazopanib	8.03%	10.92%	5.80%	10.92%	4.20%	6.80%	-	-	10.09%	5.31%
Total cost	[redacted]	£75,057	[redacted]	£75,057	[redacted]	£49,693	[redacted]	£59,855	[redacted]	£69,699

Source: Produced by the EAG using information from CS Table 69, CS Appendix Table 95 and the company's model
Ave + axi, avelumab with axitinib; Eve, everolimus; JR101, JAVELIN Renal 101, Len, lenvatinib; UK ROC study, UK renal oncology collaborative study.

4.2.6.2.5 Subsequent treatment use

We summarise the company's base case and scenario assumptions regarding the use of subsequent treatments in the favourable-risk subgroup in Table 16 below (based on CS Table 69 and Appendix P Table 95). The base case analysis uses the distribution of subsequent treatments observed for patients with favourable risk in the JAVELIN Renal 101 trial, with an adjustment to exclude nivolumab as a subsequent treatment after avelumab with axitinib as this is not usual practice (company response to clarification question B8).

We agree that the adjustment for nivolumab is appropriately applied in the model, with rescaling of other subsequent treatments. A clinical expert advising the EAG stated that rechallenge with axitinib and sunitinib after use of these agents at first line is not seen in clinical practice. We tested the effect of adjusting the company's base case to exclude subsequent use axitinib or sunitinib after first-line use, this led to an increase in subsequent treatment costs in both arms, and a small decrease in the ICER.

The company report three scenarios for subsequent treatment use in the favourable-risk subgroup, see summary in Table 16. We note the scenario based on subsequent treatment use for favourable-risk patients in the UK real world cohort reported by McGrane et al. (2024)[5] and suggest that this may be more representative of UK practice than the JAVELIN Renal 101 trial, although the number of patients in the favourable-risk subgroup treated with an immunotherapy/TKI combination at first line was low (n=66).

4.2.6.3 Adverse event incidence and costs

The model includes costs for treatment-related adverse events of grade ≥3 experienced by more than 5% of patients, see CS Table 56. In the initial version of the model, the same unit cost was used for all adverse events, based on an average of all non-elective short stay codes from the NHS National Cost Collection 2021. This is explained in the company response to clarification question B9, and adverse event specific costs were added to an updated version of the model submitted with the clarification response. We agree that this is appropriate and has minimal impact on the cost-effectiveness results.

4.2.6.4 Health state resource use

Assumptions regarding the use of additional health services (CS Table 65) are consistent with those in TA645 (ERG report Table 31).[1] Prior to progression, it is assumed that patients have a monthly GP visit and blood test and a three-monthly CT scan, in addition to services required for delivery of therapy or treatment of adverse events. After progression, it is assumed that patients have one GP visit and 1.5 community nurse visits per month, and

daily pain medication. These assumptions are also broadly consistent with the approach in the RCC Pathways Pilot analysis (Table 84, Lee et al. 2023).[57]

Unit costs for health services are reported in CS Table 66. We note that the cited cost for a CT scan is high (£193 compared with £135 from the 2023/24 National Cost Collection, code RC27Z), but this only has a small impact on the ICER.

4.2.6.5 End of life costs

The model includes a cost of £7,483 for end of life health and social care, based on estimates by Round et al. (2015), uprated for inflation.[68 69] This source was used in TA645. A higher estimate of £8,714 is used in the RCC Pathways Pilot model (Lee et al. 2023)[57] but only has a small impact on the ICER.

EAG conclusions on resource use and costs

The company's overall approach to estimating resource use and costs is mostly reasonable and consistent with the TA645, although we noted some discrepancies that we address in EAG additional analysis (see section 6). These include updated prices for sunitinib and everolimus based on the most recent version of eMIT in the EAG base case (Table 14), and additional scenario analyses for RDI adjustments for subsequent treatments (Table 15);

4.3 QALY weighting for severity

Severity is described in CS section B.3.6. The company used the QALY shortfall calculator from Schneider et al.[70] to calculate the expected QALYs for the general population, using the baseline characteristics from the economic model (see CS Table 40: age [redacted], [redacted] female). This results in an expected total QALYs for the general population of 12.29 and an estimated total QALYs for people living the disease managed with current treatment of 4.25. The absolute and proportional QALY shortfalls were 8.04 and 65.41%, respectively. Therefore, no severity modifier was applied for the favourable-risk population in this appraisal. The EAG agrees with the company's conclusion.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reports their base case pairwise cost-effectiveness analysis results for avelumab with axitinib versus sunitinib, tivozanib and pazopanib for the favourable-risk population in CS Table 75.

The company's base case analysis is conducted with a confidential PAS price discount for avelumab and a published discount on the list price for pazopanib (NICE TA215).[12]. Confidential price discounts are also available in the NHS for axitinib, tivozanib and for other drugs used in subsequent treatment. Cost-effectiveness results including all confidential price discounts are presented in a separate addendum to this report. See Table 14 and the discussion in section 4.2.6.2.1 for further information about the unit costs and price discounts applied in the company's base case, and in the confidential EAR Addendum.

In their response to the clarification questions, the company updated their model, which changed their original base case results for the favourable-risk population. The revised model received as part of the clarification response (and referred to here as 'the revised company model') includes the following changes:

- Adverse event specific costs are applied rather than a single value for all adverse events, with costs updated to the 22/23 National Cost Collection.
- Blood test, CT scan, simple intravenous infusion (IV) and complex IV costs have been updated from 21/22 to 22/23 National Cost Collection values.
- All poor risk subsequent therapies are considered (only affects the intermediate-/poor-risk population results – see Appendix 5)

A summary of the above changes is presented in Table 11 of the clarification response document. We have reproduced the cost-effectiveness results from the revised company model for the favourable-risk population in Table 17. The pairwise ICER for avelumab with axitinib versus sunitinib is [redacted] per QALY, versus tivozanib is [redacted] per QALY and versus pazopanib is [redacted] per QALY. We note that these changes had a minor impact on the model results (the change was < £1,000 per QALY for each of the comparisons).

We note that the company only report pairwise ICERs, not fully incremental results as specified in the NICE Reference Case.[55] In practice this is not important, because tivozanib and pazopanib are dominated by sunitinib in all analyses based on their relative costs, due

to the assumption that the three TKI comparators have equal effects (equal QALYs). We report fully incremental results for the EAG analyses in section 6.

Table 17 Base case results of the revised company model (favourable-risk population).

Treatment	Total		Incremental		ICER [a] (£/QALY)
	Cost (£)	QALYs	Cost (£)	QALYs	
Versus sunitinib					
Sunitinib	£93,185	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib					
Tivozanib	£136,173	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib					
Pazopanib	£165,275	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from Table 12 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company reports deterministic sensitivity analysis results in the form of tornado diagrams, showing the top 10 most influential parameters for the favourable-risk population. The comparisons versus sunitinib, tivozanib and pazopanib are shown in CS Figures 37-39. The range of variation for the input parameters was based on the available variance estimates or, when not available, the standard error was assumed to be 10% of the mean values. The company reports the impact on incremental net monetary benefit (NMB) at a willingness-to-pay (WTP) threshold of £30,000 per QALY in these diagrams. The deterministic sensitivity analysis shows that the model results are robust to reasonable variation of the parameter inputs. Across all comparators, the most influential parameters are the RDI for axitinib, the days on treatment for nivolumab and the RDI of pazopanib.

5.2.2 Scenario analysis

The scenario analyses conducted in the original company model for the favourable-risk population and their respective results are presented in CS Table 78. The EAG was able to

replicate the results from all the scenarios. The scenarios with the greatest impact on the model results are the changes in the price of axitinib, the use of alternative parametric curves for OS, alternative discount rates for costs and QALYs, shorter time horizons, change in the sources of utilities and subsequent therapies' distribution and excluding RDIs.

