NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Merck Sharp & Dohme**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Kidney Cancer Support Network
   b. Kidney Cancer UK

4. **Expert personal perspectives** from:
   a. Dr Tom Waddell – clinical expert, nominated by Kidney Cancer Support Network
   b. Dr Balaji Venugopal – clinical expert, nominated by Royal College of Physicians
   c. Michael Lee – patient expert, nominated by Kidney Cancer UK
   d. Professor Peter Clark – CDF clinical lead

5. **Evidence Review Group report** prepared by **Southampton Health Technology Assessment Centre**

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response** from **Merck Sharp & Dohme**
   a. Response form
   b. Appendix 1

   Technical engagement responses from experts:
   None received

8. **Technical engagement response from consultees and commentators:**
   a. Kidney Cancer UK
   b. Ipsen

9. **Evidence Review Group critique of company response to technical engagement prepared by Southampton Health Technology Assessment Centre**

10. Final Technical Report

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

Pembrolizumab in combination with axitinib for untreated advanced renal cell carcinoma

[ID1426]

Document B

Company evidence submission

22nd July 2019

File name	Version	Contains confidential information	Date
MSD Pembrolizumab [ID1426] DocB without Appendices [ACIC]	1.0	Yes	22nd July 2019

Contents

Tables and figures

Abbreviations

AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ASaT	All subjects as treated
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplant
AG	Assessment group
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BL	Baseline
BMI	Body mass index
BNF	British national formulary
BV	Brentuximab vedotin
CAA	Commercial access agreement
C1D1	Cycle 1 Day 1
CDF	Cancer drug fund
cHL	Classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrIs	Credible Intervals
CPS	Combined positive score
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DIC	Deviance information criterion
DMC	Data monitoring committee
DOR	Duration of response
DRAE	Drug-related adverse event
DSU	Decision support unit
ECOG	Eastern cooperative oncology group performance status
EMA	European Medicine Agency
EOC	Executive oversight committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-3L	European Quality of Life Five Dimensions 3 Level Questionnaire
ESMO	European society for medical oncology
EPAR	European public assessment report
FAS	Full analysis set
FEM	Fixed effect model
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index disease Related Symptoms
FP	Fractional polynomial
HCHS	Hospital and community health services
HNSCC`	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
IA1	Interim analysis 1
IA2	Interim analysis 2
ICER	Incremental cost-effectiveness ratio
IFN-α	Interferon alpha

Ig	Immunoglobulin
IL-2	Interleukin-2
IMDC	International Metastatic RCC Database Consortium
irRECIST	immune-related Response Evaluation Criteria in Solid Tumours
ITT	Intention-to-treat population
IV	Intravenous
IVRS/IWRS	Interactive voice response system /integrated web response system
KM	Kaplan Meier
KPS	Karnofsky performance status
MA	Marketing authorization
Mg	milligram
MSD	Merck Sharp & Dohme Ltd
mRCC	Metastatic Renal Cell Carcinoma
N	Number of patients per treatment group
NCCN	National comprehensive cancer network
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung carcinoma
N/A	Not applicable
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PBO	Placebo
PD	Progressive disease or disease progression
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	Progression-free survival
PPS	Post-progression state
PR	Partial response
PRO	Patient reported outcome
PSSRU	Personal and Social Services Research Unit
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QD	Once daily
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
REM	Random effect model
RoB	Risk of Bias
SAE	Serious adverse event
SD	Standard deviation
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SUR	Safety update report
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TTD	Time to true deterioration
VEGF	Vascular endothelial growth factor
UK	United Kingdom

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

B.1.1 Decision problem

The submission covers the technology's anticipated full marketing authorisation for this indication: [redacted].

Please see Table 1 below for a summary of the National Institute for Health and Care Excellence (NICE) decision problem.

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 locally advanced or metastatic RCC	Adults with untreated advanced RCC	The population described by MSD reflects the anticipated licence indication wording
Intervention	Pembrolizumab with axitinib	Pembrolizumab (KEYTRUDA®) in combination with axitinib	N/A
Comparator(s)	• Tivozanib • Pazopanib • Sunitinib • Cabozantinib ('for disease that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria')	• Tivozanib • Pazopanib • Sunitinib • Cabozantinib ('for disease that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria')	N/A
Outcomes	• overall survival (OS) • progression-free survival (PFS) • response rates (RR) • adverse effects of treatment (AEs) • health-related quality of life (HRQoL)	• OS • PFS • Objective response rate (ORR) • AEs • HRQoL	N/A
Subgroups to be considered		Intermediate/poor risk category as defined by the International Metastatic RCC Database Consortium (IMDC)	N/A

Abbreviations: RCC, renal cell carcinoma; NICE, National Institute for Health and Care Excellence

B.1.2 Description of the technology being appraised

The draft summary of product characteristics (SmPC) has been included in Appendix C; however, the European Public Assessment Report (EPAR) was not available at the time of the submission. The technology being appraised (pembrolizumab) is described in the Table 2 below.

Table 2. Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAb) of the IgG4/kappa isotype designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity [1].
Marketing authorisation/CE mark status	Pembrolizumab currently has a marketing authorisation (MA) covering the following indications: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. • KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

	• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. • KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Indication to which this submission relates: [redacted]
Method of administration and dosage	Pembrolizumab 200 mg every three weeks (Q3W); intravenous (IV) infusion (up to a maximum duration of 2 years). Axitinib 5 mg twice daily (BID) taken orally continuously
Additional tests or investigations	Not applicable for the proposed indication.
List price and average cost of a course of treatment	• The list price of pembrolizumab is £2,630 per 100 mg vial, the cost of a single administration being £5,260 • The list price of axitinib is £3,517 per 56, 5mg tablets. (The average cost of a course of treatment at list price is: [redacted])
Patient access scheme (if applicable)	A Commercial access agreement (CAA) has been arranged with NHS England, with a simple discount in place of [redacted] therefore 200 mg administration of pembrolizumab will cost [redacted]. A confidential patient access scheme (PAS) is in place for axitinib.

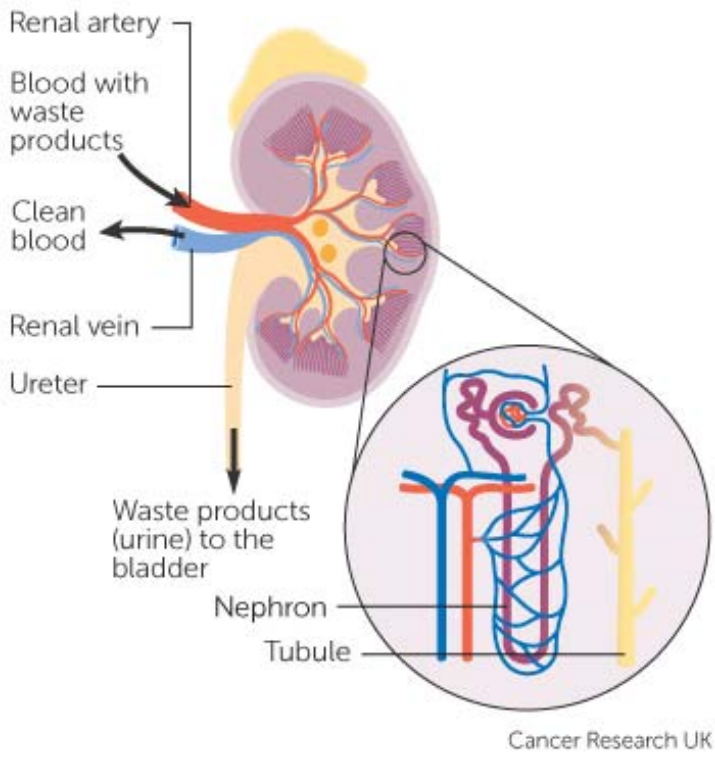
Abbreviations: PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; EGFR, Epidermal growth factor receptor; ALK, anaplastic large-cell lymphoma kinase.

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

1.3.1. Brief overview of the disease/condition for which the technology is being use

RCC is the most common form of kidney cancer in adults, accounting for approximately 80% of kidney cancer cases [2, 3]. With RCC, the cancerous cells begin to develop in the lining of the tubules (see Figure 1) which are responsible for filtering the blood and producing urine.

Figure 1. Kidney cross-section



Various subtypes of RCC exist; the naming convention is dependent on the type of cell affected, or the appearance of cells when examined microscopically. The most common subtype of RCC is clear-cell RCC (sometimes called non-papillary RCC), accounting for 75% of RCCs [4]. Under a microscope, clear-cell RCCs appear clear, with large nuclei [4]. 10-15% of RCCs are classified as papillary or chromophilic RCC – these tumours have characteristic papillae or nodules on the surface. Approximately 5% of RCCs are chromophobe RCC, and

the remaining 5-10% are comprised of either collecting-duct carcinoma, renal medullary carcinoma, mucinous tubular and spindle-cell carcinoma, renal translocation carcinomas, or unclassified RCC [4].

The actual cause of RCC has not been identified, but there are certain risk factors which have been shown to increase the risk of developing this type of cancer [5]. These include obesity (defined as a body mass index [BMI] of 30 or greater), smoking, hypertension, family history of the condition, certain genetic conditions, such as Von Hippel-Lindau syndrome, or a history of having required long-term dialysis [5]. There is also a link with deprivation: cases of kidney cancer occur more commonly in deprived areas.

In the UK, approximately 12,600 new cases of kidney cancer occur annually [6]. It is the 7th most common type of cancer in the UK, and more commonly affects males than females [6]. The incidence rates of kidney cancer have increased rapidly (by 85%) since the early 1990s, and the incidence has increased at a greater speed in females compared to males. RCC tends to affect adults above the age of 60 and is relatively rare in people under 50 years old [5].

In the early stages, RCC may be asymptomatic. The first symptoms that a patient with RCC may experience are haematuria (blood in the urine), or a persistent pain in their lower back or in their side between the ribs and hipbone [5, 7]. To diagnose RCC, patients may receive an ultrasound, CT scan of their urinary system (called a CT urogram), or a cystoscopy.

RCC cancer stages range from I to IV; stage III and IV indicate that the cancer has locally advanced (within the regional lymph nodes) or that distant metastases are present (beyond the regional lymph nodes). The general approach to treating RCC cancers is the surgical resection of the localised disease; however, despite surgery, approximately half of the patients go on to develop advanced cancer again later in their lives [8]. In England, over 40% of cases are only diagnosed at a late stage [6]. In 2015, around 44% of the people diagnosed with RCC presented a stage III or IV of their disease; of those between 25% and 31% had metastases [6].

Approximately 70% of patients with RCC live at least 1 year after diagnosis, and around 50% live at least 10 years after diagnosis [6]. Survival rates for RCC are linked to the stage of the cancer at diagnosis: for example, 95% of patients diagnosed with stage 1 kidney cancer

survived their illness for at least one year, compared with only 37% of those diagnosed at stage IV [6]. In the UK, the 5-year relative survival rate ranges from approximately 83% at stage I to 6% at stage IV for patients diagnosed with RCC [6]; approximately 4,500 people die each year due to kidney cancer, and it is the 13th most common cause of cancer deaths in the UK [6].

1.3.2. Clinical pathway of care showing the context of the proposed use of the technology

If diagnosed at an early stage, surgery is usually the most effective form of treatment for RCC and can often be curative [9]. Radical nephrectomy (removal of the entire affected kidney) is the most common method of treatment, and in most cases, this is conducted using laparoscopic (keyhole) surgery [9]. Some newer treatments (some of which remain experimental) may be appropriate when there are multiple tumours in both kidneys, or in the case of small tumours occurring in more elderly patients [9]. These include procedure such as cryotherapy (freezing of the tumour) and radio frequency ablation (heating of the tumour using high frequency electricity and high intensity focused ultrasound (HIFU00)). Radiotherapy and traditional chemotherapy have limited effect as a treatment option for RCC [9].

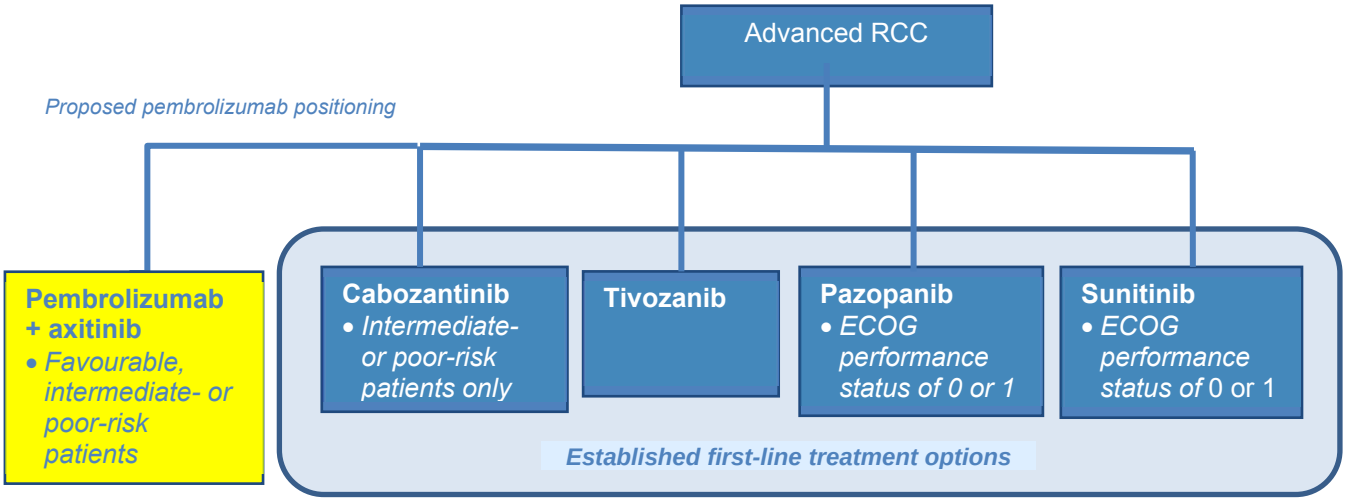
In England, the NICE pathway on RCC [10] details that the following therapies are recommended as first-line treatment options (Figure 2):

- Cabozantinib [11] is recommended, within its marketing authorisation, for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria. It is recommended only if the company provides cabozantinib according to the commercial arrangement.
- Tivozanib [12] is recommended as an option for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment and the company provides tivozanib with the discount agreed in the patient access scheme.
- Pazopanib [13] is recommended as a first-line treatment option for people with advanced renal cell carcinoma who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme.

- Sunitinib [14] is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an ECOG performance status of 0 or 1.

The updated European Association of Urologists (EAU) guideline [15] includes recommendations on the below treatment options but also states that immune checkpoint inhibitors are considered the new backbone in first-line treatment of metastatic clear-cell RCC [15]. Furthermore, the guideline reports that pembrolizumab plus axitinib should be the first-line standard of care (SoC) for patients with any IMDC favourable risk metastatic clear-cell RCC [15], and it should be a first-line SoC treatment option for patients with any IMDC intermediate/poor risk metastatic clear-cell RCC. Therefore, it is envisaged that pembrolizumab would offer an alternative first-line treatment option to the above listed therapies for patients with advanced RCC as shown in Figure 2.

Figure 2. NICE recommended first-line treatment options for Advanced RCC, and proposed positioning of Pembrolizumab



B.1.4 Equality considerations

MSD does not envisage any equality issues with the use of pembrolizumab in combination with axitinib for the treatment of advanced or metastatic RCC.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was conducted to identify clinical studies relevant to this submission. The SLR was designed to identify randomised controlled trials (RCTs) relating to the efficacy and safety of pembrolizumab in combination with axitinib and relevant comparators (as per final scope described in Table 1) in patients with untreated advanced RCC.

The SLR was originally conducted on 12 November 2018 and updated search was conducted on 21 February 2019. As the manufacturer of the technology being appraised, MSD is aware of all relevant RCTs for pembrolizumab in combination with axitinib in this indication.

In total, four RCTs were identified: three trials reporting evidence for the relevant comparators and one reporting evidence for pembrolizumab in combination with axitinib: KEYNOTE-426 [16] [17] .
Please refer to Table 3 for a summary of the evidence coming from the pivotal clinical trial KEYNOTE-426 [16] [17].

Table 3. Clinical effectiveness evidence

Study	KEYNOTE-426 [16] [17]: A Phase III Randomised, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC)
Study design	Phase III Randomised, Open-label Study
Population	• Has histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features. • Has locally advanced/metastatic disease (i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer) or has recurrent disease. • Has measurable disease per RECIST 1.1 as assessed by the investigator/site radiologist.

	• Has received no prior systemic therapy for advanced RCC. • Has Karnofsky performance status (KPS) ≥ 70% as assessed within 10 days prior to randomisation.				
Intervention(s)	Pembrolizumab + axitinib combination therapy Participants receive pembrolizumab 200 mg intravenously every 3 weeks (Q3W) PLUS axitinib 5 mg orally twice daily.				
Comparator(s)	Sunitinib Monotherapy Participants receive sunitinib 50 mg orally once daily for 4 weeks and then are off treatment for 2 weeks				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	KEYNOTE-426 [16] [17] is the pivotal clinical trial in this indication				
Reported outcomes specified in the decision problem	• **OS** • **PFS** • **ORR** • **Adverse effects (AEs) of treatment** • **HRQoL** *Bolded outcomes are included in the economic model*				
All other reported outcomes	• Time to deterioration (TTD) • Duration of response (DOR) • **Patient reported outcomes (PRO)** • Disease control rate (DCR) *Bolded outcomes are included in the economic models*				

Abbreviations: RCC, renal cell carcinoma; mg, milligram; OS, overall survival; PFS, progression free survival; HRQoL, health-related quality of life.

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

2.3.1. KEYNOTE-426 [16] trial overview

Trial Design

KEYNOTE-426 is a phase III, randomised, multi-centre, open-label trial to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic RCC [16] [17].

Approximately 840 subjects were planned to be enrolled into the study. Subjects must have had measurable disease at baseline as assessed by the investigator/site radiologist per

RECIST 1.1 and must have provided an adequate tumour tissue sample to be eligible. After a screening period of a maximum of 28 days, eligible subjects were first stratified by the following two stratification factors:

- The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk categories (favourable versus intermediate versus poor) [18] [19].
- Geographic region (North America versus Western Europe versus "Rest of the World").

IMDC risk category for each subject was determined first by assessing 6 risk factors as shown in Table 4.

Table 4. IMDC Risk Evaluation

Assessments	Risk Factor
Baseline Karnofsky Performance Status	< 80%
Interval between initial diagnosis of RCC to start of first-line systemic treatment for advanced disease (note for this study, date of randomisation will be used as the start of first-line systemic treatment)	< 1year
Baseline Haemoglobin	< Lower limit of normal
Baseline Platelet Count	> Upper limit of normal
Baseline Corrected Calcium1	> Upper limit of normal
Baseline Neutrophil	> Upper limit of normal
The IMDC risk group is determined by totalling the existing risk factors per subject.	
IMDC Risk Group	**IMDC Category**
Favourable	No risk factors
Intermediate	1 or 2 risk factors
Poor	3 or more risk factors
[1]. *Corrected calcium can be calculated based on the following formula:* ***Corrected calcium (mg/dl) = 0.8 × [4.0 - subject's albumin (g/dl)] + subject's calcium (mg/dl)***. *A subject's corrected calcium will be compared with the upper limit of normal of institution serum calcium.*	

Following stratification, subjects were randomised in a 1:1 ratio to one of the following treatment arms. Treatment randomisation occurred centrally using an interactive voice response system /integrated web response system (IVRS/IWRS).