5.2.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis results from 5,000 iterations of a Monte-Carlo simulation, using the original company model for the favourable-risk population are given in CS Table 77 (also presented in Table 18 below). The pairwise ICER per QALY gained is reported as [redacted] per QALY for avelumab with axitinib versus sunitinib, [redacted] per QALY versus tivozanib and [redacted] per QALY for pazopanib. The normal distribution was used for all the input parameters in the probabilistic sensitivity analysis, which is not consistent with usual practice because cost parameters are skewed and cannot be negative, and probabilities should be constrained to values between 0 and 1. See section 5.3.4 below for further detail and EAG corrections to the company's PSA results.

Uncertainty in the ICER calculation is demonstrated by the cost-effectiveness scatter plots for avelumab with axitinib versus comparators (CS Figures 34-36). At a WTP threshold of £30,000 per QALY, the probabilities of avelumab with axitinib to be cost-effective are 0% versus sunitinib, around 20% versus tivozanib and around 70% versus pazopanib (CS Figures 31-33).

Table 18 Probabilistic results company's base case (favourable-risk population)

Treatment	Total		Incremental		ICER [a]
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
Versus sunitinib					
Sunitinib	£93,021	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib					
Tivozanib	£137,918	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib					
Pazopanib	£168,095	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 77 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib

5.2.4 Subgroup analysis

The company report results for the intermediate/poor-risk subgroup in CS section B.3.10, with model inputs and results for the ITT population presented in CS Appendix O. The EAG discussion of the model inputs, assumptions and results for the two alternative populations is presented in Appendix 5.

5.3 Model validation and face validity check

5.3.1 Company model validation

The company's approach to validate their model is described in CS section B.3.12. Quality control checks included reviewing for potential coding errors, inconsistencies and plausibility of inputs by an independent economist who was not involved in the model development process. Some examples of the validity checks that were applied in every sheet or overall by the use of a checklist are: extreme value testing, logical relationship testing and consistency checks.

In addition, the company report clinical expert from three medical oncology specialists based in England and Wales, who currently treat patients with aRCC in NHS practice. They were asked about treatment pathway for aRCC and plausibility of survival estimates.

5.3.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations, and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources.
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses.
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- Checking individual equations within the model ('white box' checks)
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

5.3.3 Company corrections to the model

The company's corrections to their original model are described in section 5.1 above. The EAG was able to replicate the results of the revised company model after applying the changes described in clarification responses B9, B10 and B11 to the original version of the model.

5.3.4 EAG corrections to the company model

Other than the issues raised by the EAG in the clarification questions stage, the only technical errors that we identified in the company's economic model relate to the probabilistic sensitivity analysis.

The company used normal distributions for the percentage relative dose intensity (RDI) parameters, and for all cost and resource use parameters that were included in the PSA. This is not appropriate as the sampled values are not restricted to feasible ranges (0%-100% for the RDIs and ≥0 for resource use and costs). We therefore edited the model to use gamma distributions for PSA sampling of cost and resource use parameters and beta distributions for the RDI percentages.

The company used a fixed standard error of 5% of the mean for resource use, cost and RDI parameters in the PSA, so uncertainty over these parameters is not based on empirical evidence. Other parameters in the PSA are based on empirical variance-covariance estimates, as outlined below.

- **PFS and OS**: Uncertainty over the fitted survival curves is modelled using multivariate normal distributions with empirical variance-covariance matrices ('PSMs' sheet).
- **TTD**: The duration of treatment for sunitinib is sampled for the PSA in the same way as PFS and OS. However, probabilistic sampling of TTD for avelumab and axitinib is not propagated to the cost-effectiveness results: TTD parameters for avelumab and axitinib (ToT!H33-M35 and ToT!V33-AA35 respectively) are linked to the deterministic values on the PSMs sheet (column T) rather than to the probabilistic values (column Y).
- **Utilities**: Probabilistic values for the trial-based health state utilities are sampled using a multivariate normal distribution for the regression coefficients, with an empirical variance-covariance matrix. But these sampled values do not feed through to the cost-effectiveness results: the live values used in the model (in Utilities!K43-O45) link to the deterministic values (e.g. for the base case, Utilities!G29-G30 for the base case, rather than Utilities!G29-G30).

We made the following corrections to the PSA: gamma distributions for resource use and cost parameters; beta distributions for RDIs; and inclusion of probabilistic values for health state utilities and TTD for avelumab and axitinib.

Revised probabilistic results for the company's base case analysis are reported in Table 19. These results are based on 5,000 iterations, which is sufficient to show stable results: Figure 9 illustrates convergence for the comparison with sunitinib. The cost-effectiveness scatterplot in Figure 10 illustrates the extent of uncertainty for this comparison.

Table 19 EAG-corrected PSA company's base case (favourable-risk population)

Treatment	Total			Incremental			ICER [a]
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	(£/QALY)
Versus sunitinib							
Sunitinib	£93,316	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib							
Tivozanib	£138,208	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib							
Pazopanib	£168,332	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 77 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib

Figure 9 PSA convergence: company base case (avelumab + axitinib versus sunitinib)

Source: Produced by the EAG from an edited version of the company's model
INMB, Incremental Net Monetary Benefit at threshold of £30,000 per QALY gained

Figure 10 Cost-effectiveness plane (avelumab + axitinib versus sunitinib)

Source: Produced by the EAG from an edited version of the company's model
PSA, probabilistic sensitivity analysis; WTP willingness to pay (cost-effectiveness threshold)

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A full summary of EAG observations on key aspects of the company's economic model is presented in Appendix 6. Table 20 lists the additional analyses conducted by the EAG on the company's base case model. Results of these scenario analyses are reported in Table 21.

Table 20 Summary of EAG's exploratory analyses

Analysis	Company base case assumption	EAG scenario	Section in EAG report
OS avelumab with axitinib	Log-normal	• Exponential • Generalised gamma	4.2.4.1
OS sunitinib	Generalised gamma	• Weibull • Exponential	4.2.4.1
PFS avelumab with axitinib	Log-normal	• Log-logistic • Exponential • Generalised gamma	4.2.4.20
PFS sunitinib	Generalised gamma	• Log-logistic • Exponential	4.2.4.20
TTD avelumab	Generalised gamma	• Gompertz • Exponential	4.2.4.3
TTD axitinib	Generalised gamma	• Gompertz • Exponential	4.2.4.3
TTD sunitinib	Generalised gamma	• Log-logistic • Exponential	4.2.4.3
Utilities	Trial EQ-5D-5L data mapped to UK EQ-5D-3L values with the NICE recommended method (Model 1)	• Model 1 – ITT population • TA645 – ITT population	4.2.5.2
Drug acquisition costs	List prices from BNF and eMIT, with PAS price discounts for avelumab and pazopanib.	Updated eMIT prices for sunitinib and everolimus (Table 14)	4.2.6.2.1
Relative dose intensity	RDI adjustment to costs for avelumab, axitinib and sunitinib (JAVELIN Renal 101), tivozanib (TA512) and pazopanib (TA215). No RDI used for subsequent treatments.	• Exclude RDI for intervention and comparator • Include RDI for subsequent treatments (Table 15)	4.2.6.2.3

Analysis	Company base case assumption	EAG scenario	Section in EAG report
Subsequent treatment mix	JAVELIN Renal 101 trial data.	• TA645 • 100% nivolumab or cabozantinib • UK ROC study	4.2.6.2.5

Source: Produced by the EAG
RDI, relative dose intensity.

Table 21 Results of EAG scenarios on company base case (favourable-risk population, deterministic analysis)

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
Company base case	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS avelumab with axitinib: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS avelumab with axitinib: generalised gamma	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: Weibull	Sunitinib	£92,762	[redacted]	[redacted]
	Pazopanib	£164,842	[redacted]	[redacted]
	Tivozanib	£135,744	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: exponential	Sunitinib	£94,576	[redacted]	[redacted]
	Pazopanib	£166,665	[redacted]	[redacted]
	Tivozanib	£137,565	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: log-logistic	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: generalised gamma	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: log-logistic	Sunitinib	£92,342	[redacted]	[redacted]
	Pazopanib	£175,281	[redacted]	[redacted]
	Tivozanib	£141,977	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: exponential	Sunitinib	£93,241	[redacted]	[redacted]
	Pazopanib	£163,826	[redacted]	[redacted]
	Tivozanib	£135,317	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: Gompertz	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: Gompertz	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
TTD sunitinib: log-logistic	Sunitinib	£93,334	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD sunitinib: exponential	Sunitinib	£93,163	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: Model 1 – ITT population	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: TA645 – ITT population	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	[redacted]
Drug acquisition costs: updated eMIT prices for sunitinib and everolimus	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Exclude RDI for intervention and comparator	Sunitinib	£94,137	[redacted]	[redacted]
	Pazopanib	£177,713	[redacted]	[redacted]
	Tivozanib	£139,192	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Include RDI for subsequent treatment	Sunitinib	£89,012	[redacted]	[redacted]
	Pazopanib	£161,102	[redacted]	[redacted]
	Tivozanib	£132,000	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: TA645	Sunitinib	£69,013	[redacted]	[redacted]
	Pazopanib	£141,104	[redacted]	[redacted]
	Tivozanib	£112,022	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
	Sunitinib	£78,697	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
Subsequent treatment mix: 100% nivolumab or cabozantinib	Pazopanib	£150,788	[redacted]	[redacted]
	Tivozanib	£121,686	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: UK ROC study	Sunitinib	£88,078	[redacted]	[redacted]
	Pazopanib	£160,169	[redacted]	[redacted]
	Tivozanib	£131,067	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Source: Produced by the EAG from the company's model
Ave + axi, avelumab with axitinib; RDI, relative dose intensity; UK ROC study, UK renal oncology collaborative study.
[a] Pairwise ICERs for avelumab with axitinib relative to each comparator. We note that pazopanib and tivozanib are dominated by sunitinib in this analysis, as they have a higher cost and by assumption provide the same QALY gain.

6.2 EAG's preferred assumptions

We have identified a sole key aspect of the company base case with which we disagree. Our preferred model assumption is to use the updated eMIT prices for sunitinib and everolimus as presented in Table 14. The EAG preferred base case results, compared with the company base case results, are provided in Table 22 below. When implementing the EAG assumption, the ICER increases by [redacted] per QALY for avelumab with axitinib versus sunitinib. Probabilistic results for the EAG preferred analysis are shown in Table 23.

Table 22 Comparison of company base case and EAG base case results (favourable-risk population, deterministic analysis)

Base case	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
Company base case	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
EAG preferred base case	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Source: reproduced using company economic model and EAG base case model.
Ave + axi, avelumab with axitinib; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

[a] Pairwise ICERs for avelumab with axitinib relative to each comparator. We note that pazopanib and tivozanib are dominated by sunitinib in this analysis, as they have a higher cost and by assumption provide the same QALY gain.

Table 23 EAG preferred analysis (favourable-risk population, probabilistic analysis)

Treatment	Total			Incremental			ICER [a]
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	(£/QALY)
Versus sunitinib							
Sunitinib	£89,737	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib							
Tivozanib	£137,688	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib							
Pazopanib	£167,817	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 77 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib

6.3 Scenario analysis on the EAG's preferred assumptions

We repeated the same scenarios performed on the company base case on the EAG preferred base case. Results are provided in Table 24 below.

Table 24 Results of scenario analyses with the EAG's preferred assumptions (favourable-risk population, deterministic analysis)

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
EAG's preferred base case	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS avelumab with axitinib: exponential	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	[redacted]
OS avelumab with axitinib: generalised gamma	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: Weibull	Sunitinib	£89,072	[redacted]	[redacted]
	Pazopanib	£164,361	[redacted]	[redacted]
	Tivozanib	135,263	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: exponential	Sunitinib	£90,886	[redacted]	[redacted]
	Pazopanib	£166,184	[redacted]	[redacted]
	Tivozanib	£137,084	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: log-logistic	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: exponential	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: generalised gamma	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: log-logistic	Sunitinib	£88,657	[redacted]	[redacted]
	Pazopanib	£174,804	[redacted]	[redacted]
	Tivozanib	£141,500	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: exponential	Sunitinib	£89,560	[redacted]	[redacted]
	Pazopanib	£163,345	[redacted]	[redacted]
	Tivozanib	£134,836	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: Gompertz	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: exponential	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: Gompertz	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: exponential	Sunitinib	£89,495	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD sunitinib: log-logistic	Sunitinib	£89,533	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD sunitinib: exponential	Sunitinib	£89,489	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: Model 2 – favourable-risk population	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: Model 1 – ITT population	Sunitinib	£89,494	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: TA645 – ITT population	Sunitinib	£89,494	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Exclude RDI for intervention and comparator	Sunitinib	£89,738	[redacted]	[redacted]
	Pazopanib	£177,232	[redacted]	[redacted]
	Tivozanib	£138,711	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Include RDI for subsequent treatment	Sunitinib	£85,391	[redacted]	[redacted]
	Pazopanib	£160,691	[redacted]	[redacted]
	Tivozanib	£131,589	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: TA645	Sunitinib	£65,530	[redacted]	[redacted]
	Pazopanib	£140,830	[redacted]	[redacted]
	Tivozanib	£111,728	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: 100% nivolumab or cabozantinib	Sunitinib	£75,488	[redacted]	[redacted]
	Pazopanib	£150,788	[redacted]	[redacted]
	Tivozanib	£121,686	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: UK ROC study	Sunitinib	£84,766	[redacted]	[redacted]
	Pazopanib	£160,066	[redacted]	[redacted]
	Tivozanib	£130,964	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Ave + axi	[redacted]	[redacted]	

Source: Produced by the EAG from the company's model
Ave + axi, avelumab with axitinib; RDI, relative dose intensity; UK ROC study, UK renal oncology collaborative study.
[a] Pairwise ICERs for Avelumab with axitinib relative to each comparator. Pazopanib and tivozanib are dominated by sunitinib in all scenarios, as they have a higher cost and by assumption provide the same QALY gain.

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of avelumab with axitinib compared to sunitinib, pazopanib, and tivozanib for patients with aRCC. The main focus of the company submission, and therefore this report, is on the favourable-risk population. Information on the intermediate/poor-risk and ITT populations can be found in Appendix 5. For all analyses, pazopanib and tivozanib are assumed to be clinically equivalent to sunitinib, which reflects conclusions in TA645 regarding pazopanib although TA512 had concluded that tivozanib was 'at best' similar to sunitinib or pazopanib. At current prices tivozanib and pazopanib are dominated by sunitinib.

The EAG considers the structure of the model to be reasonable, appropriate, and consistent with previous cost-effectiveness models for aRCC. The company made some minor changes to the model in response to clarification questions. The company's revised base case shows a deterministic ICER of [redacted] per QALY for avelumab with axitinib versus sunitinib, including a PAS discount for avelumab of [redacted]. The mean probabilistic ICER for this base case is [redacted] per QALY, considerably higher than the deterministic equivalent due to higher estimated life years gained in the sunitinib arm. The company noted that "some probabilistic draws of the generalised gamma model for the sunitinib arm (used to model OS) result in unrealistic extrapolations" (CS B.3.9.1). The EAG considers that there were errors in the company's PSA and made some corrections (see 5.3.4). The EAG-corrected mean probabilistic ICER for the company's base case comparison with sunitinib is [redacted] per QALY, a little higher than the company's estimate due to the use of gamma (rather than normal) distributions for resource use and cost parameters in the PSA.

The EAG noted that prices for sunitinib and everolimus used in the company's model are out of date, and we used the updated eMIT prices in the EAG preferred base case (Table 14). Incorporating this change, the deterministic EAG preferred ICER increases to [redacted] per QALY for avelumab with axitinib versus sunitinib, or [redacted] per QALY in the probabilistic analysis. The scenarios with the most influential impact on the model results are the choice

of OS curve for both the intervention and comparator, excluding relative dose intensity, and changing the source of utilities.