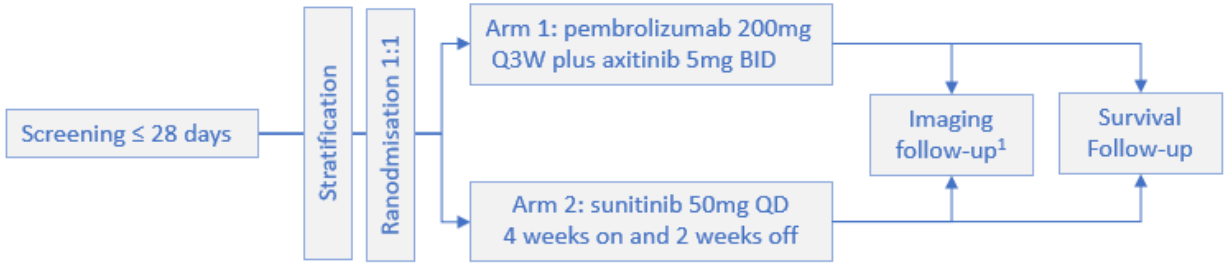
- arm 1: combination of pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W) and axitinib 5 mg twice daily (BID) taken orally continuously;

or

- arm 2: sunitinib monotherapy 50 mg daily (QD) taken orally for 4 weeks then off treatment for 2 weeks.

Study treatments continued until progressive disease (PD) was verified by blinded independent central review (BICR) or further confirmed by the investigator; unacceptable adverse events (AEs); or intercurrent illness prevented further administration of treatment; death or withdrawal of consent. A schematic of the trail design is provided below in Figure 3.

Figure 3. KEYNOTE-426 Trial design



[1]. Subjects who discontinue study treatment for reasons other than BICR-verified PD should continue with imaging assessments per the protocol defined schedule until PD is BICR verified or further confirmed by investigator, initiation of a new anti-cancer treatment, death, withdrawal of consent or study conclusion or early termination, whichever occurs first

For the combination arm, pembrolizumab was administered for a maximum of 35 doses. If a subject remained progression-free after 35 doses of pembrolizumab, treatment with axitinib was continued as monotherapy until PD was verified by BICR or further confirmed by the investigator. In addition, if 1 of the 2 compounds needed to be discontinued because of toxicity or intolerance, treatment with the other compound as monotherapy would be continued until PD was verified by BICR or further confirmed by the investigator. For both arms, if a complete response (CR) was observed in a subject, study treatment may have been discontinued at the discretion of the investigator after the CR had been confirmed and after a minimum of 8 cycles of treatment (~24 weeks) in the pembrolizumab plus axitinib arm or 4 cycles of treatment (~24 weeks) in the sunitinib arm had been received.

When a subject was first identified with PD by the investigator, the site requested PD to be verified by BICR. Subjects who were clinically stable may have continued treatment while waiting for BICR verification. After verification or confirmation of PD, subjects were permitted

to initiate any subsequent anti-cancer treatment at the discretion of the treating physician and the subject per local SoC. Pembrolizumab was not provided to subjects who progressed on the sunitinib arm.

KEYNOTE-426 [16] [17] used a group-sequential design that included three total analyses: two planned analyses for PFS (one interim analysis and then final) and three planned analyses for OS (two interim analyses and final). The first interim analysis (IA1) was performed after enrolment had been completed, once a minimum follow up of 7 months and a minimum of 305 PFS events by BICR had been achieved. At IA1, approximately 48% of the final required OS events (~ 195 death events) were expected. The second interim analysis (IA2) was due when approximately 74% of the final required OS events (or 299 death events) had accrued. At IA2, final PFS analysis was also due if statistical significance of PFS had not yet been achieved at IA1. The final OS analysis meant to be performed after a total of 404 death events had accrued. KEYNOTE-426 [16] [17] was to be considered concluded after the clinical cut-off for the final OS analysis had been achieved.

Eligibility criteria

Male and female subjects (≥18 years) with locally advanced/metastatic RCC were enrolled in KEYNOTE-426 [16] [17].

Subject inclusion criteria

- Be ≥18 years of age on day of signing informed consent.
- Have histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features.
- Have locally advanced/metastatic disease, i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer or have recurrent disease.
- Have measurable disease per RECIST 1.1 as assessed by the investigator /site radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
- Have received no prior systemic therapy for advanced RCC.
- Have provided archival tumour tissue sample or newly obtained core or excisional biopsy of a tumour lesion as required. Lesions cannot be previously irradiated.
- Have Karnofsky performance status (KPS) ≥ 70% as assessed within 10 days prior to randomisation.

- Subjects receiving bone resorptive therapy (including but not limited to bisphosphonate or RANK-L inhibitor) must have therapy initiated at least 2 weeks prior to randomisation.
- Demonstrate adequate organ function as defined in the study protocol.
- Female subjects of childbearing/reproductive potential must have a negative urine or serum pregnancy test within 72 hours prior to randomisation, and must be willing to use an adequate method of contraception
- Male subjects of childbearing potential must agree to use an adequate method of contraception.

Subject exclusion criteria

The subject must be excluded from participating in the trial if the subject:

- Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomisation.
- Has had major surgery within 4 weeks, received radiation therapy within 2 weeks prior to randomisation, or has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to prior treatment.
- Has had prior treatment with any anti-PD-1, or PD-L1, or PD-L2 agent or an antibody targeting any other immune-regulatory receptors or mechanisms. Examples of such antibodies include (but are not limited to) antibodies against IDO, PD -L1, IL-2R, and GITR.
- Has received prior systemic anti-cancer therapy for RCC (e.g., VEGF/VEGFR, chemotherapy or mTOR-targeting agents). Note: Prior neoadjuvant/adjuvant therapy for RCC is acceptable if completed > 12 months prior to randomisation.
- Has a history of severe hypersensitivity reaction to axitinib or sunitinib.
- Has a diagnosis of immunodeficiency OR is receiving a systemic steroid therapy exceeding physiologic corticosteroid dose or any other form of immunosuppressive therapy within 7 days prior to randomisation, except in the case of central nervous system (CNS) metastases.
- Has an active autoimmune disease requiring systemic treatment within the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) OR with a documented history of clinically severe autoimmune disease.
- Has a known additional malignancy that has progressed or has required active treatment in the last 3 years.
- Has known active CNS metastases and/or carcinomatous meningitis.

- Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a known history of Human Immunodeficiency Virus (HIV) infection (HIV 1
- and/or 2 antibodies).
- Has a known history of Hepatitis B or known active Hepatitis C virus.
- Has received a live virus vaccine within 30 days of randomisation
- Has a clinically significant gastrointestinal (GI) abnormality
- Has QT interval corrected for heart rate (QTc) ≥ 480 msec.
- Has a history of any of certain cardiovascular conditions (see study protocol) within 12 months of randomisation.
- Has a history of deep vein thrombosis or pulmonary embolism within 6 months of screening.
- Has poorly controlled hypertension defined as systolic blood pressure (SBP) ≥ 150 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg.
- Has evidence of inadequate wound healing.
- Has active bleeding disorder or other history of significant bleeding episodes within 30 days of randomisation.
- Has hemoptysis within 6 weeks prior to randomisation.
- Has current use (within 7 days of randomisation) or anticipated need for treatment with drugs or foods that are known strong cytochrome P450 (CYP3A4/5) inhibitors
- Has current use (within 7 days of randomisation) or anticipated need for treatment with drugs that are known strong CYP3A4/5 inducers.
- Has had a prior solid organ transplant.
- Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

Settings and Locations where data were collected

The study was conducted at 124 centres in 16 countries: Brazil, Canada, Czech Republic, France, Germany, Hungary, Ireland, Japan, Poland, Russia, South Korea, Spain, Taiwan, United Kingdom (UK), USA and Ukraine.

Globally, KEYNOTE-426 [16] [17] had 142 participating sites of which 64 were within Europe. A total of 475 patients were enrolled in Europe of which 48 were from the UK.

All treatments were administered in secondary care setting on an outpatient basis.

Trial drugs and concomitant medication

Trial drugs

Study medications used in this trial are outlined below.

Table 5. Trial Treatments

Treatment	Regimen	Route of Administration	Duration of treatment	Use in Study
Pembrolizumab/Axitinib Combination Arm				
Pembrolizumab	200 mg every 3 weeks (Q3W)	IV infusion	Up to 35 doses (about 24 months) or until PD is BICR verified or further confirmed by the investigator[a]	Experimental
Axitinib	5 mg twice daily (BID)	Orally (PO)	Continued treatment until PD is BICR verified or further confirmed by the investigator	Experimental
Sunitinib Monotherapy Arm				
Sunitinib	50 mg daily (QD) 4 weeks on, 2 weeks off	PO	Continued treatment until PD is BICR verified or further confirmed by the investigator	Comparator (SoC)

***Abbreviations**: BICR, blinded independent central review; BID, twice daily; IV, intravenous; PD, progressive disease; PO, per os/by mouth; Q3W, every 3 weeks; SoC, standard of care.*
[a] Subjects in the pembrolizumab+axitinib arm may receive a second course of treatment with additional 17 doses.

Study treatments should have begun on the day of randomisation or within 3 days of randomisation in both treatment arms. Study treatments and relevant safety assessments were cycle based. The day that the first dose of study treatment was received by each subject denotes Cycle 1 Day 1 (C1D1).

For the combination arm, each treatment cycle was 21 days, which was based on a Q3W dosing schedule of pembrolizumab. C1D1 of the combination arm started when the subject received the first dose of pembrolizumab. The first dose of axitinib should have started on the same day when first dose of pembrolizumab was administered, if possible, or started on the following day. For the sunitinib arm, each treatment cycle was 42 days. Study treatment continued in 21-day or 42-day cycles, for the combination arm and sunitinib arm, respectively, until study treatments were permanently discontinued for the subject.

Pembrolizumab was administered as a 30-minute IV infusion on Day 1 of each 21-day cycle (± 3 days) starting on C1D1. Axitinib was to be taken orally BID, at approximately the same time in the morning and evening each day with approximately 12 hours between the 2 doses. Axitinib was taken continuously with exception of dose interruptions due to drug-related AEs or intolerance.

In the sunitinib monotherapy arm, the first dose of sunitinib administration denoted C1D1 for each subject. Each treatment cycle of sunitinib was 42 days ± a 3-day window. Within each treatment cycle, sunitinib was administered orally once daily for 4 weeks and then off treatment for 2 weeks.

Acceptable Concomitant Medications

All treatments that the investigator considered necessary for a subject's welfare may have been administered at the discretion of the investigator in keeping with the community standards of medical care. Concurrent anti-cancer therapy with agents other than those assigned for each treatment arm (i.e., axitinib plus pembrolizumab or sunitinib) was not allowed. Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) were allowed.

Caution Use of Inhibitors and Inducers of CYP Enzymes (Axitinib)

Axitinib metabolism is primarily mediated by the CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. The concomitant use of strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) was avoided. Grapefruit or grapefruit juice may also cause an increase in axitinib plasma concentrations and was recommended to be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential was recommended.

Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) was avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential was recommended. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should have been avoided if possible.

Caution Use of Inhibitors and Inducers of CYP Enzymes (Sunitinib)

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential was recommended. CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential was recommended.

Hematopoietic Growth Factors

The use of hematopoietic growth factors was at the discretion of the treating physician in line with local guidelines.

Prohibited Concomitant Medications

Subjects were prohibited from receiving the following therapies during the study treatment period (including re-treatment for post-complete response relapse) of KEYNOTE-426 [16, 17]:

- Any anti-cancer therapy not assigned per protocol (e.g., systemic treatment, surgery, radiation).
- Investigational agents other than those specified in this protocol (i.e., pembrolizumab, axitinib or sunitinib based on what is assigned)
- Live vaccines within 30 days prior to the first dose of pembrolizumab and through 30 days following the last dose of pembrolizumab
- Drugs with proarrhythmic potential: Concomitant treatment with a drug having known proarrhythmic risks (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide) were not permitted during treatment with sunitinib

The following applies exclusively to subjects being treated with pembrolizumab plus axitinib:

- Prolonged therapy with systemic glucocorticoids for any purpose other than to modulate symptoms from an AE, SAE, or ECI or for use as a pre-medication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography. Brief, limited use of systemic corticosteroids (≤7 days) was permitted where such use is considered standard of care (e.g., for COPD exacerbation).
- Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) were permitted while on study, as was the use of local steroids.

Subjects who, in the assessment by the investigator, required additional anti-cancer treatments were discontinued from study treatment but continued survival follow-up. Subjects who, in the assessment by the investigator, required any other prohibited medications for the assigned study treatment for long-term clinical management, were discontinued from trial treatment but continued disease assessments and survival follow-up.

The exclusion criteria describe other medications or vaccinations that were specifically prohibited in KEYNOTE-426 [16, 17].

Outcomes used in the economic model or specified in the scope, including primary outcome

KEYNOTE-426 [16, 17] objectives were pre-specified. In male and female adult subjects (≥18 years of age) with locally advanced/metastatic RCC, the objectives were as follows:

Primary Objective(s)

1. To evaluate and compare PFS per RECIST 1.1 as assessed by BICR in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.
2. To evaluate and compare OS in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.

Progression free survival (PFS) was defined as the time from randomisation to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurred first.

OS was defined as the time from randomisation to death due to any cause. Subjects without documented death at the time of the final analysis were to be censored at the date of the last follow-up.

Secondary Objective(s)

1. To compare objective response rate (ORR) and disease control rate (DCR) per RECIST 1.1 as assessed by BICR in subjects treated with a combination of pembrolizumab plus axitinib versus sunitinib monotherapy. Duration of response (DOR) will also be evaluated.

2. To evaluate PFS rate per RECIST 1.1 as assessed by BICR at 12, 18, and 24 months based on data adequacy; to evaluate OS rates at 12, 18, and 24 months based on data adequacy
3. To evaluate and compare safety and tolerability profiles in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.
4. To compare time to deterioration (TTD) based on the Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms (FKSI-DRS) scale in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.
5. To assess the longitudinal score changes from baseline to 42 weeks as measured by European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 global health status/quality of life scale

ORR was defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR) based on assessments by BICR per RECIST 1.1.

For subjects who demonstrated CR or PR, DOR was defined as the time from first documented evidence of CR or PR, based on assessments by BICR per RECIST 1.1, until disease progression based on assessments by BICR per RECIST 1.1 or death due to any cause, whichever occurs first.

DCR was defined as the percentage of subjects who had achieved CR, PR, or SD based on assessments by BICR per RECIST 1.1.

Exploratory Objectives

1. To evaluate PFS, ORR, DOR, and DCR per immune-related RECIST (irRECIST) as assessed by BICR in subjects treated with pembrolizumab plus axitinib or sunitinib monotherapy
2. To characterize utility in subjects using the European Quality of Life (EuroQol) EQ-5D-3L.
3. To characterize the pharmacokinetics (PK) of pembrolizumab in subjects treated with pembrolizumab plus axitinib.
4. To identify molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to pembrolizumab/axitinib treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of the pembrolizumab/axitinib combination.

2.3.2 Comparative summary of the trial methodology

A summary of the trial methodology is present below in Table 6

Table 6: Summary of trial methodology

Trial number (acronym)	**KEYNOTE-426 [16] [17]**
Location	Global study conducted in 16 countries: Brazil, Canada, Czech Republic, France, Germany, Hungary, Ireland, Japan, Poland, Russia, South Korea, Spain, Taiwan, UK, USA, Ukraine.
Trial design	A phase III randomised, multi-centre, open- study to evaluate efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma (mRCC) After a screening period of ≤ 28 days, each eligible subject was stratified by the following two factors: 1) International mRCC Database Consortium (IMDC) risk categories (favourable vs. intermediate vs. poor) and 2) geographic regions (North America vs. Western Europe vs. "Rest of the World"). After stratification, subjects were randomised 1:1 to one of two treatment arms: Arm 1) pembrolizumab in combination with axitinib or Arm 2) sunitinib monotherapy
Eligibility criteria for participants	Key inclusion criteria: •Has histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features. •Has locally advanced/metastatic disease (i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer) or has recurrent disease. •Has measurable disease per RECIST 1.1 as assessed by the investigator/site radiologist. •Has received no prior systemic therapy for advanced RCC. •Has provided archival tumour tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated. •Has Karnofsky performance status (KPS) ≥ 70% as assessed within 10 days prior to randomisation. •If receiving bone resorptive therapy (including but not limited to bisphosphonate or RANK-L inhibitor) must have therapy initiated at least 2 weeks prior to randomisation.
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as out-patients.

Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication	**Intervention: n= 432** Pembrolizumab 200 mg intravenously every 3 weeks PLUS axitinib 5 mg orally twice daily **Comparator: n= 429** Sunitinib 50 mg orally once daily for 4 weeks and then are off treatment for 2 weeks. Subjects were prohibited from receiving the following during KEYNOTE-426 [16] [17]: • Any anti-cancer therapy not assigned per protocol (e.g., systemic treatment, surgery, radiation). • Investigational agents other than those specified in this protocol (i.e., pembrolizumab, axitinib or sunitinib based on what is assigned) • Live vaccines within 30 days prior to the first dose of pembrolizumab and through 30 days following the last dose of pembrolizumab • Drugs with proarrhythmic potential: Concomitant treatment with a drug having known proarrhythmic risks (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide and flecainide) were not permitted during treatment with sunitinib
Primary outcomes (including scoring methods and timings of assessments)	1) To evaluate and compare PFS per RECIST 1.1 as assessed by BICR in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy. 2) To evaluate and compare OS in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.
Other outcomes used in the economic model/specified in the scope	N/A
Pre-planned subgroups	• IMDC risk category (favourable versus intermediate versus poor; favourable versus intermediate plus poor) • Geographic region (North America versus Western Europe versus Rest of the World) • PD-L1 status (combined positive score [CPS] <1 versus CPS ≥ 1) • Age (< 65 versus ≥ 65) • Sex (male versus female) Race (white versus all others)

2.3.3. KEYNOTE-426 [16] [17]: Participants baseline characteristics

Baseline characteristics are summarised in Table 7. The baseline demographic and disease characteristics of participants for the two groups were generally well balanced and representative of a patient population with advanced RCC. Most participants were male, White, and non-Hispanic, and had a KPS score of 90/100. The most common metastatic sites were lung, lymph node, and bone. The percentage of participants in the IMDC risk categories of

favourable, intermediate, and poor risk was 31.2%, 56.2% and 12.5%, respectively. A total of 57.7% of participants had a tumour tissue PD-L1 expression score of CPS ≥1.