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8 APPENDICES

Appendix 1 EAG appraisal of systematic review methods for RCT evidence

Table 25 EAG appraisal of systematic review methods for RCT evidence

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	A PICOS for the broad SLR to support all Health Technology Assessment (HTA) applications is in CS Appendix D Table 26 and a PICOS appropriately matched to the NICE scope is in CS Appendix D Table 27.
Were appropriate sources of literature searched?	Yes	Core healthcare databases (MEDLINE and MEDLINE In-Process, Embase, Cochrane CDSR and CENTRAL, DARE and the HTA Database), four main urology and cancer conferences, and the bibliographies of relevant systematic reviews were searched (CS Appendix D.2).
What time period did the searches span and was this appropriate?	Yes	Searches for the original SLR were conducted from database inception, and the latest update searches were carried out on 4 June 2024. There were no gaps in coverage between all update searches (CS Appendix D.2). The conferences were searched from 2016 to 2024 (CS Appendix D.2.1).
Were appropriate search terms used and combined correctly?	Yes	Subject headings and free text terms were used for kidney cancer and advanced disease stage, for all the interventions in the NICE scope, and for RCT study design (CS Appendix D.1.1).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Eligibility criteria specified according to the PICOS are reported in CS Appendix D Table 26. A separate PICOS that matches the NICE final scope is reported in CS Appendix D Table 27.
Were study selection criteria applied by two or more reviewers independently?	Yes	All screening was performed by two independent reviewers and any uncertainty was checked by a third reviewer (CS Appendix D.3).
Was data extraction performed by two or more reviewers independently?	Yes	The number of reviewers is not reported, but more than two reviewers is implied because the CS states that a senior reviewer checked the extracted data against the original source article (CS Appendix D.4).
Was a risk of bias assessment or a quality assessment of the included studies	Yes	The JAVELIN Renal 101 trial was assessed using the NICE RCT checklist in the STA manual (CS Appendix D.5.2). Risk of bias assessment tools differed between SLR updates, the RCTs included in

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
undertaken? If so, which tool was used?		the ITC were assessed using the NICE checklist and the Cochrane RoB 2.0 checklist (clarification question A9).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Critical appraisal was conducted in parallel to the data extraction – all extracted data including quality checks were verified and checked by another independent reviewer (clarification question A10).
Is sufficient detail on the individual studies presented?	Mostly	All relevant study documents (CSR, protocol, SAP) and publications were provided for the pivotal JAVELIN Renal 101 trial. It is unclear whether the PRISMA flow diagram for the RCT SLR (CS Appendix D Figure 1) screening information is aligned with the PICOS in Table 26 or the PICOS that is aligned with the NICE scope in Table 27, and it is unclear how the middle column relates to each update search results. RCTs included in the ITC, were not summarised in sufficient detail in the main CS, however this was addressed by some tabulation of baseline characteristics in response to clarification question A9.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Mostly	An ITC was conducted for the intermediate-/poor-risk populations for overall survival and progression free survival. Details of the methods in the CS were limited, e.g. there was no critical appraisal of the included RCTs and no assessment of heterogeneity, but this was later provided in clarification question A.9. The ITC is discussed in sections 3.3 and 3.4

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CSR, clinical study report; DARE, Database of Abstracts of Reviews of Effects; ITC, indirect treatment comparison; NMA, network meta-analysis; PICOS, population intervention comparator outcomes study design framework; PRISMA, Preferred Reporting Items for Systematic Reviews; RCT, randomised controlled trial; RoB, risk of bias; SAP, statistical analysis plan; SLR, systematic literature review.

Appendix 2 EAG appraisal of systematic review methods for RWE evidence

Table 26 EAG appraisal of systematic review methods for RWE evidence

Systematic review components and processes	EAR response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	Comparators were not searched for nor eligible for inclusion. The review question is set up to identify supportive evidence for avelumab plus axitinib, not further comparative evidence. CS Appendix D.6.
Were appropriate sources of literature searched?	Yes	Core healthcare databases of MEDLINE, MEDLINE In-Process, Embase and Cochrane for CDSR and CENTRAL, and the bibliographies of relevant systematic reviews were searched. A broader range of conferences, than for the RCT SLR, was also searched. CS Appendix D.6.3.1.
What time period did the searches span and was this appropriate?	Yes	Databases and conferences were searched from 2019 to 29 July 2024. The start date is appropriate to the first approval date for the avelumab with axitinib combination (FDA, May 2019; EMA, May 2019; available via EAMS August 2019; EC, October 2019). The searches are only three months old. CS Appendix D.6.3.1.
Were appropriate search terms used and combined correctly?	Yes	The search included the relevant disease terms but did not search on disease stage, so the search is broader than for the RCT SLR. The RWE terms were comprehensive (CS Appendix D.6.3.2).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes. Partially.	Eligibility criteria are reported in CS Appendix D Table 34. The criteria are relevant to the company's purpose for the SLR, but it is only partially relevant to the decision problem because it is focusing on the intervention only and does not seek to identify real-world evidence for the comparator treatments.
Were study selection criteria applied by two or more reviewers independently?	Yes	Two reviewers worked independently to review all abstracts and full-text articles identified by the search strategy, and a third reviewer arbitrated any discrepancies (CS Appendix D.6.3.4).

Systematic review components and processes	EAR response (Yes, No, Unclear)	EAG comments
Was data extraction performed by two or more reviewers independently?	Yes	A second reviewer verified the extracted data against the original source paper (CS Appendix D.6.3.4). Therefore, data extraction was not performed independently, but the process is sufficient.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	Included studies (UK only) were appraised using the ROBINS-I tool (CS Appendix D.6.4.3 and Table 36). Summary results and overall risk of bias judgements were made, but no justifications or details are reported for any of the judgements.
Was a risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Critical appraisal was conducted in parallel to the data extraction – all extracted data including quality checks were verified and checked by another independent reviewer (clarification question A10).
Is sufficient detail on the individual studies presented?	Yes	The relevant study reports and publications were provided with the submission. An RWE SLR report was provided with the clarification response.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not carried out	The evidence that was identified was not suitable for statistical synthesis. A narrative summary was provided in CS section B.2.8.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; EAMS, Early Access to Medicines Scheme; EC, European Commission; EMA, European Medicines Agency; FDA, Food and Drug Administration (USA); ITC, indirect treatment comparison; NMA, network meta-analysis; PICOS, population intervention comparator outcomes study design framework; RCT, randomised controlled trial; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions; RWE, real-world evidence; SLR, systematic literature review.

Appendix 3 Risk of bias assessment for JAVELIN Renal 101

Table 27 Risk of bias assessment for JAVELIN Renal 101

Question	Company assessment	EAG comment
Was the randomisation method adequate?	Yes. Patients were centrally assigned to randomised in a 1:1 ratio to avelumab with axitinib or sunitinib treatment, via an interactive response technology system. Randomisation was stratified by ECOG performance status and region. However, subgroups were not stratified by baseline characteristics and there were minor differences between the subgroups, although baseline characteristics were generally balanced between the treatment arms with the risk subgroups.	Agree. **Low risk of bias.**
Was the allocation adequately concealed?	Due to the different routes of administration, concealment of treatment allocation was not possible. For PFS, BICR was used to minimise bias (see below).	The company comments refer to blinding. The method of allocation using an interactive response technology system usually indicates that the allocation was concealed. **Low risk of bias.**
Were the groups similar at the outset of the study in terms of prognostic factors?	In patients irrespective of PD-L1 expression as well as in patients with PD-L1 positive tumours, similar distributions of ECOG performance status, MSKCC and IMDC (Heng) prognostic criteria at baseline were observed in both treatment arms. Baseline characteristics were balanced between the treatment arms within the risk subgroups, with the exception of the sunitinib arm containing a greater proportion of male patients ([redacted]%) vs the avelumab with axitinib arm ([redacted]%) in the favourable-risk group.	Agree. **Low risk of bias** for the overall trial population (ITT analysis). Clinical expert advice to the EAG was that sex is not a prognostic factor for aRCC so the proportion of male and female participants is not a concern.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Although JAVELIN Renal 101 was an open-label study, BICR was used to minimise bias that could be introduced into the assessment by the investigator, based on the knowledge of treatment assignment at randomisation. To mitigate the potential for bias in determining disease progression, expedited BICR	As an open-label study the investigators and participants were not blind to treatment allocation. BICR assessment for disease progression was not performed after the second interim analysis.

Question	Company assessment	EAG comment
	review was performed for investigator-assessed disease progression. All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory. All patients' files and radiologic images must be available for source verification and peer review.	Therefore, the results reported in the final analysis for this submission include investigator-assessed disease progression and so may be at risk of bias. It is not possible for the EAG to verify consistency of BICR PFS assessments with the investigator PFS assessments by viewing the results on the same plot as the company do not believe it is appropriate to do so (clarification response A1) Other subjective outcomes are also at risk of bias. **Moderate risk of bias.**
Were there any unexpected imbalances in drop-outs between groups?	No. Patients discontinued avelumab (94.6%), axitinib (93.9%), and sunitinib (97.7%) in comparable proportions.	Agree. (See CS Table 11). **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the clinical study report.	Agree with company assessment of the protocol and the CSR. The CS states that time to deterioration in FKSI-DRS was assessed (CS Table 6 and 7) however clarification response A2 confirms that time to deterioration in FKSI-DRS was only assessed and presented at the first interim analysis and data was not available for the final analysis. FKSI-DRS scores by visit are reported in the final

Question	Company assessment	EAG comment
		analysis CSR. **Low risk of bias**.
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. Efficacy analyses were performed using the full analysis set, defined as all randomised patients. Unless otherwise specified, all data were evaluated as observed, and no imputation method for missing values was used.	Agree. Additionally, the favourable- and intermediate-/poor-risk subgroup analyses, relevant to this appraisal, included all randomised patients within the per protocol pre-specified subgroups. **Low risk of bias.**
Was there good quality assurance for this trial?	Yes. The trial was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki Council and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, applicable ISO 14155 guidelines, medical device guidelines, and other applicable laws and regulations, including privacy laws. A quality assurance audit was conducted	Does not affect risk of bias. No EAG comment.

Source: Reproduced from CS Table 12, with added EAG comments.
Abbreviations: BICR, blinded independent central review; CIOMS, Council for International Organization of Medical Sciences; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms (subscale of FKSI-19); GCP, good clinical practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMDC, International Metastatic RCC Database Consortium; ISO, International Organization for Standardization; ITT, intention-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death ligand 1; PFS, progression free survival.

Appendix 4 Trials included in the company NMA

Table 28 Trials included in the company NMA, their use in previous NICE appraisals and identified risk of bias.

Trial name (trial author and year)	Comparison	In NMAs for previous NICE appraisals	Domain level risk of bias concerns[a] reported in or inferred from previous appraisals
CABOSUN (Choueiri 2018)	Cabozantinib vs Sunitinib	TA645 TA858 TA964	High risk of selection bias due to dynamic allocation of treatment[57] High risk of performance and detection bias due to lack of blinding[25 71] partly mitigated by use of BICR assessments for PFS and ORR outcomes.[71] Risk of bias due to missing outcome data reported as unclear[57] with methods used to account for missing data judged either adequate[25] or inadequate[57].
CheckMate 214 (Motzer 2018)	Nivolumab + ipilimumab vs Sunitinib	TA858 TA964	High risk of performance bias due to lack of blinding for subjective outcomes[57 71] Unclear risk of attrition bias[57].
JAVELIN Renal 101 (Motzer 2019)	Avelumab + axitinib vs Sunitinib	TA645 TA964	High risk of performance[57] and detection bias due to lack of blinding[25] Some concerns about inadequate methods to account for missing data[57].
CLEAR (Motzer 2021)	Lenvatinib + pembrolizumab vs Sunitinib	TA858 TA964	High risk of performance bias due to lack of blinding[71] Unclear[57] risk of attrition bias due to very high differential attrition with unclear methods to account for missing data. Unclear reporting bias due to some trial registry outcomes not being reported in published papers.[57]
CheckMate 9ER (Choueiri 2021)	Nivolumab + cabozantinib vs Sunitinib	TA964	High risk of performance and detection bias due to lack of blinding[57] Unclear[57] risk of attrition bias due to very high differential attrition with unclear methods to account for missing data.

Source: EAG table compiled from information in the EAG reports from previous NICE appraisals
BICR, blinded independent central review; ORR, objective response rate; PFS, progression free survival.
[a] Only concerns of high or unclear risks of bias are reported here. Reports of low concerns of bias are not included in this table.

Appendix 5 EAG critique of economic analyses for intermediate-/poor-risk and ITT populations

CS Appendix O contains the model inputs and assumptions specific to the intermediate-/poor-risk and ITT subgroups. It also presents the model results for the ITT population while CS section B.3.10 shows the model results for the intermediate-/poor-risk subgroup. In their response to the clarification questions, the company updated their model. The revised model received as part of the clarification response (and referred here as 'the revised company model') includes changes to:

- Adverse event specific costs are applied rather than a single value for all adverse events, with costs updated to the 22/23 National Cost Collection.
- Blood test, CT scan, simple IV and complex IV costs have been updated from 21/22 to 22/23 National Cost Collection values.
- All poor risk subsequent therapies are considered (only affects the intermediate-/poor-risk population results)

The company's deterministic pairwise results for the intermediate-/poor-risk subgroup and the ITT population are shown in Table 29 and Table 30 below. Avelumab plus axitinib is dominated or presents ICERs above £60,000 per QALY against all the comparators in both populations.

Table 29 Revised company results for the intermediate-/poor-risk subgroup – PAS price for avelumab

Technologies	Total			Incremental		ICER (£/QALY)	INMB (£30,000 / QALY)
	Costs	LYG	QALYs	Costs	QALYs		
Versus sunitinib							
Sunitinib	£72,283	5.05	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus tivozanib							
Tivozanib	£99,613	5.05	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus pazopanib							
Pazopanib	£117,935	5.05	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus cabozantinib							
Cabozantinib	£128,584	6.49	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus nivolumab plus ipilimumab							
Nivolumab plus ipilimumab	£117,515	7.67	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus lenvatinib with pembrolizumab							
Lenvatinib with pembrolizumab	£196,392	7.09	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus cabozantinib with nivolumab							
Cabozantinib with nivolumab	£151,668	8.17	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from Table 13 of the clarification response document.
ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life-years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life-years

Table 30 Revised company results for the ITT population – PAS price for avelumab

Technologies	Total			Incremental		ICER (£/QALY)	INMB (£30,000 / QALY)
	Costs	LYG	QALYs	Costs	QALYs		
Versus sunitinib							
Sunitinib	[redacted]	5.59	[redacted]				
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus tivozanib							
Tivozanib	[redacted]	5.59	[redacted]				
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus pazopanib							
Pazopanib	[redacted]	5.59	[redacted]				
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from Table 14 of the clarification response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life-years; NMB, net monetary benefit.

EAG best case scenario analysis for intermediate/poor-risk and ITT populations

The EAG has changed the model inputs and assumptions for these two subgroups in order to obtain the most optimistic results for avelumab with axitinib. See Table 31 for the results and Table 31 below for the model inputs and assumptions of the best-case scenarios. Please note that this is just an exploratory exercise to show how the model behaves for these populations and some of the inputs and assumptions might lack face validity and not be plausible. Also, we note that these results use the PAS price discount for avelumab and the agreed discount for pazopanib, but no confidential price discounts are applied for axitinib or for any comparator or subsequent.