Table 7. Subject Characteristics (ITT Population) – KEYNOTE-426 [16] [17]

	Pembrolizumab + axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	432		429		861	
Gender						
Male	308	(71.3)	320	(74.6)	628	(72.9)
Female	124	(28.7)	109	(25.4)	233	(27.1)
Age (Years)						
< 65	260	(60.2)	278	(64.8)	538	(62.5)
≥ 65	172	(39.8)	151	(35.2)	323	(37.5)
Subjects with data	432		429		861	
Mean	61.2		60.8		61.0	
SD	10.0		10.2		10.1	
Median	62.0		61.0		62.0	
Range	30 to 89		26 to 90		26 to 90	
Race						
Asian	66	(15.3)	71	(16.6)	137	(15.9)
Black or African American	10	(2.3)	8	(1.9)	18	(2.1)
White	343	(79.4)	341	(79.5)	684	(79.4)
Other	4	(0.9)	4	(0.9)	8	(0.9)
Missing	9	(2.1)	5	(1.2)	14	(1.6)
Ethnicity						
Hispanic or Latino	19	(4.4)	18	(4.2)	37	(4.3)
Not Hispanic or Latino	377	(87.3)	387	(90.2)	764	(88.7)
Not Reported	14	(3.2)	12	(2.8)	26	(3.0)
Unknown	21	(4.9)	11	(2.6)	32	(3.7)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
Geographic Region of Enrolling Site						
North America	104	(24.1)	103	(24.0)	207	(24.0)
Western Europe	106	(24.5)	104	(24.2)	210	(24.4)
Rest of the World	222	(51.4)	222	(51.7)	444	(51.6)
Region						
EU	161	(37.3)	156	(36.4)	317	(36.8)
Ex-EU	271	(62.7)	273	(63.6)	544	(63.2)
Karnofsky Performance Scale						
90/100	347	(80.3)	341	(79.5)	688	(79.9)
70/80	84	(19.4)	88	(20.5)	172	(20.0)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
IMDC Risk Category						
Favourable	138	(31.9)	131	(30.5)	269	(31.2)

	Pembrolizumab + axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Intermediate	238	(55.1)	246	(57.3)	484	(56.2)
Poor	56	(13.0)	52	(12.1)	108	(12.5)
IMDC Risk Category 2						
Favourable	138	(31.9)	131	(30.5)	269	(31.2)
Intermediate or Poor	294	(68.1)	298	(69.5)	592	(68.8)
PD-L1 Status						
CPS ≥ 1	243	(56.3)	254	(59.2)	497	(57.7)
CPS < 1	167	(38.7)	158	(36.8)	325	(37.7)
Not Available	4	(0.9)	2	(0.5)	6	(0.7)
Missing	18	(4.2)	15	(3.5)	33	(3.8)
Sites of Metastatic Disease*						
Lung						
Yes	312	(72.2)	309	(72.0)	621	(72.1)
No	120	(27.8)	120	(28.0)	240	(27.9)
Lymph Node						
Yes	199	(46.1)	197	(45.9)	396	(46.0)
No	233	(53.9)	232	(54.1)	465	(54.0)
Bone						
Yes	103	(23.8)	103	(24.0)	206	(23.9)
No	329	(76.2)	326	(76.0)	655	(76.1)
Adrenal Gland						
Yes	67	(15.5)	76	(17.7)	143	(16.6)
No	365	(84.5)	353	(82.3)	718	(83.4)
Liver						
Yes	66	(15.3)	71	(16.6)	137	(15.9)
No	366	(84.7)	358	(83.4)	724	(84.1)
Number of Organs Involved with Disease at Baseline						
1	114	(26.4)	96	(22.4)	210	(24.4)
≥ 2	315	(72.9)	331	(77.2)	646	(75.0)
Missing	3	(0.7)	2	(0.5)	5	(0.6)
RCC Histology						
Clear Cell	403	(93.3)	401	(93.5)	804	(93.4)
Clear Cell Component	28	(6.5)	27	(6.3)	55	(6.4)
Other	1	(0.2)	1	(0.2)	2	(0.2)
Sarcomatoid Feature						
Yes	51	(11.8)	54	(12.6)	105	(12.2)
No	234	(54.2)	239	(55.7)	473	(54.9)
Unknown	146	(33.8)	135	(31.5)	281	(32.6)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
RCC Tumour Fuhrman Grade						
Grade 1	23	(5.3)	24	(5.6)	47	(5.5)
Grade 2	138	(31.9)	127	(29.6)	265	(30.8)
Grade 3	120	(27.8)	138	(32.2)	258	(30.0)
Grade 4	104	(24.1)	93	(21.7)	197	(22.9)

	Pembrolizumab + axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Missing	47	(10.9)	47	(11.0)	94	(10.9)
Disease Status at Baseline						
Recurrent	238	(55.1)	231	(53.8)	469	(54.5)
Newly Diagnosed	194	(44.9)	198	(46.2)	392	(45.5)
RCC Stage at Initial Diagnosis						
I	68	(15.7)	62	(14.5)	130	(15.1)
II	55	(12.7)	38	(8.9)	93	(10.8)
III	96	(22.2)	101	(23.5)	197	(22.9)
IV	209	(48.4)	227	(52.9)	436	(50.6)
Missing	4	(0.9)	1	(0.2)	5	(0.6)
Prior Oncologic Radiation						
Yes	41	(9.5)	40	(9.3)	81	(9.4)
No	391	(90.5)	389	(90.7)	780	(90.6)
Prior Nephrectomy						
Yes	357	(82.6)	358	(83.4)	715	(83.0)
No	75	(17.4)	71	(16.6)	146	(17.0)

**The sites are five most common metastatic sites and ordered decreasingly by the frequency in total of the two treatment arms.*

Database Cut-off Date: 24Aug2018.

Abbreviations: *n, sample size; SD, standard deviation; IMDC, International RCC Database Consortium; PD-L1, program death-ligand 1; KPS, Karnofsky performance status; CPS, combined positive score; RCC, renal cell carcinoma.*

B.2.4 KEYNOTE-426: Statistical analysis and definition of study groups

This section reports the relevant statistical methodology of KEYNOTE-426 [16] [17].

Table 8. Statistical Analysis Plan Summary

Study Design Overview	This is a randomised, open-label, multi-centre Phase III trial to evaluate efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic RCC.
Treatment Assignment	Approximately 840 subjects were randomised 1:1 into the following two treatment arms: - Arm 1 received the combination therapy of pembrolizumab 200 mg administered IV Q3W and axitinib 5 mg BID taken orally. - Arm 2 received sunitinib monotherapy 50 mg QD taken orally for 4 weeks then off treatment for 2 weeks. Stratification factors are provided in Section 2.3.1. This is an open-label study.

Analysis Populations	*Efficacy*: Intention to Treat (ITT) - population consisted of all randomised subjects included in this population. Subjects were analysed in the treatment group to which they were randomised. *Safety*: All Subjects as Treated (ASaT) population - consisted of all randomised subjects who received at least one dose of study treatment. Subjects were analysed in the treatment group corresponding to the study treatment they actually received.
Primary Endpoints	1. PFS per RECIST 1.1 by BICR review • Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to PFS as assessed by BICR per RECIST 1.1 2. OS • Hypothesis: The combination therapy of pembrolizumab plus axitinib is superior to sunitinib monotherapy with respect to OS.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses for PFS and OS was evaluated by comparing pembrolizumab in combination with axitinib to sunitinib using a stratified log-rank test. Estimation of the hazard ratio was done using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method. Stratified Miettinen and Nurminen's method with weights proportional to the stratum size will be used for comparison of the ORR between the treatment arms.
Statistical Methods for Key Safety Analyses	The analysis of safety results followed a tiered approach. The tiers differ with respect to the analyses that was performed. There were no Tier 1 events in this trial. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages are provided using the Miettinen and Nurminen method.
Interim and Final Analyses	Planned Two interim analyses were planned for the study. Results were reviewed by an external data monitoring committee (eDMC). 1. Interim Analysis 1 (IA1) • Timing: performed after enrolment completion, once a 7-month minimum follow up (i.e. 7 months since last subject is randomised) has been achieved and a minimum of 305 PFS events have accrued. It is expected to be 22 months after the first subject randomised (study start). • Approximately 48% of the final required OS events (or 195 deaths) were expected at that time. • Purpose: First interim analysis for PFS and OS. 2. Second Interim Analysis (IA2) • Timing: performed when approximately 74% of the final required OS events (or 299 deaths) have accrued, expected to be 31 months after study start. At IA2, approximately 487 PFS events were expected. • Purpose: Final analysis for PFS and IA2 for OS. 3. Final analysis (event-driven trial)

	• Timing: When approximately 404 deaths have accrued, expected to be 43 months after study start. • Purpose: Final analysis for OS (assuming not declared successful at the interim analysis) Actual 1. IA1 was conducted as above described; the data cut-off was 24th August 2018 (data presented in Section 2.6.1. KEYNOTE-426 results) 2. IA2 as above described, was no longer conducted due to a second data cut-off analysis dated January 2019 that took place for regulatory purposes (safety update report (SUR) to FDA) (data presented in Section 2.6.1. KEYNOTE-426 results) 3. Final analysis still follows the planned description.
Multiplicity	The overall Type I error rate was strongly controlled at 2.5% (1-sided) with 0.2% initially allocated to PFS and 2.3% initially allocated to OS. A group sequential approach was used to allocate alpha between the interim and final analyses. The study was considered a success if either PFS or OS demonstrated to be statistically significant under multiplicity control. Note that the study would continue for OS even if PFS is shown to be statistically significant at IA1.
Sample Size and Power	The sample size was planned for 840 but the following power calculations are based on the actual final number of randomised subjects (N = 861). There are 2 primary endpoints for this study, PFS, and OS. The expected median PFS time in the control group is 13 months. Based on 487 PFS events, the study has ~99% power to detect a hazard ratio of 0.60 for PFS (pembrolizumab+axitinib combination vs. sunitinib) at alpha=0.2% (1-sided). The expected median OS time in the control group is 33 months. Based on 404 death events, the study has 80% power to detect a hazard ratio of 0.75 for OS at alpha=2.3% (1-sided). The median PFS and median OS assumptions in the control group were based on emerging data of sunitinib from the CheckMate 214 study [20].

Abbreviations: *n, sample size; IV, intravenously; Q3W, every 3 weeks; BID, twice daily; QD, daily; PFS, progression free survival; OS, overall survival; ORR, objective response rate; CI, confidence interval.*

Discontinuation of Treatment

Subjects were permitted to discontinue treatment at any time for any reason or be dropped from study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from study treatment by the investigator or the study sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject, who discontinued the study treatment, continued to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Subjects with AEs meeting discontinuation criteria as described in the study protocol

- The subject has a medical condition or is non-compliance to study treatments or procedures which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk from continued administration of study drug.
- Female subject with confirmed positive serum pregnancy test.

Subjects in the combination arm, who discontinued pembrolizumab after receiving 35 doses, could continue to receive axitinib until disease progression.

Second Course Phase (Retreatment)

Subjects enrolled in the pembrolizumab plus axitinib arm who stop pembrolizumab with SD or better may have been eligible for up to 17 additional infusions of pembrolizumab therapy if they progressed after stopping. This re-treatment was termed the "Second Course Phase" of this study and was only available if the study remained open and the subject met the following conditions:

- Stops initial treatment with pembrolizumab after a confirmed CR according to RECIST 1.1 per investigator assessment and has received at least 8 doses of pembrolizumab.

OR

- Has completed 35 doses (approximately 2 years) of pembrolizumab treatment without PD.

AND

- Experiences an investigator-confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab.
- Does not receive any anti-cancer treatment since the last dose of pembrolizumab.
- Has a KPS of ≥ 70%.
- Demonstrate adequate organ function.
- Does not have a history or current evidence of any condition, therapy, or laboratory. abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

2.4.1 Statistical methods used to compare groups for primary and secondary outcomes and approach to missing data

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints are summarised in the Table 9 below.

Table 9. KEYNOTE-426 [16] [17] – Analysis strategy for key efficacy endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data/ Censoring Approach
Primary Hypothesis #1			
PFS per RECIST 1.1 by BICR	Test: Stratified Logrank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
Primary Hypothesis #2			
OS	Test: Stratified Logrank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last date the subject was known to be alive
Secondary Hypothesis			
ORR per RECIST 1.1 by BICR	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomisation will be applied to the analysis model.
.‡ Miettinen and Nurminen method.
***Abbreviations**: BICR, blinded independent central imaging review; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.*

The non-parametric Kaplan Meier (KM) method was used to estimate the PFS and OS curves in each treatment group. The treatment differences in PFS and OS were assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment groups. The stratification factors used for the randomisation were applied to both the stratified log-rank test and the stratified Cox model.

Since PD was assessed periodically, PD could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. The true date of disease progression was approximated by the date of the first assessment at which PD was objectively documented per RECIST 1.1 by BICR. Death was always considered as a confirmed PD event. Subjects who do not experience a PFS event were censored at the last disease assessment.

Sensitivity analyses were performed for comparison of PFS based on investigator's assessment and PFS with PD determined per irRECIST by BICR. To evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, one primary and two sensitivity analyses (SAs) with a different set of censoring rules were performed. The censoring rules for primary and sensitivity analyses are summarised in Table 10.

Table 10. Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary analysis	SA1	SA2
PD or death documented after ≤ 1 missed disease assessment and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥ 2 consecutive missed disease assessment or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anti-cancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment
No PD and no death; and new anti-cancer treatment is initiated	Censored at last disease assessment before new anti-cancer treatment	Censored at last disease assessment	

Abbreviations: PD, progressive disease; SA, sensitivity analysis

The proportional hazards assumption on PFS was examined using both graphical and analytical methods if warranted.

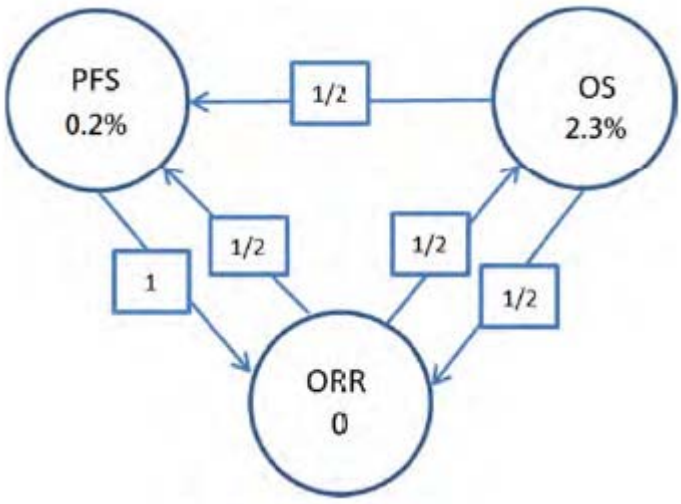
IA1 was performed after enrolment completion, when a minimum of 305 PFS events had accrued and all participants were followed for at least 7 months after randomisation. The Maurer and Bretz multiplicity strategy was applied for the 2 primary hypotheses (superiority of pembrolizumab + axitinib relative to sunitinib on PFS or OS) and the secondary hypothesis of

superiority of pembrolizumab + axitinib relative to sunitinib in ORR. Study success was demonstrated if either PFS or OS was statistically significant under multiplicity control.

Multiplicity strategy for PFS, OS and ORR

The multiplicity strategy followed the graphical approach of Maurer and Bretz [21] depicted in Figure 4. The arrows on the diagram show how the Type I error allocated to a hypothesis that was successfully tested will be re-distributed for the testing of the other two hypotheses. Initially, α=2.3% (23/25 of the overall total α = 2.5% for testing the OS, PFS and ORR) is allocated to the OS hypothesis and α =0.2% (2/25 of the overall total α =2.5%) is allocated to the PFS hypothesis.

Figure 4. Maurer and Bretz multiplicity strategy approach used for hypothesis testing in KEYNOTE-426



Abbreviations: PFS, progression free survival; OS, overall survival; ORR, objective response rate

The testing of the OS, PFS, and ORR occurred as follows.

- PFS Hypothesis: the study allocated α=0.2%, one-sided, to test PFS hypothesis initially. If the null hypothesis for OS was rejected, Figure 4 shows that half of its α =2.3% was reallocated to PFS hypothesis testing (α =1.35%). If null hypotheses for OS and ORR were both rejected, all α were reallocated to test PFS hypothesis (α =2.5%).
- OS Hypothesis: The OS hypothesis may be tested at α=2.3% (initially allocated α) or at α=2.5% (if both the ORR and PFS null hypotheses are rejected). The nominal Type I error rates for the interim analysis and final analysis that will allow tight control of the

overall Type I error for testing the OS hypothesis was derived using the alpha-spending function approach based on the overall Type I error allocated to the OS hypothesis.

ORR Hypothesis: was tested with all subjects, since all subjects will have “mature ORR information”. The ORR hypothesis was initially allocated a Type I error α =0% and thus, could be tested unless one or both PFS or OS null hypotheses were rejected. Depending on the results of the OS and PFS hypotheses testing, the ORR hypothesis could be tested at an overall Type I error levels of α =0.2%, 1.15%, or 2.5%. If the testing of ORR hypothesis did not reach statistical significance at interim analysis 1 (IA1), the p-value from the IA1 analysis could be compared to an updated α-level if the null hypothesis for PFS or OS was rejected later.

2.4.2 Subgroup Analyses

The estimate of the between-group treatment effect (with a nominal 95% CI) for the dual primary endpoints were estimated and plotted within each category considered.

Please refer to Section 2.7 for details on statistical tests used in the primary analysis of the subgroups and results.

2.4.3 Statistical analysis

Table 11. Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-426 [16] [17]	1. PFS, per RECIST 1.1 by BICR review 2. OS	The primary hypotheses for PFS and OS were evaluated by comparing pembrolizumab in combination with axitinib to sunitinib using a stratified log-rank test. Estimation of the HR was done using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method. Stratified Miettinen and Nurminen's method with weights proportional to the stratum size will be used for comparison of the ORR between the treatment arms	The sample size was planned for 840 but the following power calculations are based on the actual final number of randomised subjects (N = 861). There were 2 primary endpoints for this study, PFS, and OS. The expected median PFS time in the control group was 13 months. Based on 487 PFS events, the study has ~99% power to detect a hazard ratio of 0.60 for PFS pembrolizumab+axitinib combination vs. sunitinib) at alpha=0.2% (1-sided). The expected median OS time in the control group was 33 months. Based on 404 death events, the study had 80% power to detect a hazard ratio of 0.75 for OS at alpha=2.3% (1-sided).	Subjects may withdraw from the trial at any time for any reason. If a subject withdrew from the trial, h/she no longer received treatment or was followed at scheduled protocol visits. A subject was withdrawn from the trial if: • The subject or subject's legally acceptable representative withdrew consent from the trial. • The subject was lost to follow-up Subjects who withdrew from treatment prior to completion of the trial were encouraged to continue to be followed for all remaining study visits. When a subject withdrew from participation in the trial, all applicable activities scheduled for the End of Treatment visit were performed at the time of discontinuation. Detail of handling missing/censored data are provided in Table 9.

***Abbreviations**: PFS, progression free survival; OS, overall survival; HR, hazard ratio; n, sample size, BICR, blinded independent central review.*

2.4.5 Participant flow in the relevant randomised controlled trials

Details of the participant flow in KEYNOTE-426 [16] [17] are provided in Appendix D (section D1.3).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

2.5.1 & 2 Summary of quality assessment

Quality Assessment of KEYNOTE-426 [16] [17] was conducted using the Cochrane risk of bias tool [22]. Based on this analysis, the study was determined to be at 'low risk' across four of six key domains, with "unclear risk" in one domain and 'high risk' for the blinding bias domain, due to the open-label nature of this study and subsequent lack of blinding; nevertheless it is important to note that there was an element of blinding in this study as independent central imaging review was performed without knowledge of the treatment group assignments of the participants. The complete quality assessment is included in Appendix D1.4 (Table 22). A tabulated summary of the quality assessment results is presented below in Table 12.

Table 12. Quality assessment results for KEYNOTE-426 [16] [17]

Cochrane RoB domain	KEYNOTE-426 [16] [17]
Sequence generation	LOW RISK: Random assignment was stratified by IMDC risk category and geographic region
Allocation concealment	UNCLEAR RISK: Procedures used to maintain allocation concealment was not described.
Blinding of participants, personnel and outcome assessors	HIGH RISK: Open-label study-- patients, participating centres, and physicians delivering therapy and assessing recurrences were not masked to treatment assignment.
Incomplete outcome data	LOW RISK: There were no notable unexpected differences in the drop-outs between groups.
Selective outcome reporting	LOW RISK: There is no evidence to suggest that additional outcomes were excluded from the publication
Other sources of bias	LOW RISK: No blinding, but all outcomes are based on independent-review

Abbreviations: *RoB, risk of bias.*

2.5.3. Consideration of UK clinical practice

Currently in the UK, there is no innovative immuno-oncology treatment available for the first-line treatment of patients with locally advanced or metastatic RCC. Data from KEYNOTE-426 [16] [17] show that pembrolizumab in combination with axitinib is a promising treatment option which has demonstrated efficacy, including significant survival benefits, in all RCC patients, regardless of IMDC risk category, and has an acceptable tolerability profile [16, 17].

KEYNOTE-426 [16] [17] recruited 55% of patients in Europe and baseline demographics suggest these patients were representative of those typically seen in UK clinical practice. The control treatment in KEYNOTE-426 was sunitinib, which has been acknowledged to have comparable efficacy with other TKIs available in UK clinical practice (tivozanib and pazopanib [12, 13]). In contrast, the data from KEYNOTE-426 [16] [17] suggest that pembrolizumab in combination with axitinib could offer a significant step-change in benefit for these patients.