We conclude that, even in the best-case scenario explored by the EAG, avelumab plus axitinib is not cost-effective at a WTP threshold of £30,000 per QALY, except in the following situations:

- **Poor-/intermediate-risk population**: avelumab with axitinib is dominant versus pembrolizumab + lenvatinib and cabozantinib + nivolumab. However, we note that some of the assumptions behind these results are not clinically valid. For example, the HRs for OS are assumed to be the same as for sunitinib, in which avelumab with axitinib has a greater survival than the comparators. If a lower or equal survival is assumed for avelumab with axitinib and these two comparators, the ICERs are higher than £30,000 per QALY.

- **ITT population**: avelumab with axitinib has ICERs lower than pairwise £30,000 per QALY versus tivozanib and pazopanib. This is driven by the change in the RDIs as shown in Table 31, which might not be clinically valid. The RDIs for avelumab with axitinib are much lower than in the base case (around 60%) and also much lower than the RDIs for tivozanib and pazopanib (around 90%). This assumption seems counter-intuitive, and it is not supported by the available evidence. By changing this, the ICER for avelumab with axitinib versus tivozanib and pazopanib is above £30,000 per QALY.

Based on the above findings, we have not conducted a detailed critique of the model inputs and assumptions for the intermediate-/poor-risk and ITT subgroups.

Table 31 EAG exploratory best-case scenario results

Comparator	Pairwise ICERs (£/QALY)	
	Intermediate-/poor-risk	ITT population
Sunitinib	[redacted]	[redacted]
Tivozanib	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]
Cabozantinib	[redacted]	-
Nivolumab + ipilimumab	[redacted]	-
Pembrolizumab + Lenvatinib	[redacted]	-
Cabozantinib + nivolumab	[redacted]	-

Source: Produced by the EAG from the company's model
CS, company submission; HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; RDI, relative dose intensity; ToT, time on treatment.

Table 32 EAG exploratory best-case scenarios parameters and assumptions

Model feature		Intermediate-/poor-risk	ITT population
Comparator treatments and dosing details		CS Appendix O Table 49	CS Appendix O Table 49
Baseline characteristics		CS Appendix O Table 50	CS Appendix O Table 51
OS curves	Avelumab + axitinib	Log-normal	Log-normal
	Sunitinib/ tivozanib/ pazopanib	Weibull	Weibull
OS HRs	Cabozantinib	0.88	-
	Nivolumab + ipilimumab	0.88	-
	Pembrolizumab + Lenvatinib	0.88	-
	Cabozantinib + nivolumab	0.88	-
PFS curves	Avelumab + axitinib	Gompertz	Gompertz
	Sunitinib/ tivozanib/ pazopanib	Exponential	Exponential
PFS HRs	Cabozantinib	0.64	-
	Nivolumab + ipilimumab	[redacted]	-
	Pembrolizumab + Lenvatinib	[redacted]	-
	Cabozantinib + nivolumab	[redacted]	-
ToT curves	Avelumab	Exponential	Exponential
	Axitinib	Exponential	Exponential
	Sunitinib/tivozanib/pazopanib	Log-logistic	Log-logistic
	Cabozantinib	Log-logistic	-
HRQoL	Progression-free	0.80 (TA417)	0.80 (TA417)
	Progressed disease	0.76 (TA417)	0.76 (TA417)

Model feature		Intermediate-/poor-risk	ITT population
RDIs	Avelumab	94%	62.9%
	Axitinib	94%	62.9%
	Sunitinib	94%	94%
	Tivozanib	94%	94%
	Pazopanib	94%	94%
	Cabozantinib	94%	-
	Nivolumab	94%	-
	Ipilimumab	94%	-
	Pembrolizumab	62.9%	-
	Lenvatinib	62.9%	-
Subsequent therapies		CS Appendix O Table 91	CS Appendix O Table 93

Source: Produced by the EAG
CS, company submission; HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; RDI, relative dose intensity; ToT, time on treatment.

Appendix 6 Summary of EAG conclusions on the company's model

Table 33 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG additional analysis
Key model features			
Model structure	Partitioned survival model	We agree	No change
Population	Untreated aRCC favourable-risk subgroup in base case. Results for poor / intermediate risk (CS B.3.10) and ITT population (Appendix O).	We agree. Results are less favourable for poor-intermediate risk and ITT groups. We check that this conclusion applies with all confidential drug price discounts.	EAG to report base case results for the poor-intermediate risk and ITT groups in the EAR confidential price addendum
Comparators	Sunitinib, pazopanib and tivozanib	We agree	No change
Perspective	NHS and PSS	We agree	No change
Time horizon	40 years	We agree	No change
Discounting	3.5% for costs and outcomes	We agree	No change
Model inputs			
Baseline characteristics	Based on favourable-risk subgroup in JAVELIN Renal 101 trial (mean age [redacted] years, [redacted] female)	We agree	No change
Clinical effectiveness			
OS avelumab with axitinib	Log-normal	AIC/BIC best fit: log-logistic. The EAG considers the choice of parametric curve for OS to be a key issue. See Key Issue 2.	No change to base case EAG scenarios: • Log-logistic, exponential, and generalised gamma
OS sunitinib	Generalised gamma	AIC/BIC best fit: Weibull. Pathways model: base case exponential, scenario Weibull.	No change to base case EAG scenarios:

Parameter	Company base case	EAG comment	EAG additional analysis
		The EAG considers the choice of parametric curve for OS to be a key issue. See Key Issue 2.	• Weibull and exponential
PFS avelumab with axitinib	Log-normal	AIC/BIC best fit: log-normal.	No change to base case EAG scenarios: • Log-logistic, exponential, and generalised gamma
PFS sunitinib	Generalised gamma	AIC/BIC best fit: log-normal and exponential. Pathways model: base case log-logistic, scenario Weibull.	No change to base case EAG scenarios: • Log-logistic and exponential
TTD avelumab	Generalised gamma	AIC/BIC best fit: Gompertz and exponential.	No change to base case EAG scenarios: • Gompertz and exponential
TTD axitinib	Generalised gamma	AIC/BIC best fit: Gompertz and exponential.	No change to base case EAG scenarios: • Gompertz and exponential
TTD sunitinib	Generalised gamma	AIC/BIC best fit: exponential. Pathways model: base case log-logistic, scenario generalised gamma.	No change to base case EAG scenarios: • Log-logistic and exponential

Parameter	Company base case	EAG comment	EAG additional analysis
Adverse event incidence	CS Table 56, based on treatment related grade ≥ 3 from the JAVELIN Renal 101 trial	We agree	No change
Utilities			
Health state utilities	Trial EQ-5D-5L data mapped to UK EQ-5D-3L values with the NICE recommended method.	We agree with the company's base case health state utilities (Model 1), and the scenario with treatment status (Model 2). Age-adjustment of utilities is appropriate.	No change to base case EAG scenarios (see Table 13): • Model 2 - favourable risk • Model 1 - ITT population • TA645 - ITT population
Adverse event disutilities	Not included, as disutility from AEs is reflected in trial EQ-5D data.	We agree. Accepted in TA645	No change
Severity modifier	Not applicable.	We agree	No change
Resource use and costs			
Drug acquisition costs	List prices from BNF and eMIT, with PAS price discounts for avelumab and pazopanib. Scenarios for potential price reductions for axitinib.	eMIT 2023-24 has lower prices for sunitinib and everolimus. Results with other all available discounts in confidential EAR addendum. We do not report alternative price scenarios for axitinib, as this is not usual practice.	EAG base case: Update eMIT prices for sunitinib and everolimus (Table 14) EAG addendum: include all available price discounts from the NICE Pricing Tracker form
Relative dose intensity	RDI adjustment to costs for avelumab, axitinib and sunitinib (JAVELIN Renal 101), tivozanib (TA512) and pazopanib (TA215). No RDI used for subsequent treatments.	We agree with the approach for the intervention and comparators, but note that RDI estimates for subsequent treatments in clinical trials are available (Table 15)	No change

Parameter	Company base case	EAG comment	EAG additional analysis
Administration costs	Delivery costs for IV drugs only: avelumab and nivolumab. No costs for administration of oral therapies.	TA645 included costs for oral drugs as well as IV. Costs for initiation and ongoing delivery of oral medications are available from RCC Pathway pilot model	No change
Subsequent treatment mix	JAVELIN Renal 101 trial data. Scenarios based on TA645[1]; assumption of 100% nivolumab or cabozantinib, and RWE from the UK ROC study (McGrane 2024)[5]	We agree with the base case and scenarios reported by the company. We McGrane et al. scenario may be more reflective of UK practice than the JAVELIN Renal 101 trial, although the sample size is limited (n=66 with favourable-risk disease treated IO/TKI combination at first line was low	No change to EAG base case EAG scenarios: • TA645 • 100% nivolumab or cabozantinib • UK ROC study
Other health state costs	Various (CS Tables 65 and 66)	We agree	No change
Adverse event costs	Updated in response to clarification question B.9	We agree	No change
End of life costs	Estimate from Round et al. (2015), uprated for inflation.[68 69]	We agree	No change

Source: produced by the EAG from information in the CS and model, and from various other sources
NHS, National Health Service; PAS, Patient Access Scheme; PD, progressed disease; PF, progression-free; PSS, personal social services; RDI, relative dose intensity.

Single Technology Appraisal

Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645) [ID6294]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 4 February** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Responses to EAG's identified issues

Description of problem	Company response	EAG response
EAG Issue 1: Effectiveness of avelumab with axitinib versus comparators for people with non-clear-cell aRCC "*A key uncertainty from TA645 (paragraph 3.19 of the NICE guidance document) was the lack of data on whether avelumab with axitinib is effective for non-clear-cell disease. The committee agreed that this was one of two uncertainties that could be resolved by collecting further data to monitor whether there is a difference in effectiveness in comparison to those with clear-cell histology (paragraph 3.7 of the NICE guidance document). Data collected from patients treated within the Cancer Drugs Fund shows that median overall survival (OS) in the non-clear cell population (n=[redacted]) is [redacted] shorter than for the clear cell aRCC population (n=[redacted]). However, as*	The company recognises that there is no direct comparative evidence for avelumab plus axitinib against relevant comparators for people with non-clear-cell aRCC. To address this, the company consulted two clinical experts who advised that real-world datasets support the use of avelumab plus axitinib in these patients, including those with favourable-risk disease (e.g., UK EAMS RWE, Japan RWE, SACT) (1–3). Additional to the SACT data collected as part of this CDF review, the UK EAMS RWE (n=15) show a median overall survival (mOS) of 21.5 months for people with non-clear-cell aRCC. In a post-marketing surveillance study in people with aRCC treated with avelumab + axitinib in Japan, the mOS was not reached in patients with non-clear cell aRCC (n=22). Non-clear-cell aRCC includes various histological subtypes. Clinical experts noted that when these subtypes are grouped together, the expected outcomes are worse than those for people with clear-cell aRCC (4). The SACT data does not distinguish between the subtypes of non-clear-cell aRCC. Furthermore, it does not indicate the proportion of IMDC favourable risk patients	This is not a factual inaccuracy therefore no change made to the EAG's report. As far as we are aware one of the three references cited by the company was included in the CS, but data for non-clear cell aRCC from these references were not presented in any detail or discussed.

the Cancer Drugs Fund does not include data for people with non-clear-cell disease treated with the possible comparator treatments the effectiveness of avelumab with axitinib in comparison to relevant comparators in this group of patients is still unknown." The EAG requests clinical expert opinion on whether the JAVELIN Renal 101 trial results in people advanced renal cell carcinoma (aRCC) with clear-cell histology are likely to be generalisable to people with aRCC of non-clear-cell histology.	with non-clear-cell aRCC compared with those with clear-cell histology. Patients with non-clear-cell aRCC have been excluded from all Phase 3 registrational trials of relevant comparators across all IMDC groups. Despite the absence of evidence from these Phase 3 studies, ESMO guidelines recommend immune checkpoint inhibitors combined with TKIs (IO+TKIs) for various non-clear-cell aRCC subtypes, including chromophobe, sarcomatoid (predominant), and papillary aRCC (5). This recommendation was further supported by the clinical experts. Although there are no comparative effectiveness data of avelumab plus axitinib for patients with non-clear-cell aRCC, there remains a significant unmet need for those with favourable-risk non-clear-cell aRCC. If access to the avelumab and axitinib combination is withdrawn, these patients will have no options for immune checkpoint inhibitors in the first-line setting.	
Clarification regarding the application of the on-treatment coefficient in the scenario utility model 2. **Section 4.2.5.2., page 71** *"We note a discrepancy in the reporting of the Model 2 'On treatment' status coefficient as a*	Thank you to the EAG for highlighting this discrepancy. To clarify, the application in the cost-effectiveness model is correct. The dossier had a missing minus symbol in front of the coefficient. This has been corrected in the CS document B as part of the factual accuracy and confidentiality check.	Thank you for confirming the correct coefficient. We have added a clarification on this point in EAR section 4.2.5.2 (page 71) and removed the reference to this as an uncertainty in EAR section 1.8. In addition, we have deleted the EAG scenarios relating to this issue from EAR

positive value ([redacted]) in CS Table 57, and the way that it is applied in the company's model as a decrement (due to an adjustment in cells X160-X162 on the Parameters sheet). It is not clear from the company's reporting of the utility regression which of these interpretations is correct."		Tables 19, 20, 22 and 31 and the corresponding tables in the EAR confidential Addendum.

Issue 2 Missing or incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The text notes that the EAG believes there is an error in CS Table 32 which reports only 57 (13.1%) infusion-related reactions of all grades **Section 3.2.5.7.1, page 41** "We believe there is an error in CS Table 32 which reports only 57 (13.1%) infusion-related reactions of all grades."	Removal of the following text from Section 3.2.5.7.1, page 41 "We believe there is an error in CS Table 32 which reports only 57 (13.1%) infusion-related reactions of all grades."	This is not an error and is what the JAVELIN Renal 101 FA CSR reports. Please see: Table 21 in the CSR Table 31 in CS is Summary of adverse events during the on-treatment period (see CSR Table 20) Table 32 in CS is Summary of most common TEAEs (any grade in ≥10% of participants or Grade ≥3 in ≥5% participants in any treatment arms) by maximum CTCAE	Thank you for highlighting our concern. We did not understand why CS Table 31 (Adverse events) reports [redacted] of participants in the avelumab arm experiencing infusion related reactions whereas CS Table 32 (Summary of most common TEAEs) reports 13.1% of participants in the avelumab arm experiencing infusion

		grade during the on-treatment period (see CSR Table 21)	related reactions. As we could not explain the difference, we suggested there might be an error. Text in Section 3.2.5.7.1 of our report has been amended and now reads "CS section B.2.11.4.2 and CS Table 31 report that infusion-related reactions were experienced by [redacted]% of participants. CS Table 32 reports TEAEs which included 57 (13.1%) infusion-related reactions of all grades with [redacted]%) Grade >3 infusion-related reactions. It is not clear to us why the proportion of patients with infusion-related reactions differs between CS Table 31 and CS Table 32."