B.2.6 Clinical effectiveness results of the relevant trials

2.6.1. KEYNOTE-426 results

Early results are presented from the KEYNOTE-426 [16] [17] study, based on the first interim analysis (IA1), which had a data cut-off date of 24 August 2018. Further details are provided below.

A further data-cut, dated 02 January 2019, was conducted for a Safety Update Report (SUR) database lock, which was not pre-specified but instead produced for the Food and Drug Administration (FDA), to meet regulatory requirements. The SUR provides data with another 4 more months of follow-up. From a statistical point of view, there is no further formal hypothesis testing in SUR given that statistical significance of all pre-specified tests was already achieved at IA1. With the press release of the success of the KEYNOTE-426 study [16] [17] at IA1, more confounding factors, such as subsequent therapy use, may bias the estimate of the treatment effect, which should be taken into consideration when interpreting the SUR results. The rate of subsequent therapy use in the sunitinib arm of KEYNOTE-426 was high; in particular there was disproportionately high use of nivolumab in the second-line setting, which exceeds that expected in UK clinical practice [23] (please refer to Appendix P). Nevertheless, the results based on the January 2019 data-cut provide supportive evidence that [redacted] of pembrolizumab plus axitinib versus sunitinib is [redacted] with additional follow-up. Pembrolizumab in combination with axitinib continued to demonstrate a

statistically significant and clinically meaningful improvement in OS and PFS compared with sunitinib for the 1L treatment of participants with advanced RCC [redacted] Efficacy results from the January 2019 data-cut are presented in Appendix O, with safety results presented in Appendix F.

IA1 – data cut-off 24 August 2018

IA1 occurred after meeting the cut-off criteria of accruing at least 305 PFS events and with a minimum follow up of 7 months. The data monitoring committee (DMC) meeting for IA1 was held on 16 October 2018, at which time the DMC recommended that the study stop further efficacy testing, due to statistically significant improvement in both primary endpoints (PFS and OS) and key secondary endpoint (ORR) in the pembrolizumab plus axitinib combination arm compared with the sunitinib arm. The Executive Oversight Committee (EOC) subsequently decided to unblind the study.
A total of 1062 participants were screened (first participant screened on 06 October 2016) and 861 were randomly allocated from 24 October 2016 to 24 January 2018 across 124 global study sites in 16 countries. 854 subjects received study treatment. The participant flow and subject disposition from KEYNOTE-426 [16] [17] are provided in Appendix D1.3

Primary efficacy endpoints: clinical outcome measures included within the health economic model

At IA1, KEYNOTE-426 [16] [17] had met both of its primary endpoints of PFS and OS, with p-values crossing the prespecified boundary for statistical significance of 0.0013 and 0.0001, respectively. As of the data cut-off date (24 August 2018) for IA1, the median duration of follow up was 13.2 months (range: 0.1 to 21.5 months) in the pembrolizumab + axitinib group and 12.1 months (range: 0.4 to 22.0 months) in the sunitinib group.

- *OS: IA1 August 2018 data-cut*

Pembrolizumab in combination with axitinib demonstrated a statistically significant and clinically meaningful improvement in OS compared with sunitinib for the 1L treatment of participants with advanced RCC. The OS HR of 0.53 (95% CI: 0.38, 0.74; p=0.00005) represents a 47% reduction in the risk of death for participants in the pembrolizumab + axitinib group compared with the sunitinib group (Table 13). The number of OS events (97 in 429 participants) reported for the sunitinib group in Table 13 differs from the number of deaths (95

in 429 participants) reported for that group in Table 32 due to data collected during the protocol-defined survival follow-up period.

Median OS was not reached in either group by the time of the data cut-off. OS rates at Months 6, 12, and 18 favour pembrolizumab + axitinib compared with sunitinib (Table 14). The OS KM curves separated early in favour of pembrolizumab + axitinib and remained separated over time (Figure 5).

Table 13. Analysis of OS (ITT): IA1 August 2018 data-cut

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	432	59 (13.7)	5670.0	1.0	Not Reached (., .)	89.9 (86.4, 92.4)
Sunitinib	429	97 (22.6)	5183.8	1.9	Not Reached (., .)	78.3 (73.8, 82.1)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value§**
Pembrolizumab + Axitinib vs. Sunitinib					0.53 (0.38, 0.74)	0.00005

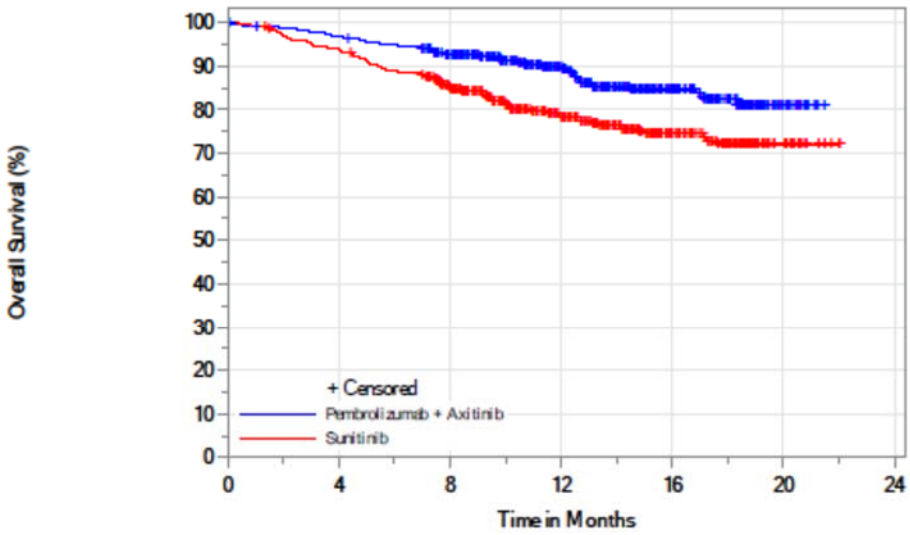
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favourable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
§ One-sided p-value based on log-rank test stratified by the same strata as above.

Table 14. Summary of OS Rate Over Time (ITT); IA1 August 2018 data-cut

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
OS rate at 6 Months in % (95% CI)†	94.9 (92.3, 96.6)	89.0 (85.6, 91.6)
OS rate at 12 Months in % (95% CI)† OS	89.9 (86.4, 92.4)	78.3 (73.8, 82.1)
rate at 18 Months in % (95% CI)†	82.3 (77.2, 86.3)	72.1 (66.3, 77.0)

† From the product-limit (Kaplan-Meier) method for censored data. Database Cut-off

Figure 5: KM Estimates of OS (ITT); IA1 August 2018 data-cut



Number of subjects at risk

Pembrolizumab + Axitinib	432	417	378	256	136	18	0
Sunitinib	429	401	341	211	110	20	0

- *PFS: IA1 August 2018 data-cut*

Pembrolizumab in combination with axitinib demonstrated a statistically significant and clinically meaningful improvement in PFS (per RECIST 1.1 by BICR) compared with sunitinib for the 1L treatment of participants with advanced RCC. The PFS HR of 0.69 (95% CI: 0.57, 0.84; p=0.00014) represents a 31% reduction in the risk of progression or death for participants in the pembrolizumab + axitinib group compared with the sunitinib group (Table 15). The median PFS was longer in the pembrolizumab + axitinib group compared with the sunitinib group (15.1 months vs 11.1 months).

In the pembrolizumab + axitinib group, the PFS rates at 6 and 12 months were higher compared with the sunitinib group (Table 16). The KM curves separated early and remained separated for the duration of the evaluation period (Figure 6).

Table 15. Analysis of PFS (Primary Censoring Rule) based on BICR assessment per RECIST 1.1 (ITT): IA1 August 2018 data-cut

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Axitinib	432	183 (42.4)	3949.7	4.6	15.1 (12.6, 17.7)	59.6 (54.3, 64.5)
Sunitinib	429	212 (49.4)	3280.7	6.5	11.1 (8.7, 12.5)	46.2 (40.6, 51.6)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value§**
Pembrolizumab + Axitinib vs. Sunitinib					0.69 (0.57, 0.84)	0.00014

† *From product-limit (Kaplan-Meier) method for censored data.*

‡ *Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favourable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).*

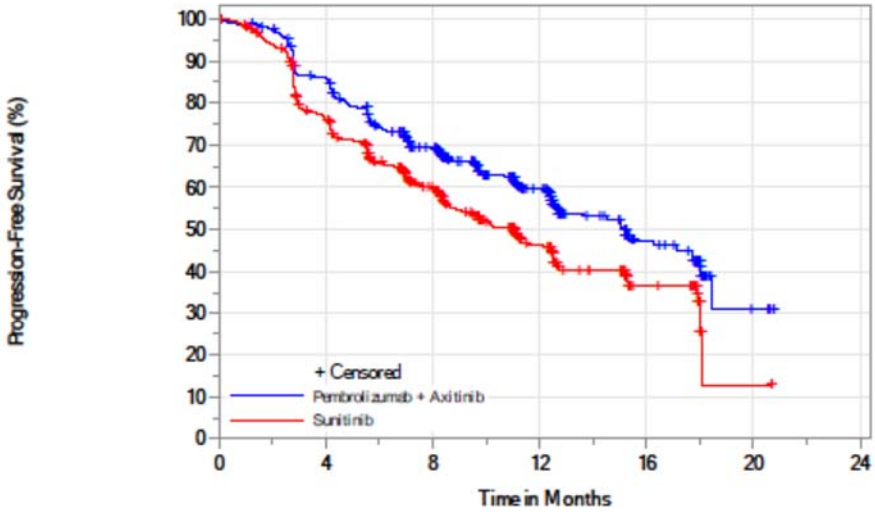
§ *One-sided p-value based on log-rank test stratified by the same strata as above*

Table 16. Summary of PFS Rate Over Time (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT Population): IA1 August 2018 data-cut

	Pembrolizumab + Axitinib (N=432)	Sunitinib (N=429)
PFS rate at 6 Months in % (95% CI)†	74.0 (69.5, 77.9)	66.0 (61.1, 70.4)
PFS rate at 12 Months in % (95% CI)† PFS	59.6 (54.3, 64.5)	46.2 (40.6, 51.6)
rate at 18 Months in % (95% CI)†	41.1 (33.5, 48.5)	32.9 (25.4, 40.5)

† *From the product-limit (Kaplan-Meier) method for censored data. BICR = Blinded independent central review.*

Figure 6. KM Estimates of PFS (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT): IA1 August 2018 data-cut



Number of subjects at risk

Pembrolizumab + Axitinib	432	357	251	140	42	3	0
Sunitinib	429	302	193	89	29	1	0

Secondary Efficacy Endpoints

- *ORR: IA1 August 2018 data-cut*

Pembrolizumab + axitinib demonstrated a statistically significant and clinically meaningful improvement in ORR compared with sunitinib for the 1L treatment of participants with advanced RCC. The confirmed ORR (per RECIST 1.1 by BICR) was 59.3% for the pembrolizumab + axitinib group compared with 35.7% for the sunitinib group, with an estimated difference of 23.6% (95% CI: 17.2, 29.9; p<0.0001) (Table 17).

A total of 25 (5.8%) participants treated with pembrolizumab + axitinib achieved a CR, while 8 (1.9%) participants treated with sunitinib achieved a CR (Table 18). Participants receiving pembrolizumab + axitinib were more likely to experience a reduction in tumour size than those receiving sunitinib. Among participants with measurable disease and at least one post-baseline assessment, 94% in the pembrolizumab + axitinib group and 85% in the sunitinib group had a decrease in the sum of their target tumour diameters (Figure 7 and Figure 8).

Table 17. Analysis of ORR (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT); IA1 August 2018 data-cut

Treatment	N	Number of Objective Responses	ORR Rate (%) (95% CI)	Difference in % vs. Sunitinib	
				Estimate (95% CI)†	p-Value††
Pembrolizumab + Axitinib	432	256	59.3 (54.5,63.9)	23.6 (17.2,29.9)	<0.0001
Sunitinib	429	153	35.7 (31.1,40.4)		

† *Based on Miettinen & Nurminen method stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favourable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).*

†† *One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on BICR assessment per RECIST 1.1.*

BICR = Blinded independent central review.

Table 18. Summary of ORR (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT); IA1 August 2018 data-cut

Response Evaluation	Pembrolizumab + Axitinib			Sunitinib		
	n	%	95% CI†	n	%	95% CI†
Subjects in population	**432**			**429**		
Complete Response (CR)	25	5.8	(3.8, 8.4)	8	1.9	(0.8, 3.6)
Partial Response (PR)	231	53.5	(48.6, 58.3)	145	33.8	(29.3, 38.5)
Objective Response (CR+PR)	**256**	**59.3**	**(54.5, 63.9)**	**153**	**35.7**	**(31.1, 40.4)**
Stable Disease (SD)	106	24.5	(20.5, 28.9)	169	39.4	(34.7, 44.2)
Disease Control (CR+PR+SD ≥ 6 months)	**309**	**71.5**	**(67.0, 75.7)**	**260**	**60.6**	**(55.8, 65.3)**
Progressive Disease (PD)	47	10.9	(8.1, 14.2)	73	17.0	(13.6, 20.9)
Non-evaluable (NE) ‡	8	1.9	(0.8, 3.6)	6	1.4	(0.5, 3.0)
No Assessment §	15	3.5	(2.0, 5.7)	28	6.5	(4.4, 9.3)

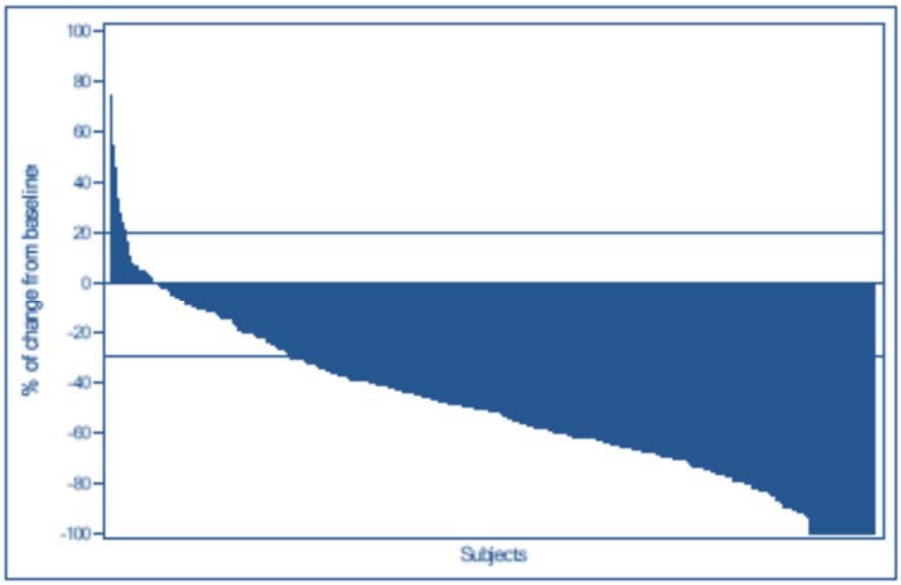
† *Based on binomial exact confidence interval method for binomial data.*

‡ *NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) with insufficient data for assessment of response per RECIST 1.1. or CR/PR/SD < 6 weeks from randomisation).*

§ *No Assessment: no post-baseline assessment available for response evaluation. For best overall response of CR and PR, only confirmed responses are included.*

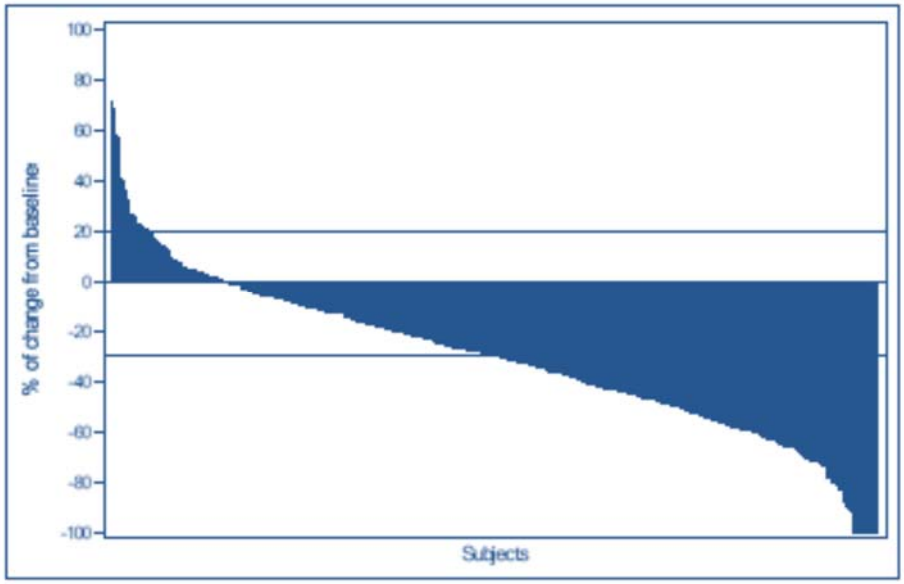
BICR = Blinded independent central review.

Figure 7. Waterfall Plot of Maximum Tumour Change from Baseline Based on BICR Assessment per RECIST 1.1 Subjects with Measurable Disease at Baseline (Pembrolizumab + Axitinib Arm); IA1 August 2018 data-cut



Percentage of subjects with tumour shrinkage: 94%
Including subjects with measurable disease at baseline and at least one post-baseline measurement

Figure 8. Waterfall Plot of Maximum Tumour Change from Baseline Based on BICR Assessment per RECIST 1.1 Subjects with Measurable Disease at Baseline (Sunitinib Arm); IA1 August 2018 data-cut



Percentage of subjects with tumour shrinkage: 85%
Including subjects with measurable disease at baseline and at least one post-baseline measurement

- *DCR: IA1 August 2018 data-cut*

A higher DCR (defined as CR + PR + SD for >6 months) was demonstrated in the pembrolizumab + axitinib group (71.5%; 95% CI: 67.0, 75.7) compared with the sunitinib group (60.6%; 95% CI: 55.8, 65.3) based on data from the August 2018 data cut-off (Appendix L, Table 9). The analysis of DCR based on investigator assessment per RECIST 1.1 (Table 10, Appendix L) was consistent with the results of the analysis by BICR.

- *DOR: IA1 August 2018 data-cut*

The responses in the pembrolizumab + axitinib group for the 1L treatment of participants with advanced RCC were more durable compared with the sunitinib group (Appendix L, Table 7), based on data from the August 2018 data cut-off. The median DOR was not reached by the time of the data cut-off in the pembrolizumab + axitinib group and was 15.2 months in the sunitinib group. In the pembrolizumab + axitinib group, a higher percentage of participants had extended responses for ≥6 months and ≥12 months by KM estimation (Appendix L, Figure 4).

Patient Reported Outcomes

- ***PRO Compliance Rate and Completion Rate – IA1 August 2018 data-cut***

In the pembrolizumab + axitinib group, PROs were assessed on Day 1 of each cycle. In the sunitinib group, PROs were assessed on Days 1 and 29 of each cycle up to Cycle 4, then on Day 1 of each subsequent cycle following the two-week-off treatment period. Compliance rates for the FKSI-DRS by visit and by treatment at baseline through week 30 were high (range: 85.9% through 97.1%) in both groups (Appendix L, Table 14). The compliance rates for EORTC QLQ-C30 and EQ-5D-3L (Appendix L, Table 14) were similar to that for the FKSI-DRS. As expected, completion rates generally decreased at each time point as more participants discontinued the study treatment.

- *EQ-5D-VAS Health Status/Quality of Life change from baseline to Week 30: IA1 August 2018 data-cut*

There were no clinically meaningful differences from baseline to week 30 in the EQ-5D-VAS health status/QoL score for participants in both the pembrolizumab + axitinib group and the sunitinib group based on data from the August 2018 data-cut (Table 19). Changes from

baseline to week 30 were generally similar between the treatment groups at week 30 (Table 19 and Figure 9).

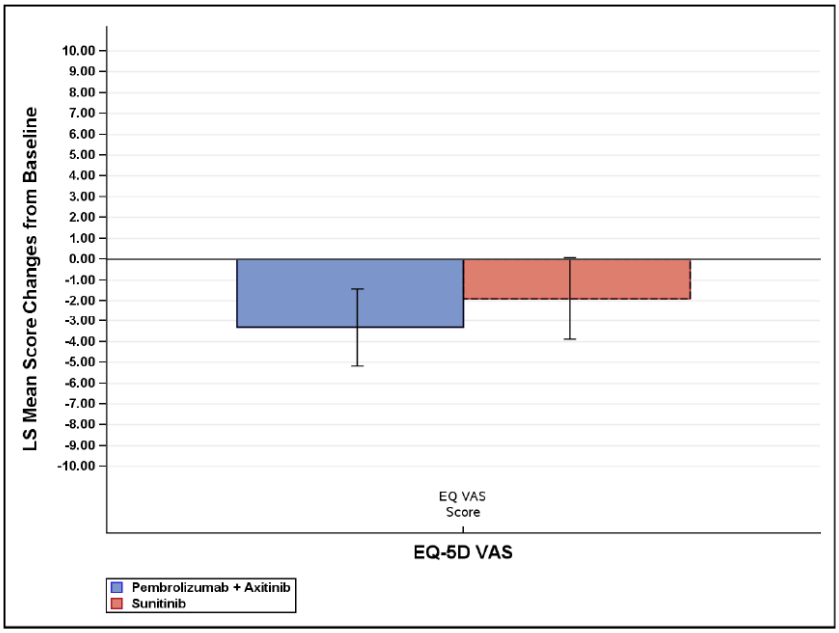
Table 19. Analysis of change from baseline in EQ-5D VAS at week 30: August 2018 data-cut

Treatment	Baseline		Week 30		Change from baseline at week 30	
	N	Mean (SD)	N	Mean (SD)	N	LS mean (95% CI)
Pembrolizumab + Axitinib	390	73.82 (18.71)	291	71.68 (17.23)	427	-3.31 (-5.18, -1.43)
Sunitinib	406	74.58 (19.32)	248	75.62 (17.38)	421	-1.92 (-3.90, 0.05)

Pairwise comparison	Differences in LS mean (95% CI)	p-value
Pembrolizumab + axitinib vs sunitinib	-1.38 (-3.89, 1.12)	0.277

Based on cLDA model with the PRO scores as the response variable, and treatment by timepoint interaction, stratification factors
For baseline and Week 30, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group. Two-sided p-value.

Figure 9. Change from baseline for EQ-5D VAS at week 30; LS mean change and 95% CI; August 2018 data-cut



For EQ-5D VAS: a higher score denotes better quality of life.

B.2.7 Subgroup analysis

2.7.1. Subgroup analyses carried out

Subgroup analyses were pre-specified in the KEYNOTE-426 [16] [17] study protocol to determine whether the treatment effect was consistent across subgroups. The estimate of the between-group treatment effect (with a nominal 95% CI) for the dual primary endpoints were estimated and plotted within each category of the following classification variables:

- IMDC risk category (favourable versus intermediate versus poor; favourable versus
- intermediate plus poor)
- Geographic region (North America versus Western Europe versus Rest of the World)
- PD-L1 status (combined positive score [CPS] <1 versus CPS ≥ 1)
- Age (< 65 versus ≥ 65)
- Sex (male versus female)
- Race (white versus non-white)

OS by Subgroup: IA1 August 2018 data-cut

The improvement in OS for pembrolizumab + axitinib compared with sunitinib (based on the August 2019 data-cut) was consistent across all subgroups analysed, including by PD-L1 status, IMDC risk category, and geographic region (Appendix E, Figure 1). OS results for the < 65, ≥ 65 to < 75, and ≥ 75 to < 85-year-old age groups were consistent with the primary analysis. The small sample size in the ≥ 85-year-old age group precluded a meaningful analysis (Figure 1; Appendix E). Analysis of OS is presented for the subgroups based on IMDC risk categories (favourable, intermediate/poor) in Appendix E (Table 1-2 and Figure 3-4).

Subgroup analyses results for OS based on the January 2019 data-cut are presented in Appendix E.

PFS by Subgroup: IA1 August 2018 data-cut

The improvement in PFS for pembrolizumab + axitinib compared with sunitinib (based on the August 2019 data-cut) was consistent across all subgroups, including by PD-L1 status, IMDC risk category, and geographic region (Figure 2; Appendix E). PFS results for the < 65, ≥ 65 to < 75, and ≥ 75 to < 85-year-old age groups were consistent with the primary analysis. The small sample size in the ≥ 85-year-old age group precluded a meaningful analysis (Figure 2; Appendix E). Analysis of PFS is presented for the IMDC risk categories (favourable, intermediate/poor) in Appendix E (Table 3-4 and Figure 5-6).

Subgroup analyses results for PFS based on the January 2019 data-cut are presented in Appendix E.

B.2.8 Meta-analysis

There is only one phase III randomised, controlled trial of pembrolizumab + axitinib compared with a relevant comparator, in our specific population of interest (patients with advanced RCC): KEYNOTE-426 [16] [17]. Therefore, it was not possible to conduct a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

Please refer to Appendix D for full details of the methodology used for the NMA.

2.9.1 Summary of trials included in the network meta-analysis (NMA)

Trials included in the NMA were identified through the SLR and are presented in Table 20. An overview of the patients' characteristics in all included studies is provided in Table 21. The full network of evidence identified in the SLR for pembrolizumab + axitinib in first-line setting is depicted in Figure 10.

Table 20. Summary of the RCTs used to carry out the NMA

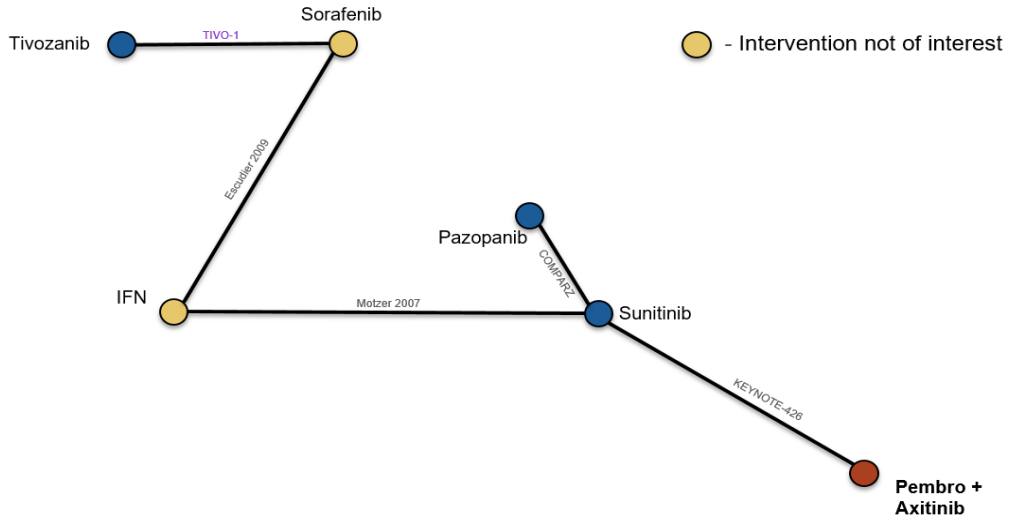
Trial ID	Intervention A	Intervention B
CABOSUN [24]	Cabozantinib	Sunitinib
COMPARZ [25]	Pazopanib	Sunitinib
KEYNOTE-426 [16] [17]	Pembrolizumab + Axitinib	Sunitinib
TIVO-1 [26]	Tivozanib	Sorafenib

Abbreviations: RCT, randomised controlled trials; NMA< network meta-analysis.

Table 21. Patient characteristics of randomised controlled trials included in the feasibility assessment

Trial ID	Intervention	N	Median age (range)	Female (%)	Caucasian (%)	Asian (%)
CABOSUN [24]	Cabozantinib	79	63 (40-82)	13 (16.5)	70 (88.6)	1 (1.3)
	Sunitinib	78	64 (21-87)	21 (26.9)	75 (96.2)	0 (0)
COMPARZ [25]	Pazopanib	557	61 (18-88)	159 (29)	--	--
	Sunitinib	553	62 (23-86)	138 (25)	--	--
KEYNOTE-426 [16] [17]	Pembrolizumab + axitinib	432	62 (30-89)	124 (28.7)	343 (79.4)	66 (15.3)
	Sunitinib	429	61 (26-90)	109 (25.4)	341 (79.5)	71 (16.6)
TIVO-1 [26]	Tivozanib	260	59 (23-83)	75 (29)	249 (96)	10 (4)
	Sorafenib	257	59 (23-85)	68 (26)	249 (97)	8 (3)

Figure 10. Network of evidence for all included RCTs in 1L for treating RCC (all outcomes)



Note: Interventions not of interest (IFN and sorafenib) were included in the NMA to facilitate an indirect comparison between tivozanib and other interventions of interest. The CABOSUN trial (Cabozantinib vs. sunitinib) is not included in this network diagram as this trial included IMDC intermediate/poor risk category patients only

2.9.2 NMA – Overview of analyses and the base case

As described earlier in Section B.2.9, four trials were deemed eligible for inclusion in the NMA. The base case analysis included trials conducted among treatment naïve advanced/metastatic RCC patients and trials that reported subgroup data for this population. One trial included both first-line and second-line treatment [TIVO-1] [26]. Therefore, subgroup data from TIVO-1 [26] including only 1L patients was included in analyses, where feasible. Trials restricted to intermediate/poor risk participants were excluded from the base case

analyses (i.e. CABOSUN, which evaluated cabozantinib versus sunitinib [24]). This exclusion left two trials assessing comparators of relevance to the decision problem for possible inclusion in the base case analyses. NMAs for the base-case analyses were deemed feasible for PFS and OS, using NMAs of published HRs and Kaplan-Meier (KM) curves. Additionally, subgroup analyses to address effect modifiers were feasible for (1) intermediate/poor risk and (2) favourable risk.

Random-effects models (REMs) were more plausible than fixed-effect models (FEMs); however, for all analyses of constant HRs, including subgroup analyses, data availability and network structure prevented estimation of between-study heterogeneity. Because all network connections were described by a single trial, REMs were not feasible and only FEMs were conducted for all analyses. Furthermore, NMAs allowing HRs to vary over time were carried out where feasible. Fractional polynomial (FP) models were fit to the data, under a variety of different assumptions about the shape of the hazard function. Of all models assessed, the best-fitting time-varying HR models were determined based upon the lowest DIC. Constant and time-varying HR analyses of PFS and OS were feasible for the intermediate/poor risk subgroup. However, only constant HR analyses of PFS and OS were feasible for the favourable risk subgroup.

The section below will first present results for the base case scenario and then intermediate/poor risk group analyses as described within the decision problem (Table 1). Results for the favourable risk group are presented in Appendix E for information only, given this subgroup is not of relevance to the Decision Problem (Table 1).

2.9.3 NMA results

2.9.3.1 Base case scenarios

PFS: August 2018 data-cut

PFS was reported in two trials eligible for inclusion in the base case analysis that evaluated three interventions. However, to connect tivozanib to the network of evidence, two interventions not of interest to the UK perspective were included for PFS (IFN-α and sorafenib). Therefore, the network of evidence for PFS consists of five trials corresponding to six interventions to estimate relative treatment effects for interventions of interest relevant to

the UK: tivozanib, pazopanib, sunitinib, and pembrolizumab + axitinib. The PFS HRs for the comparator(s) vs the reference intervention are shown for each trial in Table 22.

The network of evidence for the constant and time-varying HR analyses is shown in Figure 11. All analyses were conducted using FEMs because data availability and network structure prevented estimation of between study heterogeneity. The results of the FEM constant hazard NMA are shown in Table 23. The results showed that treatment with pembrolizumab + axitinib resulted in a [redacted] in the duration of PFS compared to all competing interventions including [redacted].

[redacted] Results based on the January 2019 data-cut are provided in Appendix N. These show [redacted] results compared with the results presented below.

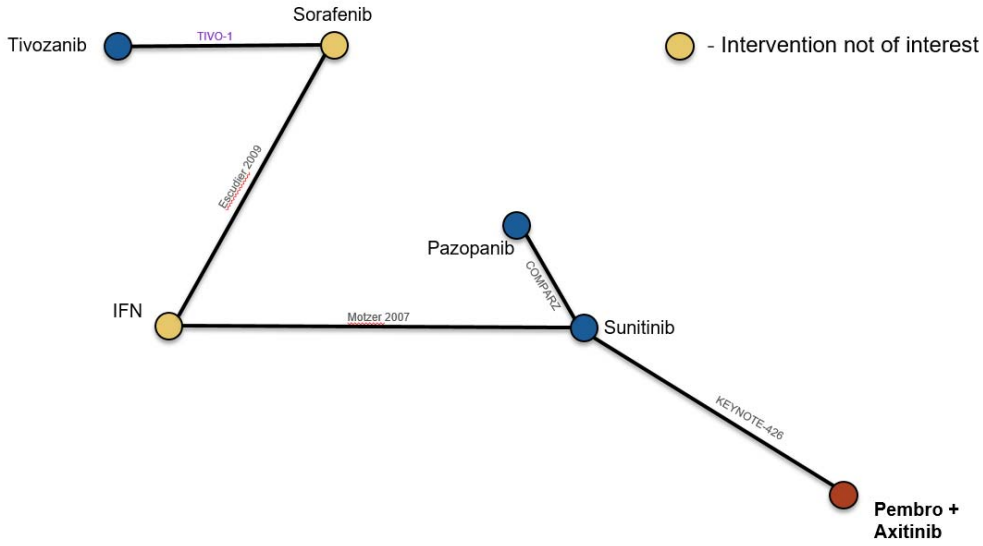
Please refer to Appendix M for the results of the time varying hazard ratios, including model fit estimate based on DIC; HRs at selected time points and basic parameter estimates of 2nd order FP model.

Table 22: Constant HRs for PFS; base case

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
COMPARZ [25]	Sunitinib	Pazopanib	[redacted]	[redacted]
Escudier 2009 [27]	IFN-α	Sorafenib	[redacted]	[redacted]
KEYNOTE-426 (IA1 Aug 2018 data cut) [16] [17]	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]
Motzer 2007 [28]	Sunitinib	IFN-α	[redacted]	[redacted]
TIVO-1* [26]	Sorafenib	Tivozanib	[redacted]	[redacted]

*Note: * denotes trials in grey used subgroup first-line data*
Grey rows represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.

Figure 11. Network of evidence for 1L PFS; base case; HRs and KM curves



PFS August 2018 data-cut results

Table 23. HRs estimated from fixed-effects constant hazard NMA of PFS; base case

Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**IFN-a**	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Sorafenib**	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Pazopanib**	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Tivozanib**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Pembrolizumab +axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
Grey cells represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 9.34; Deviance: 4.36

OS: August 2018 data-cut

OS was reported in two trials eligible for inclusion in the base case analysis that evaluated three 3 interventions. The network of evidence for the constant and time-varying HR analyses for both data cut-offs is shown in Figure 12. All analyses were conducted using FEMs due to data availability and network structure, which prevented estimation of between study

heterogeneity. The OS HRs for the comparator(s) vs the reference intervention are shown for each trial in Table 24.

The results of the fixed effects constant HR NMA are shown in Table 25. The results of the constant HR analysis showed that treatment with pembrolizumab + axitinib resulted in a [redacted] in the duration of OS compared to both pazopanib [redacted] and sunitinib [redacted] were obtained with the January 2019 data (**Error! Reference source not found.**). Furthermore, pazopanib was [redacted] from sunitinib with respect to OS.

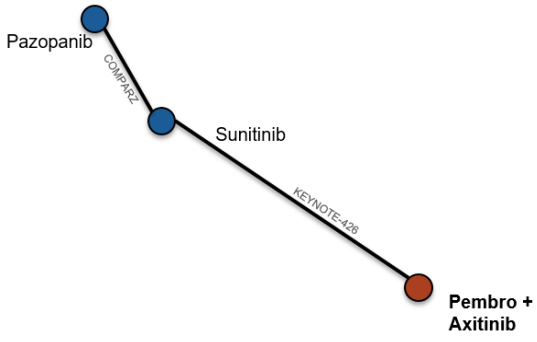
Results based on the January 2019 data-cut are provided in Appendix N. These show [redacted] results compared with the results presented below.

Please refer to Appendix M for: time-varying HRs, including model fit estimate based on DIC; HRs at selected time points and basic parameter estimates of 2nd order FP model.

Table 24: Constant HRs for OS; base case

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
COMPARZ [25]	Sunitinib	Pazopanib	[redacted]	[redacted]
KEYNOTE-426 (IA1 - Aug 2018 data-cut) [16] [17]	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Figure 12. Network of evidence for 1L RCC OS; base case; HRs and KM curves



OS August 2018 data-cut results

Table 25. HRs estimated from fixed-effects constant hazard NMA of OS; base case

Sunitinib	[redacted]	[redacted]
[redacted]	**Pazopanib**	**1.73 (1.21, 2.49)**
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 3.39; Deviance: 1.39

2.9.3.2 Intermediate/poor risk subgroup analyses

For intermediate and poor risk subgroup analyses, the ITT population OS/PFS data was used from the CABOSUN trial [24], and subgroup data was used from KEYNOTE-426 [16] [17].

PFS: August 2018 data-cut

PFS among intermediate/poor risk participants was reported in two trials evaluating three interventions. The same network of evidence was available for both the constant and time-varying HR analyses (Figure 13) and for both data cut-off available. All three trials assessed risk using IMDC risk criteria. KEYNOTE-426 [16] [17] used subgroup data, while CABOSUN [24] used survival data from the ITT population because the trial was restricted to intermediate and poor risk participants. All analyses were conducted using FEMs due to data availability and network structure, which prevented the estimation of between-study heterogeneity. The PFS HRs for the comparator(s) vs the reference intervention are shown for each trial in Table 26.

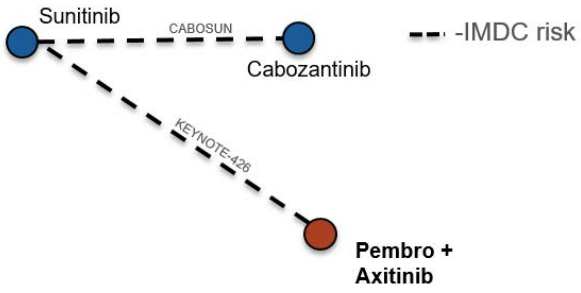
The results of the fixed effects constant HR NMA are shown in Table 27. The results of the constant HR analysis showed that both pembrolizumab + axitinib and cabozantinib are [redacted] to sunitinib [redacted] Although the results [redacted] cabozantinib [redacted] pembrolizumab + axitinib, this differentiation [redacted] were obtained when using the January 2019 data (see Appendix N).

Please refer to Appendix M for: time-varying hazard ratios, including model fit estimate based on DIC; HRs at selected time points and basic parameter estimates of 2nd order FP model.