Section 3.2.5.7.2, page 42 *"CS section B.3.3.3 states that time to treatment discontinuation was reported separately for avelumab and axitinib in the JAVELIN Renal 101 data, but it is not clear where in the CSR it is reported."*	Removal of the following text from Section 3.2.5.7.2, page 42 *"CS section B.3.3.3 states that time to treatment discontinuation was reported separately for avelumab and axitinib in the JAVELIN Renal 101 data, but it is not clear where in the CSR it is reported."*	Time to treatment discontinuation (TTD) is not reported in the CSR. TTD used in the model was derived from the JAVELIN Renal 101 trial data.	Thank you for clarifying that TTD is not reported in the CSR. We have removed the text indicated from Section 3.2.5.7.2, page 42 and amended the first sentence of the second paragraph in section 3.2.5.7.2 so this now reads "Time to treatment discontinuation is used in the economic model (CS Table 6; CS section B.3.3.3) and was derived from the JAVELIN Renal 101 trial data."
The text notes hazard plots might help to resolve the key issue. OS hazard plots from JAVELIN Renal 101 for the favourable risk population are available in the company response to clarification document (response to question B2). **Section 1.6, Issue Table 2**	Removal of following text from Issue Table 2: *"Hazard plots from the JAVELIN Renal 101 trial OS data to show how hazards changed over time for patients with favourable-risk disease in the avelumab with axitinib and sunitinib arms"*	Hazard plots were requested by the EAG and included in the company response at the clarification stage (question B2).	The comment in EAG Table 2 relates to hazard plots of the mortality hazard against time *on the hazard scale*. This would provide a better means of visualising whether and how hazards change over time than the log-cumulative

"Hazard plots from the JAVELIN Renal 101 trial OS data to show how hazards changed over time for patients with favourable-risk disease in the avelumab with axitinib and sunitinib arms"			hazards plot in Figure 3 of the company's response to clarification question B2. This reflects the TSD21 recommendation that fitted (and extrapolated) hazard functions should be presented.
Incorrect estimated 5-year PFS for the sunitinib generalised gamma extrapolation. **Section 4.2.4.2, Table 11** [redacted]	Value should be [redacted]	Correction of value	Thank you for identifying this error. We have corrected the value from [redacted]
Incorrect estimated 20-year TTD for the sunitinib Gompertz extrapolation. **Section 4.2.4.3, Table 11** [redacted]	Value should be 0.1%	Correction of value	This is not a factual inaccuracy. We note that Table 11 of the EAG report concerns PFS: TTD is reported in Table 12. According to the updated economic model provided to the EAG with the clarification response, the estimated 20-year TTD value for sunitinib using the Gompertz

			extrapolation is [redacted] The corresponding PFS value using the Gompertz model is [redacted] This is in line with the values reported in Table 11 (PFS) and Table 12 (TTD) of the EAG report.
Everolimus stated in place of cabozantinib in three instances. **Section 6.1, Table 19** *"Updated eMIT prices for sunitinib and everolimus"* **Appendix 6, Table 31** *"eMIT 2023-24 has lower prices for sunitinib and everolimus"* *"EAG base case: Update eMIT prices for sunitinib and everolimus"*	Text should read: **Section 6.1, Table 19** *"Updated eMIT prices for sunitinib and **cabozantinib**"* **Appendix 6, Table 31** *"eMIT 2023-24 has lower prices for sunitinib and **cabozantinib**"* *"EAG base case: Update eMIT prices for sunitinib and **cabozantinib**"*	Correction of drug name	Thank you for raising this discrepancy. We have not changed the price of cabozantinib in EAG analysis, it is the prices of sunitinib and *everolimus* that we updated based on more recent eMIT data (as stated in EAR section 4.2.6.2.1 and Table 14, and in the results tables in Chapter 6). We have corrected the references to updated prices for cabozantinib in EAR sections 1.2, 1.8, 6.2 and 6.4. Sorry for the confusion.

Please can we clarify the *"Utilities: Model 1 – ITT population"* scenario. Our understanding is that the scenarios in this table relate to the favourable-risk population. However, the ICERs presented for this scenario are achieved by changing the **population** (i.e., not the utility values) from favourable-risk to ITT. We believe the results should have been calculated by changing the **utility source** from favourable-risk to ITT. **Section 6.1, Table 20** All results associated with *"Utilities: Model 1 – ITT population results"*	The scenario should be calculated by changing the utility source in the model, not the population, from favourable-risk to ITT The results should be: Total costs: avelumab + axitinib [redacted], sunitinib [redacted], pazopanib [redacted], tivozanib [redacted] Total QALYs: avelumab + axitinib [redacted], sunitinib [redacted], pazopanib [redacted], tivozanib [redacted] ICERs: vs sunitinib [redacted], pazopanib [redacted] and tivozanib [redacted]	We believe this scenario has been implemented incorrectly.	Thank you for highlighting this issue. We agree and have amended the results as requested.
Per row above, please can we clarify the *"Utilities: Model 1 – ITT population"* scenario. Our understanding is that the scenarios in this table relate to the favourable-risk population.	The scenario should be calculated by changing the utility source in the	We believe this scenario has been implemented incorrectly.	Again, thank you for highlighting this issue. We have corrected the scenario results.

However, the ICERs presented for this scenario are achieved by changing the **population** (i.e., not the utility values) from favourable-risk to ITT. We believe the results should have been calculated by changing the **utility source** from favourable-risk to ITT. **Section 6.3, Table 22** All results associated with *"Utilities: Model 1 – ITT population results"*	model, not the population, from favourable-risk to ITT. The results should be: Total costs: avelumab + axitinib [redacted], sunitinib [redacted] pazopanib [redacted] tivozanib [redacted] Total QALYs: avelumab + axitinib [redacted], sunitinib [redacted], pazopanib [redacted], tivozanib [redacted] ICERs: vs sunitinib [redacted], pazopanib [redacted] and tivozanib [redacted]		
There is a discrepancy in the way a scenario is applied in Table 20 and Table 22. Please can we have clarification on the *"Utilities: TA645 – ITT population results"* scenario. In Table 20, the utilities from TA645 are applied to the **favourable risk population**. In Table 22, the	The scenario in Table 22 should be calculated with the favourable-risk	We believe the scenario in Table 22 has been implemented incorrectly.	Thank you for highlighting this discrepancy. We have amended the scenario results.

utilities from TA645 are applied to the **ITT population**. We believe the results should have been calculated using the **favourable-risk population**. **Section 6.3, Table 22** All results associated with *"Utilities: TA645 – ITT population results"*	population. The results should be: Total costs: avelumab + axitinib [redacted], sunitinib [redacted] pazopanib [redacted] tivozanib [redacted] Total QALYs: avelumab + axitinib [redacted], sunitinib [redacted], pazopanib [redacted], tivozanib [redacted] ICERs: vs sunitinib [redacted], pazopanib [redacted] and tivozanib [redacted]		

Issue 3 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, page 11 *"Data collected from patients treated within the Cancer Drugs Fund shows that median overall survival (OS) in the non-clear cell population ([redacted]) is [redacted] than for the clear cell aRCC population ([redacted])."* **Section 3.6, page 57** *"It shows that median OS in the non-clear cell population ([redacted]) is [redacted] than for the clear cell aRCC population (n=1019)"*	Text should read: *"([redacted])."* (in both instances)	Incorrect number	Thank you. We have corrected both instances of this typographical error.
Section 4.2.6.2.4, page 74 *"National Cost Collection 2022/34"*	Text should read: *"National Cost Collection 2022/**23"***	Incorrect year	Thank you. This typographical error has been corrected.

References

1. Nathan PD, Frazer R, McGrane J. A UK real-world observational study of avelumab + axitinib (A+Ax) in advanced renal cell carcinoma (RCC): exploratory analysis of 24-month interim results in patients with non-clear cell histology. In: International Kidney Cancer Symposium: Europe. 2023.

2. Nonomura N, Ito T, Sato M, Morita M, Kajita M, Oya M. Post-marketing surveillance data for avelumab + axitinib treatment in patients with advanced renal cell carcinoma in Japan: Subgroup analyses by pathological classification. Int J Urol. 2024 Dec 19;

3. Data on file. NHS England (NDRS). Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma. Data review. Report for the NICE Appraisal Committee.

4. Urman D, Deshler L, Weise N, Shabaik A, Derweesh I, Bagrodia A, et al. Outcomes of Patients With Advanced Renal Cell Carcinoma With Non-Clear Cell Histology Treated With Systemic Therapy. Clinical Genitourinary Cancer. 2023 Dec 1;21(6):660-668.e1.

5. Powles T, Albiges L, Bex A, Comperat E, Grünwald V, Kanesvaran R, et al. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024 Aug;35(8):692–706.