Table 26: Constant HRs for PFS; intermediate/poor risk subgroup

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN [24]	Sunitinib	Cabozantinib	[redacted]	[redacted]
KEYNOTE-426 (IA1 - Aug 2018 data-cut) [16] [17]	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Figure 13. Network of evidence for 1L RCC PFS, intermediate/poor risk subgroup; HRs and KM curves



PFS August 2018 data-cut results

Table 27. HRs estimated from fixed-effects constant hazard NMA of PFS; intermediate/poor risk subgroup

Sunitinib	[redacted]	[redacted]
[redacted]	**Cabozantinib**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 3.38; Deviance: 1.38

OS: August 2018 data-cut

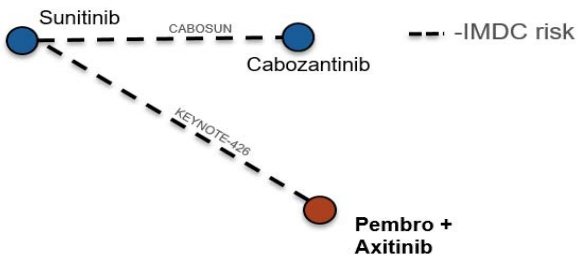
OS among intermediate/poor risk participants was reported in two trials evaluating three interventions. The same network of evidence was available for both the constant and time-varying HR analyses for both data cut-off available (Figure 14). All three trials assessed risk using IMDC risk criteria. KEYNOTE-426 [16] [17] used subgroup data, while CABOSUN [24] used survival data from the ITT population because the trial was restricted to intermediate and poor risk participants. All analyses were conducted using FEMs due to data availability and network structure, which prevented the estimation of between study heterogeneity. The OS HRs for the comparator(s) vs the reference intervention are shown for each trial in Table 28. The results of the fixed effects constant HR NMA are shown in Table 29. The results [redacted] pembrolizumab + axitinib [redacted] cabozantinib, [redacted] Pembrolizumab + axitinib was [redacted] to sunitinib [redacted] with respect to OS. [redacted] were obtained with the January 2019 data (see Appendix N).

Please refer to Appendix M for: time-varying HRs including model fit estimate based on DIC; HRs at selected time points and basic parameter estimates of 2nd order FP model.

Table 28: Constant HRs for OS; intermediate/poor risk subgroup

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN [24]	Sunitinib	Cabozantinib	[redacted]	[redacted]
KEYNOTE-426 (IA1 - Aug 2018 data-cut) [16] [17]	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Figure 14. Network of evidence for 1L RCC OS, intermediate/poor risk subgroup; HRs and KM curves



OS August 2018 data-cut results

Table 29. HRs estimated from fixed-effects constant hazard NMA of OS; intermediate/poor risk subgroup

Sunitinib	[redacted]	[redacted]
[redacted]	**Cabozantinib**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 3.37; Deviance: 1.37

2.9.4 Heterogeneity and inconsistency

As each connection in the network was only described by a single trial, stable estimates of between-study heterogeneity could not be obtained, and results of random-effects analyses were not meaningful. Therefore, only the results of fixed-effects analyses were presented.

In order to gauge the appropriateness of proceeding with an NMA the feasibility assessment included: 1) determination of whether the RCT evidence for the interventions of interest do form one evidence network for each population and outcome of interest; and 2) assessment of the distribution of treatment, outcomes, study and patient characteristics that may affect treatment effects across direct comparisons of the evidence networks. The most important treatment-effect modifiers were identified as risk score, PD-L1 status, age, and performance score (ECOG or KPS), which were included subgroups of interest. The feasibility assessment to assess heterogeneity in terms of treatment and outcome characteristics as well as the study and patient characteristics was performed, which identified several important differences (see section below). Although the studies were determined to be of good quality overall, most trials were open-label. Differences in terms of risk score were accounted for by evaluating subgroups. Subgroup analyses did not identify trends in estimated relative treatment effects that substantially differed from the base case analyses. Given the limited number of trials included in all analyses, there was insufficient data to reliably estimate between-study heterogeneity.

Uncertainties in the indirect and mixed treatment comparisons

The validity of the findings based on the current NMA depends on the quality of the RCTs and the extent of any violations in the similarity and consistency assumptions across studies. In a NMA of RCTs involving multiple treatment comparisons, the randomisation holds only within the individual trials and not across trials. If the different direct comparisons show systematic differences in study and patient characteristics, and these differences are treatment effect modifiers, then the estimates of any indirect comparison as obtained with the NMA will be biased. The feasibility assessment to assess heterogeneity in terms of treatment and outcome characteristics as well as the study and patient characteristics was performed which identified several important differences. Although the studies were determined to be of good quality overall, most trials were open-label. Despite robust statistical methods, comparisons of study, treatment, and patient characteristics across trials revealed some differences that may have introduced bias into the NMA results. For example, one trial included both first-line and second-line treatment (TIVO-1 [26]). TIVO-1 subgroup data with only 1L patients was included in analyses, where feasible. The use of subgroup data results in smaller sample sizes, which may reduce precision. Additionally, for intermediate and poor risk subgroup analyses, the ITT population OS/PFS data was used for CABOSUN [24] and subgroup data was used for the KEYNOTE-426 trial [16] [17]. Importantly, smaller sample sizes seen in subgroups may result in more uncertainty and wider CrIs, especially among connections informed by only one trial. This likely will not result in a biased point estimate but does limit the ability to draw statistically meaningful conclusions from the analysis. However, subgroup analyses did not identify trends in estimated relative treatment effects that substantially differed from the base case analyses. With respect to PFS in the base case analysis, under the assumption of constant HR results, pembrolizumab + axitinib had [redacted] PFS compared to competing interventions of interest (sunitinib, pazopanib, and tivozanib); however, these results must be interpreted with caution due to violations of the proportional hazards assumption. Based on time-varying HR results (Appendix M and N), pembrolizumab + axitinib versus sunitinib demonstrated [redacted] PFS compared to tivozanib and pazopanib after 6 months as shown by the non-overlapping CrIs. Unlike the PFS analysis for the base case, constant HR results were appropriate for OS as both interventions in the network (pembrolizumab + axitinib and pazopanib) versus sunitinib did not significantly vary over time. Pembrolizumab + axitinib [redacted] compared to both sunitinib and pazopanib. Relative estimates of PFS did not considerably differ between the base case and intermediate/poor risk subgroup analysis. However, the network of evidence between these

two analyses differed and comparisons between these analyses must be interpreted with caution. Constant HR analysis was considered appropriate for the analysis of PFS in this subgroup, as both pembrolizumab + axitinib and cabozantinib versus sunitinib did not vary over time significantly. Unlike PFS, violations to the proportional hazards' assumption were observed for pembrolizumab + axitinib for OS in the intermediate/poor risk subgroup analysis. However, given the low number of events in this subgroup, which contributes to large uncertainty because the 2nd order FP models are more sensitive to fluctuations in observed hazards when sample sizes of the at-risk becomes small over time, the constant HR NMA is still considered to provide stable and appropriate relative treatment effects. Although pembrolizumab + axitinib versus sunitinib had improved OS HR point estimates up until 12 months compared to cabozantinib versus sunitinib this was not sustained after 12 months. However, although pembrolizumab + axitinib versus sunitinib HRs did significantly increase over time it was not statistically differentiated from cabozantinib versus sunitinib as evidenced by overlapping CrIs. The constant HR NMA for OS in the intermediate/poor risk OS subgroup support time-varying HR NMA results; pembrolizumab + axitinib is not statistically differentiated from cabozantinib but does offer statistically improved OS compared to sunitinib.

B.2.10 Adverse reactions

The primary safety analyses of IA1 were based on data from the ASaT population of 854 participants as of the cut-off date of 24 August 2018. In all tables, individuals are counted only once for a specific AE term by the worst severity recorded.

Please refer to Appendix E for information related to the following:

- Drug Related AEs
- Grade 3-5 AEs
- Serious AEs
- Death to AEs
- Discontinuation due to AEs
- Interruptions due to AEs
- Dose reductions due to AEs
- AEs of special interest
- Hepatic AEs

A summary of AEs from the January 2019 data cut-off is presented in Appendix O.

IA1: August 2018 data-cut

Extent of exposure

The median duration of exposure was greater for pembrolizumab + axitinib compared with sunitinib (Table 30). When adjusted for exposure, there were no clinically meaningful differences in overall event rates between the two groups, including SAEs and drug-related SAEs (Table 34). The rate of drug-related AEs was lower for pembrolizumab + axitinib compared with sunitinib.

Table 30: Extent of Exposure - Summary of Duration on Therapy (ASaT Population)

	Pembrolizumab + Axitinib	Sunitinib
Subjects in population	429	425
Duration on Therapy† (days)		
N	429	425
Mean	320.6	255.6
SD	163.2	165.6
Median	317.0	238.0
Range	1 to 646	2 to 623
Duration on Both Study Drugs in the Combination Arm‡ (days)		
N	429	
Mean	263.5	
SD	176.8	
Median	253.0	
Range	0 to 645	
Duration on Pembrolizumab in the Combination Arm§ (days)		
N	429	
Mean	287.0	
SD	175.0	
Median	279.0	
Range	1 to 646	
Duration on Axitinib in the Combination Arm‖ (days)		

	Pembrolizumab + Axitinib	Sunitinib
Subjects in population	429	425
N Mean SD Median Range	429 297.0 169.8 292.0 1 to 645	

† *Duration on Therapy is calculated as the days between first dose date and last dose date in each treatment arm.*

‡ *Only applicable to the combination arm, defined as from the first date when both drugs were taken until the date when one of the two drugs was first discontinued.*

§ *Only applicable to the combination arm, defined as from the first date when Pembrolizumab was taken until the date when Pembrolizumab was discontinued.*

" *Only applicable to the combination arm, defined as from the first date when Axitinib was taken until the date when Axitinib was discontinued.*

Duration on both drugs will be 0 day if a subject has the same start and end date for one drug prior to the start date of the other drug on the combo arm.

In the pembrolizumab + axitinib group, more participants had a duration of exposure of ≥6, ≥12, and ≥18 months compared with participants in the sunitinib group (Table 31)

Table 31: Exposure by Duration (ASaT Population)

	Pembrolizumab + Axitinib (N=429)		Sunitinib (N=425)	
	n	Person-time	n	Person-time
Duration of Exposure				
> 0 m	429	4,519.0	425	3,569.6
≥ 1 m	418	4,512.7	387	3,543.5
≥ 3 m	382	4,441.1	333	3,424.7
≥ 6 m	334	4,225.9	270	3,150.2
≥ 12 m	173	2,763.3	108	1,714.4
≥ 18 m	41	778.5	18	346.9

Each subject is counted once on each applicable duration category row.

Duration of exposure is the time from the first dose date to the last dose date.

Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).

Adverse events

The overall incidence of AEs was similar in the two groups. The incidence of SAEs, and drug-related SAEs was higher for pembrolizumab + axitinib compared with sunitinib; however, Grade 5 AEs and Grade 5 drug-related AEs were lower for pembrolizumab + axitinib. For AEs

leading to discontinuation, the primary comparison conducted was for both components (pembrolizumab + axitinib) versus sunitinib. In the pembrolizumab + axitinib group, 12.1% of participants discontinued both drugs due to AEs. In the sunitinib group, 13.4% of participants discontinued study treatment due to AEs (Table 32). The incidence of AEs leading to the simultaneous discontinuation of both pembrolizumab + axitinib was 7.7%; the incidence of AEs leading to discontinuation of sunitinib was 13.9% (Table 33).

Table 32: Disposition of Subjects (ITT Population)

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	432		429		861	
Status for Trial						
Discontinued	64	(14.8)	104	(24.2)	168	(19.5)
Death	59	(13.7)	95	(22.1)	154	(17.9)
Withdrawal By Subject	5	(1.2)	9	(2.1)	14	(1.6)
Trial Ongoing	368	(85.2)	325	(75.8)	693	(80.5)
Status for Study Medication in Trial						
Started	429	(100.0)	425	(100.0)	854	(100.0)
Discontinued	176	(41.0)	242	(56.9)	418	(48.9)
Adverse Event	52	(12.1)	57	(13.4)	109	(12.8)
Clinical Progression	12	(2.8)	16	(3.8)	28	(3.3)
Complete Response	3	(0.7)	0	(0.0)	3	(0.4)
Excluded Medication	1	(0.2)	0	(0.0)	1	(0.1)
Non-Compliance With Study Drug	0	(0.0)	1	(0.2)	1	(0.1)
Physician Decision	3	(0.7)	8	(1.9)	11	(1.3)
Progressive Disease	90	(21.0)	141	(33.2)	231	(27.0)
Withdrawal By Subject	15	(3.5)	19	(4.5)	34	(4.0)
Treatment Ongoing	253	(59.0)	183	(43.1)	436	(51.1)

Each subject is counted once for Trial Status based on the latest Survival Follow-up record.
Each subject is counted once for Study Medication Status based on the latest corresponding disposition record

Table 33: Adverse Event Summary (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	422	(98.4)	423	(99.5)
with no adverse event	7	(1.6)	2	(0.5)
with drug-related† adverse events	413	(96.3)	415	(97.6)
with toxicity grade 3-5 adverse events	325	(75.8)	300	(70.6)
with toxicity grade 3-5 drug-related adverse events	270	(62.9)	247	(58.1)
with serious adverse events	173	(40.3)	133	(31.3)

with serious drug-related adverse events	102	(23.8)	60	(14.1)
who died	11	(2.6)	15	(3.5)
who died due to a drug-related adverse event	4	(0.9)	7	(1.6)
discontinued any drug due to an adverse event	131	(30.5)	59	(13.9)
▪ discontinued Pembrolizumab	89	(20.7)	0	(0.0)
▪ discontinued Axitinib	88	(20.5)	0	(0.0)
▪ discontinued Both Pembrolizumab and Axitinib	33	(7.7)	0	(0.0)
discontinued any drug due to a drug-related adverse event	111	(25.9)	43	(10.1)
▪ discontinued Pembrolizumab	80	(18.6)	0	(0.0)
▪ discontinued Axitinib	66	(15.4)	0	(0.0)
▪ discontinued Both Pembrolizumab and Axitinib	27	(6.3)	0	(0.0)
discontinued any drug due to a serious adverse event	73	(17.0)	42	(9.9)
▪ discontinued Pembrolizumab	50	(11.7)	0	(0.0)
▪ discontinued Axitinib	50	(11.7)	0	(0.0)
▪ discontinued Both Pembrolizumab and Axitinib	25	(5.8)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	53	(12.4)	28	(6.6)
▪ discontinued Pembrolizumab	42	(9.8)	0	(0.0)
▪ discontinued Axitinib	31	(7.2)	0	(0.0)
▪ discontinued Both Pembrolizumab and Axitinib	19	(4.4)	0	(0.0)

† Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Table 34: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (ASaT Population)

	Event Count and Rate (Events/100 person-months)†			
	Pembrolizumab + Axitinib		Sunitinib	
Number of Subjects exposed	429		425	
Total exposure‡ in person-months	4766.94		3924.64	
Total events (rate)				
adverse events	7,017	(147.20)	7,052	(179.69)
drug-related§ adverse events	3,992	(83.74)	4,955	(126.25)
toxicity grade 3-5 adverse events	846	(17.75)	823	(20.97)
toxicity grade 3-5 drug-related adverse events	551	(11.56)	565	(14.40)
serious adverse events	284	(5.96)	201	(5.12)
serious drug-related adverse events	137	(2.87)	78	(1.99)
adverse events leading to death	11	(0.23)	16	(0.41)
drug-related adverse events leading to death	4	(0.08)	7	(0.18)
adverse events resulting in drug discontinuation	180	(3.78)	65	(1.66)
drug-related adverse events resulting in drug discontinuation	152	(3.19)	47	(1.20)

serious adverse events resulting in drug discontinuation	80	(1.68)	43	(1.10)
serious drug-related adverse events resulting in drug discontinuation	59	(1.24)	28	(0.71)

† *Event rate per 100 person-months of exposure = event count *100/person-months of exposure.*

‡ *Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cut-off date.*

§ *Determined by the investigator to be related to the drug. Grades are based on NCI CTCAE version 4.0.*

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Overall AEs

The overall incidence of AEs was similar in the pembrolizumab + axitinib (98.4%) and sunitinib (99.5%) (Table 35). The most frequently reported AEs (incidence ≥30%) in both treatment groups were:

• Pembrolizumab + axitinib: diarrhoea, hypertension, fatigue, and hypothyroidism

• Sunitinib: hypertension, diarrhoea, palmar-plantar erythrodysesthesia syndrome, fatigue, hypothyroidism, nausea, and dysgeusia

Table 35: Subjects With Adverse Events By Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) (ASaT Population)

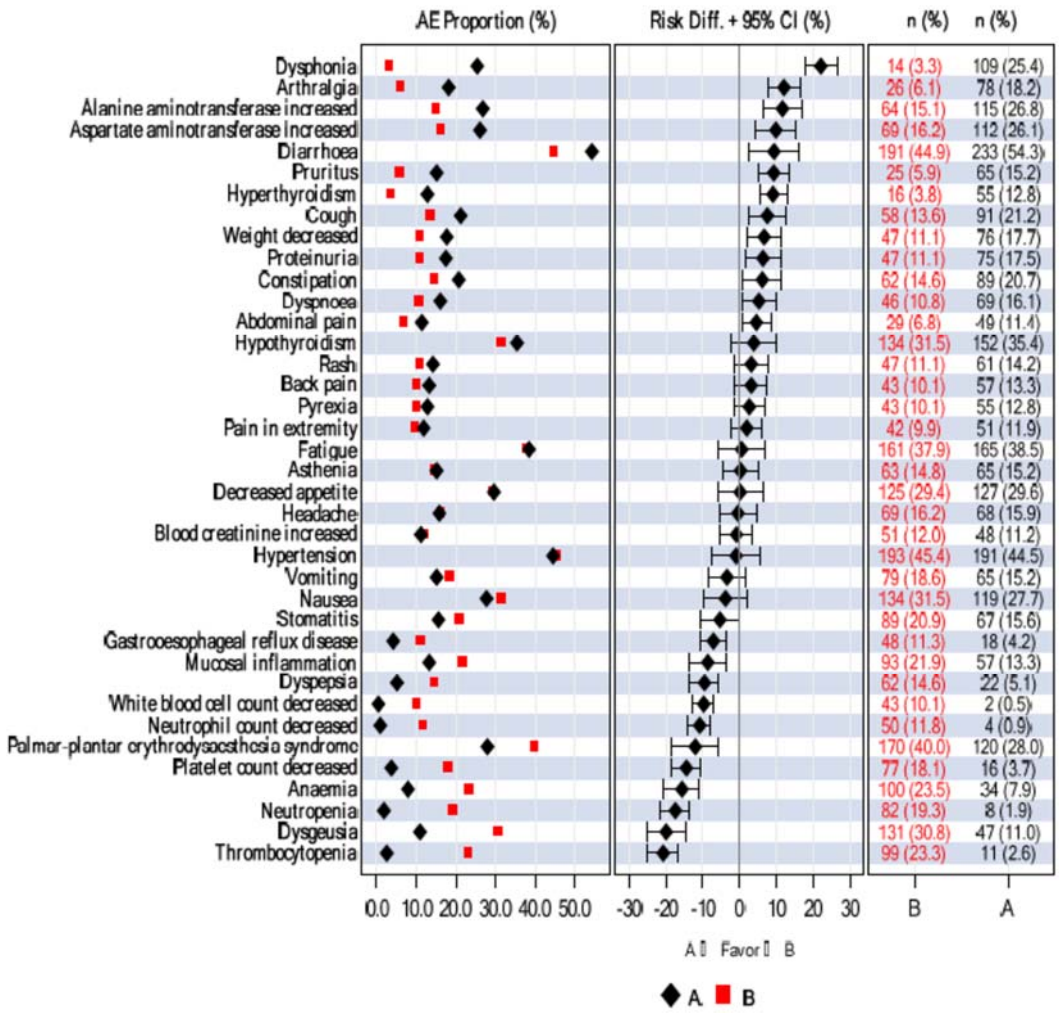
	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	422	(98.4)	423	(99.5)
with no adverse events	7	(1.6)	2	(0.5)
Diarrhoea	233	(54.3)	191	(44.9)
Hypertension	191	(44.5)	193	(45.4)
Fatigue	165	(38.5)	161	(37.9)
Hypothyroidism	152	(35.4)	134	(31.5)
Decreased appetite	127	(29.6)	125	(29.4)
Palmar-plantar erythrodysaesthesia syndrome	120	(28.0)	170	(40.0)
Nausea	119	(27.7)	134	(31.5)
Alanine aminotransferase increased	115	(26.8)	64	(15.1)
Aspartate aminotransferase increased	112	(26.1)	69	(16.2)
Dysphonia	109	(25.4)	14	(3.3)
Cough	91	(21.2)	58	(13.6)
Constipation	89	(20.7)	62	(14.6)

Arthralgia	78	(18.2)	26	(6.1)
Weight decreased	76	(17.7)	47	(11.1)
Proteinuria	75	(17.5)	47	(11.1)
Dyspnoea	69	(16.1)	46	(10.8)
Headache	68	(15.9)	69	(16.2)
Stomatitis	67	(15.6)	89	(20.9)
Asthenia	65	(15.2)	63	(14.8)
Pruritus	65	(15.2)	25	(5.9)
Vomiting	65	(15.2)	79	(18.6)
Rash	61	(14.2)	47	(11.1)
Back pain	57	(13.3)	43	(10.1)
Mucosal inflammation	57	(13.3)	93	(21.9)
Hyperthyroidism	55	(12.8)	16	(3.8)
Pyrexia	55	(12.8)	43	(10.1)
Pain in extremity	51	(11.9)	42	(9.9)
Abdominal pain	49	(11.4)	29	(6.8)
Blood creatinine increased	48	(11.2)	51	(12.0)
Dysgeusia	47	(11.0)	131	(30.8)
Anaemia	34	(7.9)	100	(23.5)
Dyspepsia	22	(5.1)	62	(14.6)
Gastroesophageal reflux disease	18	(4.2)	48	(11.3)
Platelet count decreased	16	(3.7)	77	(18.1)
Thrombocytopenia	11	(2.6)	99	(23.3)
Neutropenia	8	(1.9)	82	(19.3)
Neutrophil count decreased	4	(0.9)	50	(11.8)
White blood cell count decreased	2	(0.5)	43	(10.1)

Every subject is counted a single time for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. The adverse events are ordered decreasingly by the incidence in the first column.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

The risk differences of the most frequently reported AEs (incidence ≥10% in either treatment group) are shown in (Figure 15). AEs with greater risk for pembrolizumab + axitinib relative to sunitinib were dysphonia, arthralgia, ALT increased, AST increased, diarrhoea, pruritus, and hyperthyroidism. AEs with greater risk (≥10%) in sunitinib relative to pembrolizumab + axitinib were thrombocytopenia, dysgeusia, neutropenia, and anemia. Dysphonia is a known AE associated with axitinib; arthralgia, ALT increased, AST increased, diarrhoea, pruritus, and hyperthyroidism have been described for both pembrolizumab and axitinib.

Figure 15: Between-Treatment Comparisons in Adverse Events Selected Adverse Events (>= 10% Incidence) and Sorted by Risk Difference (ASaT Population) A (N=429) vs. B (N=425)



Note: A stands for pembrolizumab + axitinib and B for sunitinib

Overall, exposure-adjusted rates of AEs were generally lower for pembrolizumab + axitinib compared with sunitinib. Exposure-adjusted rates of AEs across the various system organ classes (SoCs) were either lower for pembrolizumab + axitinib or similar between the two groups. Notably, the exposure-adjusted incidence of diarrhoea was similar in the pembrolizumab + axitinib and the sunitinib (Table 36). The exposure-adjusted incidences of ALT increased, and AST increased by observation period, indicated a higher risk in the first six months of treatment with pembrolizumab + axitinib compared to sunitinib (Table 36). In both treatment groups, most AEs occurred in the first three months with the exposure-adjusted event rate decreasing at 3 to 6 months in most cases and continuing to decrease through >12 months.

The exposure-adjusted AE rate for pembrolizumab + axitinib was lower compared with sunitinib during the first 3 months, similar between 3 to 6 months, and higher after 6 months (Table 36).

Table 36: Exposure-Adjusted Adverse Events by Observation Period (Including Multiple Occurrences of Events) (Incidence ≥ 10% in One or More Treatment Groups) (ASaT Population)

	Event Count and Rate (Events/100 person-months) †							
	Pembrolizumab + Axitinib				Sunitinib			
Observation period of drug exposure	0-3 months	03-06 months	06-12 months	Beyond 12 months	0-3 months	03-06 months	06-12 months	Beyond 12 months
Number of subjects exposed‡	429	400	349	187	425	375	295	126
Total exposure§ in person-months	1261.3	1121.4	1624.1	760.1	1219.6	966.2	1237.1	501.8
Total events (rate)	3096 (245.5)	1561 (139.2)	1660 (102.2)	700 (92.1)	4148 (340.1)	1395 (144.4)	1102 (89.1)	407 (81.1)
Blood and lymphatic system disorders	**28(2.2)**	**23(2.1)**	**28(1.7)**	**12(1.6)**	**285(23.4)**	**137(14.2)**	**117(9.5)**	**38(7.6)**
Anaemia	11(0.9)	11(1.0)	9(0.6)	5(0.7)	71(5.8)	44(4.6)	26(2.1)	14(2.8)
Neutropenia	2(0.2)	3(0.3)	5(0.3)	1(0.1)	67(5.5)	31(3.2)	43(3.5)	11(2.2)
Thrombocytopenia	6(0.5)	2(0.2)	3(0.2)	2(0.3)	98(8.0)	45(4.7)	24(1.9)	1(0.2)
Cardiac disorders	**36(2.9)**	**8(0.7)**	**11(0.7)**	**9(1.2)**	**24(2.0)**	**11(1.1)**	**7(0.6)**	**3(0.6)**
Endocrine disorders	**140(11.1)**	**71(6.3)**	**43(2.6)**	**24(3.2)**	**97(8.0)**	**46(4.8)**	**37(3.0)**	**16(3.2)**
Hyperthyroidism	47(3.7)	3(0.3)	5(0.3)	5(0.7)	6(0.5)	4(0.4)	6(0.5)	2(0.4)
Hypothyroidism	77(6.1)	58(5.2)	27(1.7)	16(2.1)	89(7.3)	41(4.2)	30(2.4)	14(2.8)
Eye disorders	**25(2.0)**	**13(1.2)**	**19(1.2)**	**12(1.6)**	**54(4.4)**	**21(2.2)**	**7(0.6)**	**5(1.0)**
Gastrointestinal disorders	**516(40.9)**	**349(31.1)**	**378(23.3)**	**159(20.9)**	**847(69.4)**	**266(27.5)**	**223(18.0)**	**71(14.1)**
Abdominal pain	18(1.4)	13(1.2)	27(1.7)	8(1.1)	16(1.3)	5(0.5)	10(0.8)	2(0.4)
Constipation	52(4.1)	30(2.7)	20(1.2)	5(0.7)	49(4.0)	12(1.2)	7(0.6)	2(0.4)
Diarrhoea	144(11.4)	123(11.0)	158(9.7)	83(10.9)	188(15.4)	92(9.5)	80(6.5)	24(4.8)
Dyspepsia	13(1.0)	6(0.5)	5(0.3)	2(0.3)	54(4.4)	12(1.2)	6(0.5)	1(0.2)

Gastroesophageal reflux disease	6(0.5)	4(0.4)	4(0.2)	4(0.5)	35(2.9)	11(1.1)	10(0.8)	5(1.0)
Nausea	82(6.5)	44(3.9)	39(2.4)	11(1.4)	124(10.2)	41(4.2)	27(2.2)	13(2.6)
Stomatitis	49(3.9)	18(1.6)	12(0.7)	7(0.9)	89(7.3)	7(0.7)	12(1.0)	3(0.6)
Vomiting	31(2.5)	24(2.1)	33(2.0)	11(1.4)	69(5.7)	27(2.8)	25(2.0)	6(1.2)
General disorders and administration site conditions	**317(25.1)**	**120(10.7)**	**140(8.6)**	**45(5.9)**	**466(38.2)**	**114(11.8)**	**105(8.5)**	**26(5.2)**
Asthenia	43(3.4)	18(1.6)	22(1.4)	5(0.7)	57(4.7)	9(0.9)	11(0.9)	4(0.8)
Fatigue	122(9.7)	42(3.7)	32(2.0)	12(1.6)	147(12.1)	35(3.6)	25(2.0)	7(1.4)
Mucosal inflammation	47(3.7)	14(1.2)	14(0.9)	3(0.4)	101(8.3)	26(2.7)	16(1.3)	2(0.4)
Pyrexia	29(2.3)	14(1.2)	19(1.2)	6(0.8)	36(3.0)	0(0.0)	10(0.8)	1(0.2)
Hepatobiliary disorders	**34(2.7)**	**14(1.2)**	**9(0.6)**	**3(0.4)**	**38(3.1)**	**15(1.6)**	**7(0.6)**	**1(0.2)**
Infections and infestations	**111(8.8)**	**98(8.7)**	**109(6.7)**	**46(6.1)**	**137(11.2)**	**60(6.2)**	**54(4.4)**	**15(3.0)**
Injury, poisoning and procedural complications	**26(2.1)**	**11(1.0)**	**16(1.0)**	**8(1.1)**	**22(1.8)**	**15(1.6)**	**9(0.7)**	**3(0.6)**
Investigations	**337(26.7)**	**225(20.1)**	**208(12.8)**	**96(12.6)**	**522(42.8)**	**199(20.6)**	**141(11.4)**	**82(16.3)**
Alanine aminotransferase increased	66(5.2)	53(4.7)	33(2.0)	12(1.6)	54(4.4)	13(1.3)	11(0.9)	3(0.6)
Aspartate aminotransferase increased	66(5.2)	54(4.8)	35(2.2)	13(1.7)	56(4.6)	19(2.0)	14(1.1)	6(1.2)
Blood creatinine increased	21(1.7)	15(1.3)	23(1.4)	20(2.6)	35(2.9)	20(2.1)	8(0.6)	9(1.8)
Neutrophil count decreased	1(0.1)	1(0.1)	2(0.1)	2(0.3)	44(3.6)	29(3.0)	22(1.8)	14(2.8)
Platelet count decreased	6(0.5)	6(0.5)	7(0.4)	2(0.3)	90(7.4)	26(2.7)	25(2.0)	10(2.0)
Weight decreased	32(2.5)	23(2.1)	22(1.4)	9(1.2)	27(2.2)	20(2.1)	4(0.3)	3(0.6)
White blood cell count decreased	0(0.0)	2(0.2)	0(0.0)	0(0.0)	46(3.8)	22(2.3)	18(1.5)	11(2.2)
Metabolism and nutrition disorders	**193(15.3)**	**123(11.0)**	**144(8.9)**	**79(10.4)**	**247(20.3)**	**81(8.4)**	**78(6.3)**	**30(6.0)**
Decreased appetite	65(5.2)	43(3.8)	49(3.0)	17(2.2)	101(8.3)	34(3.5)	17(1.4)	4(0.8)
Musculoskeletal and connective tissue disorders	**210(16.6)**	**94(8.4)**	**107(6.6)**	**42(5.5)**	**159(13.0)**	**54(5.6)**	**51(4.1)**	**17(3.4)**
Arthralgia	49(3.9)	20(1.8)	15(0.9)	12(1.6)	19(1.6)	4(0.4)	8(0.6)	3(0.6)

Back pain	29(2.3)	15(1.3)	18(1.1)	4(0.5)	30(2.5)	7(0.7)	5(0.4)	4(0.8)
Pain in extremity	27(2.1)	14(1.2)	22(1.4)	6(0.8)	22(1.8)	15(1.6)	8(0.6)	3(0.6)
Nervous system disorders	**154(12.2)**	**72(6.4)**	**64(3.9)**	**32(4.2)**	**277(22.7)**	**77(8.0)**	**47(3.8)**	**18(3.6)**
Dysgeusia	26(2.1)	14(1.2)	10(0.6)	2(0.3)	136(11.2)	27(2.8)	15(1.2)	7(1.4)
Headache	56(4.4)	21(1.9)	11(0.7)	7(0.9)	60(4.9)	16(1.7)	9(0.7)	3(0.6)
Psychiatric disorders	**52(4.1)**	**23(2.1)**	**26(1.6)**	**9(1.2)**	**51(4.2)**	**18(1.9)**	**9(0.7)**	**7(1.4)**
Renal and urinary disorders	**103(8.2)**	**43(3.8)**	**49(3.0)**	**20(2.6)**	**95(7.8)**	**29(3.0)**	**16(1.3)**	**16(3.2)**
Proteinuria	55(4.4)	16(1.4)	23(1.4)	11(1.4)	44(3.6)	15(1.6)	7(0.6)	11(2.2)
Respiratory, thoracic and mediastinal disorders	**274(21.7)**	**89(7.9)**	**86(5.3)**	**51(6.7)**	**188(15.4)**	**61(6.3)**	**41(3.3)**	**25(5.0)**
Cough	55(4.4)	22(2.0)	22(1.4)	9(1.2)	39(3.2)	15(1.6)	9(0.7)	3(0.6)
Dysphonia	95(7.5)	18(1.6)	9(0.6)	4(0.5)	12(1.0)	2(0.2)	4(0.3)	0(0.0)
Dyspnoea	39(3.1)	13(1.2)	17(1.0)	14(1.8)	30(2.5)	9(0.9)	8(0.6)	4(0.8)
Skin and subcutaneous tissue disorders	**273(21.6)**	**110(9.8)**	**131(8.1)**	**41(5.4)**	**378(31.0)**	**143(14.8)**	**88(7.1)**	**29(5.8)**
Palmar-plantar erythrodysaesthesia syndrome	84(6.7)	26(2.3)	24(1.5)	8(1.1)	127(10.4)	65(6.7)	34(2.7)	10(2.0)
Pruritus	40(3.2)	16(1.4)	18(1.1)	4(0.5)	23(1.9)	5(0.5)	4(0.3)	1(0.2)
Rash	36(2.9)	19(1.7)	21(1.3)	8(1.1)	41(3.4)	9(0.9)	8(0.6)	2(0.4)
Vascular disorders	**229(18.2)**	**58(5.2)**	**69(4.2)**	**10(1.3)**	**227(18.6)**	**38(3.9)**	**47(3.8)**	**5(1.0)**
Hypertension	211(16.7)	47(4.2)	56(3.4)	5(0.7)	204(16.7)	31(3.2)	42(3.4)	3(0.6)

*† Event rate per 100 person-months of exposure = event count *100/person-months of exposure.*
‡ Number of subjects exposed to drug at the start of indicated time interval.
§ Drug exposure is defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cut-off date.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded. Including adverse events that occurred in ≥ 10% of subjects in ASaT population in one or more treatment groups.

Grade 3-5 AEs – IA1 (August 2018 data)

The overall incidence of Grade 3 to 5 AEs was similar for pembrolizumab + axitinib (75.8%) compared with sunitinib (70.6%). The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) were:

- Pembrolizumab + axitinib: hypertension, ALT increased, diarrhoea, AST increased, and palmar-plantar erythrodysesthesia syndrome.
- Sunitinib: hypertension, platelet count decreased, neutrophil count decreased, fatigue, neutropenia, and thrombocytopenia

When adjusted for exposure, the overall event rate of Grade 3 to 5 AEs was similar in the pembrolizumab + axitinib (17.75 events/100 person-months) compared with sunitinib (20.97 events/100 person-months).

The risk differences of the most frequently reported Grade 3 to 5 AEs (incidence ≥5% in either treatment group) are shown in **Error! Reference source not found.**. The Grade 3 to 5 AEs with greater risk difference for pembrolizumab + axitinib were ALT increased, AST increased, and diarrhoea; these are all known AEs associated with both pembrolizumab and axitinib. The Grade 3 to 5 AEs (Table 37) with greater risk difference for sunitinib were platelet count decreased, neutrophil count decreased, neutropenia, thrombocytopenia, and fatigue.

Table 37.Subjects with Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	325	(75.8)	300	(70.6)
with no adverse events	104	(24.2)	125	(29.4)
Hypertension	95	(22.1)	82	(19.3)
Alanine aminotransferase increased	57	(13.3)	13	(3.1)
Diarrhoea	39	(9.1)	20	(4.7)
Aspartate aminotransferase increased	30	(7.0)	10	(2.4)
Palmar-plantar erythrodysaesthesia syndrome	22	(5.1)	16	(3.8)
Fatigue	12	(2.8)	28	(6.6)
Neutropenia	1	(0.2)	28	(6.6)
Neutrophil count decreased	1	(0.2)	29	(6.8)
Platelet count decreased	1	(0.2)	31	(7.3)
Thrombocytopenia	0	(0.0)	25	(5.9)

Every subject is counted a single time for each applicable row and column. A SOC or specific AE appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. The adverse events are ordered decreasingly by the incidence in the first column.

Drug-related Grade 3-5 AEs

The overall incidence of drug-related Grade 3 to 5 AEs was similar between pembrolizumab +axitinib (related to at least one drug or both) (62.9%) and sunitinib (58.1%) (Table 38). The most frequently reported drug-related Grade 3 to 5 AEs (incidence ≥5%) in both treatment groups were:

• Pembrolizumab + axitinib: hypertension, ALT increased, diarrhoea, AST increased, and palmar-plantar erythrodysesthesia syndrome.
• Sunitinib: hypertension, platelet count decreased, neutrophil count decreased, neutropenia, and thrombocytopenia.

When adjusted for exposure, the overall event rates of drug-related Grade 3 to 5 AEs were similar for pembrolizumab + axitinib (11.56 events/100 person-months) compared with sunitinib (14.40 events/100 person-months) (Table 34).
The incidence of drug-related Grade 3 to 5 ALT increased, and AST increased was higher for pembrolizumab + axitinib compared with sunitinib (>5% difference) (Table 38). ALT increased, and AST increased are known AEs associated with both pembrolizumab and axitinib.

Table 38: Subjects With Drug-Related Grade 3-5 Adverse Events By Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	270	(62.9)	247	(58.1)
with no adverse events	159	(37.1)	178	(41.9)
Hypertension	91	(21.2)	78	(18.4)
Alanine aminotransferase increased	52	(12.1)	11	(2.6)
Diarrhoea	31	(7.2)	19	(4.5)
Aspartate aminotransferase increased	29	(6.8)	7	(1.6)
Palmar-plantar erythrodysaesthesia syndrome	22	(5.1)	15	(3.5)
Neutropenia	1	(0.2)	28	(6.6)
Neutrophil count decreased	1	(0.2)	29	(6.8)
Platelet count decreased	1	(0.2)	31	(7.3)
Thrombocytopenia	0	(0.0)	22	(5.2)

Every subject is counted a single time for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

The adverse events are ordered decreasingly by the incidence in the first column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Drug-related Serious AEs

The overall incidence of drug-related SAEs was higher for pembrolizumab + axitinib (23.8%) compared with sunitinib (14.1%). The most frequently reported drug-related SAEs (incidence >1%) for pembrolizumab + axitinib were diarrhoea, ALT increased, AST increased, and pneumonitis. Pneumonitis is a known AEs associated with pembrolizumab; diarrhoea, ALT increased, and AST increased have been described for both pembrolizumab and axitinib. There were no drug-related SAEs in more than 4 participants (0.9%) for sunitinib.

When adjusted for exposure, the overall event rate of drug-related SAEs was similar for pembrolizumab + axitinib (2.9 events/100 person-months) compared with sunitinib (2.0 events/100 person-months).

B.2.11 Ongoing studies

The KEYNOTE-426 [16] [17] study is ongoing, with an estimated study completion date of January 2020 [29].

B.2.12 Innovation

Prior to 2005, patients with advanced RCC were treated with immunotherapies such as IFNα and IL-2, which had overall limited clinical activity. High-dose IL-2, however, had demonstrated durable responses in a small number of highly selected patients in Phase 2 nonrandomised studies [17]. Since then, novel anticancer agents have demonstrated significant improvement in clinical efficacy (largely in terms of PFS and response rates) and acceptable safety profiles in patients with advanced RCC in large randomised Phase 3 studies [17]. Despite these newer treatment options, most patients will progress within 2 years after receiving standard 1L treatment, indicating an unmet medical need for these patients [17]. Therefore, further development of novel agents with durable clinical benefit and potential curative effects is still highly needed for the treatment of patients with advanced RCC.

Axitinib, a potent VEGFR TKI, has established single agent clinical efficacy in advanced RCC. Although the phase III randomised study of axitinib versus sorafenib in the first-line setting did not demonstrate statistically significant improvement in the primary endpoint of PFS for axitinib compared to sorafenib, the efficacy results of axitinib (PFS of 10.1 months and ORR of 32%) were comparable to that of other standard-of-care first-line agents [30, 31]. On the basis of

these results, axitinib is listed as a choice of treatment by NCCN for treatment-naïve advanced RCC patients [8]. In the UK, axitinib is already an approved agent for advanced RCC patients who have failed a prior therapy [32].

RCC has long been considered an immune-reactive tumour based on anecdotal reports of spontaneous remissions in patients with advanced RCC with evidence of antigen-specific lymphocyte infiltration of tumour tissues [33] and the fact that high dose IL-2 could produce a durable long-term response in a small subset of patients with advanced RCC patients. Immune check-point inhibitors such as pembrolizumab, restore T-cell function improving the anti-tumoural response and therefore the anti-tumoural effect. This mechanism of action also provides a longer anti-tumoural response due to the facilitation in producing new growing memory T-cells. The evidence supports targeting RCC with an immunotherapeutic approach. Preliminary results in 52 patients from KEYNOTE-035 (A4061079) [34], a Phase 1b study evaluating the safety, PK, and pharmacodynamics of pembrolizumab + axitinib in treatment-naïve patients with advanced RCC, showed promising efficacy results (ORR of 67.3% [CR = 3.8%, PR = 63.5%]) and an acceptable safety profile. Based on the scientific rationale of targeting angiogenesis and immune-check point pathways, as well as the promising data from study KEYNOTE-035 [34], further evaluation of the pembrolizumab + axitinib regimen was warranted. To that end, KEYNOTE-426 [16] [17] was initiated to evaluate the efficacy and safety of pembrolizumab + axitinib versus sunitinib as 1L treatment for participants with advanced RCC.

Based on the scientific rationale of targeting angiogenesis and immune-check point pathways, the innovative combination regimen of pembrolizumab plus axitinib represents a step-change in the management of RCC and demonstrates additional clinical benefit in advanced RCC compared to the current standard of care in the first-line setting. The significant OS advantage demonstrated by pembrolizumab in combination with axitinib in KEYNOTE-426 [16] [17], is particularly noteworthy given this has not been previously achieved in first-line treatment of RCC with the use of anti–VEGF-based therapy administered either as monotherapy or in combination [16] [31, 35-39].

The innovative nature of pembrolizumab was first recognised by the US Food and Drug Administration (FDA) in January 2013 by granting it Breakthrough Therapy Designation (BTD) for advanced melanoma [40] .The FDA's BTD is intended to expedite the development and review of a drug that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically

significant endpoint [41]. Since 2013, the FDA has granted BTD for a range of pembrolizumab indications, including ttreatment of patients with advanced (metastatic) NSCLC whose disease has progressed after other treatments; treatment of patients with metastatic NSCLC whose tumours express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy; first-line treatment of patients with advanced non–small cell lung cancer whose tumours express PD-L1; second-line treatment of patients with locally advanced or metastatic urothelial cancer with disease progression on or after platinum-containing chemotherapy; treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma; treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy; treatment of adult and pediatric patients with: unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; treatment of patients with hematological malignancies: Hodgkin Lymphoma.

In the UK, in March 2015 pembrolizumab became the first medicine to be granted positive scientific opinion under the MHRA's Early Access to Medicines Scheme (EAMS) for the treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care [42]. Pembrolizumab received Promising Innovative Medicines (PIM) designation (EAMS Step 1) in November 2015, and in March 2016 a positive Scientific Opinion was granted (MHRA EAMS number 00025/0001) for "*the treatment as monotherapy of adults with metastatic NSCLC whose tumours express PD-L1 as determined by a validated test and who have not received prior systemic therapy and are negative for EGFR sensitising mutation and ALK translocation or whose disease has progressed on or after platinum-containing chemotherapy. Patients who have an EGFR sensitising mutation or an ALK translocation should also have had disease progression on approved therapies for these aberrations prior to receiving pembrolizumab* " [42]. EAMS aims to give earlier access to promising new unlicensed or 'off label' medicines to UK patients that have a high unmet clinical need. This validates MSD's position that pembrolizumab should be considered innovative in its potential to make a significant and substantial impact on health-related benefits in an area of high unmet need.

B.2.13 Interpretation of clinical effectiveness and safety evidence

At IA1, KEYNOTE-426 [16] [17] met the predefined criteria for statistical significance for both of its primary endpoints of OS and PFS, as well as its key secondary endpoint of ORR. The results from KEYNOTE-426 [16] [17] IA1 provide unequivocal evidence that treatment with pembrolizumab + axitinib is superior to sunitinib for the 1L treatment of participants with advanced RCC and provides a clinically meaningful improvement in OS, PFS and ORR. Results for OS, PFS, and ORR showed consistent benefit of pembrolizumab + axitinib across all subgroups analysed.

KEYNOTE-426 [16] [17] is the first study evaluating a combination therapy that demonstrated positive results for both primary endpoints of OS and PFS in the 1L treatment of advanced RCC in an ITT population, regardless of IMDC risk category. The combination reduced the risk of death by 47% compared with sunitinib. At 18 months, 82% in the pembrolizumab + axitinib group were still alive, compared with 72% in the sunitinib group. The OS benefit with pembrolizumab + axitinib was apparent even though 34% of participants in the sunitinib group received subsequent systemic anti-cancer therapy, including 21.2% receiving subsequent treatment with a PD-1 or PD-L1 checkpoint inhibitor.

The results for pembrolizumab + axitinib in this study compare favourably with the results of studies that have evaluated either pembrolizumab or axitinib monotherapy. In KEYNOTE-426 [16] [17], the median PFS in the pembrolizumab + axitinib group is substantially longer (15.1 months) than that observed with either pembrolizumab (6.9 months) or axitinib (10.1 months) monotherapy in participants with advanced RCC [43] [31]. Similarly, the confirmed ORR for pembrolizumab + axitinib (59.3%) in KEYNOTE-426 [16] [17] is substantially higher than the confirmed ORR for either pembrolizumab (33.6%) or axitinib (32%) monotherapy in the 1L treatment of participants in advanced RCC [44] . These findings demonstrate the clear contribution of each component of the combination regimen. Importantly, results for the comparator sunitinib were generally consistent with those in other Phase 3 studies [20] [25].

Safety data from KEYNOTE-426 [16] [17] demonstrated that the safety profile of pembrolizumab + axitinib was generally comparable with the safety profile of sunitinib, with the exception of a higher incidence of Grade 3 to 4 ALT and AST elevations. When adjusted for exposure, the difference between treatment groups for Grade 3 to 4 elevations of ALT and AST was smaller. In both groups, the most common reason for study treatment discontinuation was PD, and the proportion of participants who discontinued study treatment due to AEs was similar between the two groups.

The overall incidence of AEOSI in each AE category was higher for pembrolizumab + axitinib compared with sunitinib. The incidence of AEOSI in the pembrolizumab + axitinib group was also higher than would be expected for pembrolizumab monotherapy. The higher incidence of AEOSI was primarily driven by thyroid-related events: hypothyroidism, hyperthyroidism, and thyroiditis. Hypothyroidism is a known AEOSI for pembrolizumab and is a known AE for axitinib and the incidence in the pembrolizumab + axitinib group was similar to that seen in the sunitinib group. Hyperthyroidism is a known AEOSI for pembrolizumab. Most of the events of hypothyroidism and hyperthyroidism were of Grade 1 or 2 and, therefore, of limited clinical significance.

ALT and AST elevations were generally manageable with interruption or discontinuation of pembrolizumab and axitinib, with or without concomitant steroid therapy. Most participants had recovered at the time of data cut-off and were re-challenged with pembrolizumab + axitinib, pembrolizumab alone, or axitinib alone. Importantly, there were no fatal hepatic events. There were no meaningful differences between the demographic characteristics of participants with hepatic AEs compared with the overall participant population. Overall, these findings may be a result of the hepatic toxicities associated with both pembrolizumab monotherapy and axitinib monotherapy. Prompt dose interruption or discontinuation upon AE onset, adequate evaluation of other contributing/confounding factors, and adequate monitoring of liver function are key for the management of treatment-emergent hepatic events. The key efficacy and safety findings from the KEYNOTE-426 [16] [17] study are summarised below:

Pembrolizumab + axitinib demonstrates a significant overall survival benefit and progression-free survival benefit versus sunitinib

At the IA1 of KEYNOTE-426 [16] [17] (median duration of follow-up of 13.2 months in the pembrolizumab + axitinib group and 12.1 months in the sunitinib group), treatment with pembrolizumab + axitinib demonstrated a statistically significant and clinically meaningful improvement in OS and PFS (per RECIST 1.1 by BICR) compared with sunitinib, in patients with untreated advanced RCC. The OS HR of 0.53 (95% CI: 0.38, 0.74; p=0.00005) represents a 47% reduction in the risk of death for participants in the pembrolizumab + axitinib group compared with the sunitinib group. The PFS HR of 0.69 (95% confidence interval [CI]: 0.57, 0.84; p=0.00014) represents a 31% reduction in the risk of progression or death for participants in the pembrolizumab + axitinib group compared with the sunitinib group.

Pembrolizumab + axitinib demonstrated a statistically significant and clinically meaningful improvement in ORR compared with sunitinib. The confirmed ORR (per RECIST 1.1 by BICR) was 59.3% for the pembrolizumab + axitinib group compared with 35.7% for the sunitinib group, with a significant difference of 23.6% (95% CI: 17.2, 29.9; p<0.0001). The responses in the pembrolizumab + axitinib group were durable compared with those in the sunitinib group. The treatment benefit in OS, PFS, and ORR for pembrolizumab + axitinib compared with sunitinib was consistent across all subgroups analysed, including by PD-L1 status, IMDC risk category, and geographic region.
Pembrolizumab + axitinib did not result in meaningful changes in the EQ-5D VAS quality of life scale compared with sunitinib.

The efficacy results observed in the sunitinib group were consistent with the results reported in other Phase 3 studies for the 1L treatment of advanced RCC. Data from KEYNOTE-426 [16] [17] demonstrate pembrolizumab + axitinib provides clinically meaningful benefit in the 1L setting.

Pembrolizumab + axitinib is generally tolerable and has a safety profile that is largely consistent with the combined safety profile of pembrolizumab monotherapy and axitinib monotherapy

At IA1 for KEYNOTE-426 [16] [17], the overall incidence of AEs, Grade 3 to 5 AEs, and Grade 3 to 5 drug-related AEs was similar in the 2 treatment arms of the study. The incidence of SAEs and drug-related SAEs was higher for pembrolizumab + axitinib compared with sunitinib. When adjusted for exposure, there were no clinically meaningful differences in overall event rates between the 2 groups for SAEs, and drug-related SAEs. A similar percentage of participants in the 2 groups discontinued study treatment due to an AE.

In the pembrolizumab + axitinib group, the most commonly reported AEs of greater than 30% were diarrhoea, hypertension, fatigue, and hypothyroidism; the most commonly reported Grade 3 to 5 AEs of greater than 5% included hypertension, ALT increased, diarrhoea, AST increased and palmar-plantar erythrodysesthesia syndrome. Four of the 11 deaths due to AEs (myocarditis, necrotizing fasciitis, myasthenia gravis, and pneumonitis) were considered by the investigator to be related to treatment.

The overall safety profile of sunitinib observed in this trial is consistent with the reported sunitinib safety profile in 1L advanced RCC [45] [46]. The safety profile of pembrolizumab + axitinib observed in this study is generally consistent with the established safety profile of

pembrolizumab monotherapy in solid tumours and the observed safety profile for axitinib monotherapy in first line advanced RCC [31] [47], except for a higher than expected incidence of Grade 3 to 4 hepatic AEs and a higher incidence of all hyperthyroidism grades. Grade 3 to 4 ALT and AST elevations were generally managed with interruption or discontinuation of the 2 agents, with or without concomitant steroid therapy. Most participants with treatment-emergent ALT ≥3 × ULN recovered and were re-challenged with one or both study treatments. Among those who were re-challenged, more than half had no recurrence of ALT ≥3 x ULN; the remaining participants who had recurrence all recovered. There were no fatal hepatic events in the pembrolizumab + axitinib group.

Except for hypothyroidism, the incidence of AEOSIs in each AE category, as expected, was higher for pembrolizumab + axitinib compared with sunitinib. Hypothyroidism is a known AEOSI for pembrolizumab and a known AE for axitinib. The incidence of hypothyroidism was similar in the pembrolizumab + axitinib group and in the sunitinib group

Internal validity

KEYNOTE-426 [16] [17] is a robust, multi-centre, randomised, active controlled phase III trial of pembrolizumab + axitinib versus sunitinib in patients with advanced RCC who have not received prior therapy. Prior to randomisation, eligible subjects were first stratified by IMDC risk categories (favourable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of world”).

The co-primary endpoints were to compare OS and PFS (per RECIST 1.1 as assessed by BICR) in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy. OS is a clinically relevant endpoint, that was directly referenced in the final scope for this appraisal and the decision problem. This endpoint selected is consistent with that used in studies of other therapeutic agents in the population of advanced RCC. The definition of progression when evaluating PFS in KEYNOTE-426 [16] [17] followed an established response evaluation criteria (RECIST 1.1), in line with European Guidance [48].

HRQoL was explored under both secondary and exploratory endpoints in the KEYNOTE-426 [16] [17] study, with changes from baseline in patients treated with pembrolizumab + axitinib compared to sunitinib recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC QLQ-C30

KEYNOTE-426 [16] [17] was an open-label study, with study sponsor, investigator and participant aware of the treatment administered. However, analyses or summaries generated by randomised treatment assignment and/or actual treatment received were limited and

documented. In addition, there was an element of blinding in this study as independent central imaging review was performed without knowledge of the treatment group assignments of the participants.

External validity

KEYNOTE-426 [16] [17] is a global study conducted in 142 centres in 16 countries, including 64 sites in Europe. Of the patients participating in the study, 475 were enrolled at sites in Europe, including 48 from the UK.

Baseline characteristics of patients enrolled in KEYNOTE-426 [16] [17] were as expected for patients with advanced RCC. Most patients were male, white, and had undergone prior nephrectomy (Table 7). Subgroup analyses confirm the benefit of pembrolizumab + axitinib versus sunitinib in patients of all histologies and regardless of PD-L1 biomarker status (Appendix E).

With regards to risk factors, most subjects in both arms were of the 'intermediate/poor' IMDC risk category and had recurrent disease status at baseline. The treatment arms were generally well balanced by all baseline characteristics.

The observed safety profile of pembrolizumab + axitinib in KEYNOTE-426 [16] [17] was generally consistent with the established safety profile of pembrolizumab monotherapy in solid tumours and the observed safety profile for axitinib monotherapy in first line advanced RCC [31, 46, 47] , except for a higher than expected incidence of Grade 3 to 4 hepatic AEs and a higher incidence of all hyperthyroidism grades [17].

End-of-life criteria

MSD does not consider pembrolizumab in combination with axitinib to meet the end of life criteria in the all-comer patient population. However, MSD considers that patients in the poor risk sub-group (as defined by the IMDC criterion) would meet end of life criteria with a life expectancy of less than 24 months, and an expected increase in life expectancy of greater than 3 months as described in Table 39.

Table 39. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	A randomised, phase III trial of sunitinib compared with interferon alfa as first line treatment for metastatic RCC reported median OS of 26.4 months in the sunitinib arm [36].	Appendix D

	A randomised, open label phase II trial comparing cabozantinib with standard-of-care sunitinib in IMDC intermediate and poor risk patients with advanced RCC in the first line setting reported median OS of 21.8 months with sunitinib and 30.3 months with cabozantinib [24]. This patient population has inferior clinical outcomes compared to an all comer population.	Appendix D
	A randomised, open-label, phase III trial of pazopanib versus sunitinib reported median OS as 29.3 months in the sunitinib group and 28.4 months in the pazopanib group [25].	Appendix D
	Final results from an extended follow-up of a global, expanded-access trial that, prior to regulatory approval, provided sunitinib to metastatic renal cell carcinoma (mRCC) patients, ineligible for registration-directed trials [49]. Median OS was reported for the all comer population of 18.7 months. The sub-populations stratified by risk group of favourable, intermediate and poor reported median OS of 56.5 months, 20.0 months and 9.1 months, respectively. The patient population included within this study had a proportion of patients that had received prior systemic therapy.	Section B.3.3
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS does not accurately capture the OS benefit in patients treated with pembrolizumab in combination with axitinib; instead, the mean provides a more reliable statistical measure for estimated OS in patients treated with pembrolizumab in combination with axitinib, due to the longevity of the benefit observed in some patients. Median OS was not reached in KEYNOTE426 [16] [17]; however at IA1 (August 2018) there was an improvement in 12 months OS rate with pembrolizumab + axitinib versus sunitinib of 11.6% (89.9% vs 78.3%) [16]. Based on economic modelling there is an estimated improvement in 2 years OS rate of 14.1% (78.0% vs 63.9%) and 3 years OS rate of 17.7% (68.8% vs 51.1%).	Section B.3.3 Appendix J

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted in two phases; an original search and a subsequent update, to identify relevant cost-effectiveness studies from the published literature. The search was conducted on the 14 March 2018, except for searches of MEDLINE and EconLit databases, which were conducted on the 7 April 2018. An updated search of all the previously searched bibliographic databases and grey literature was conducted on 20 February 2019.

No cost-effectiveness studies evaluating pembrolizumab in combination with axitinib in the specified population were identified. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

B.3.2 Economic analysis

There was no cost-effectiveness study found that met the relevant inclusion criteria for this submission, indicating that a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab in combination with axitinib compared with the relevant comparators.

Patient population

The patient population included in the economic evaluation consisted of patients with untreated advanced RCC. This is in line with the anticipated licence and with the NICE final scope [50]. The patient characteristics were based on KEYNOTE-426 [16] [17] trial and are presented in Table 40, below.

Table 40. Baseline characteristics of patients included in the model

Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age*	61.5	-	KEYNOTE-426 [16] [17]
Proportion male*	71.3	-	
Average patient weight (kg) *	81.5	SD = 19.7	

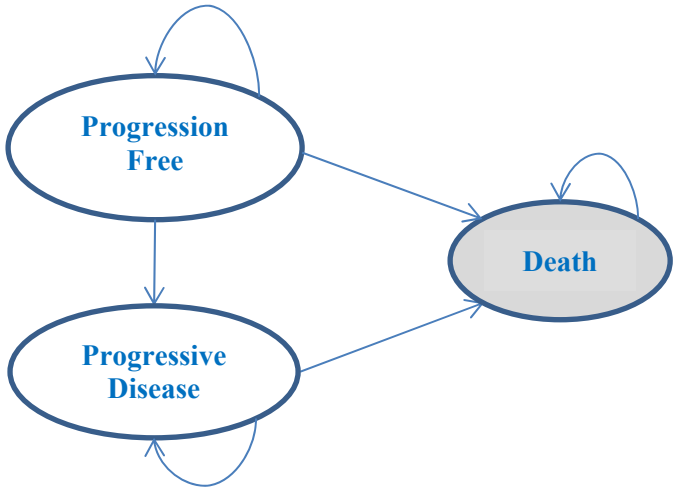
**These values refer to patients recruited from European sites participating in KEYNOTE-426*

Model structure

Consistent with economic models developed for recent NICE oncology submissions in RCC [11, 12, 51, 52]. A partitioned survival cohort simulation model was developed to estimate health outcomes and costs for pembrolizumab in combination with axitinib and comparator

regimens in the target patient population. The transition diagram of the cohort simulation model is presented in Figure 16, below.

Figure 16. Model structure

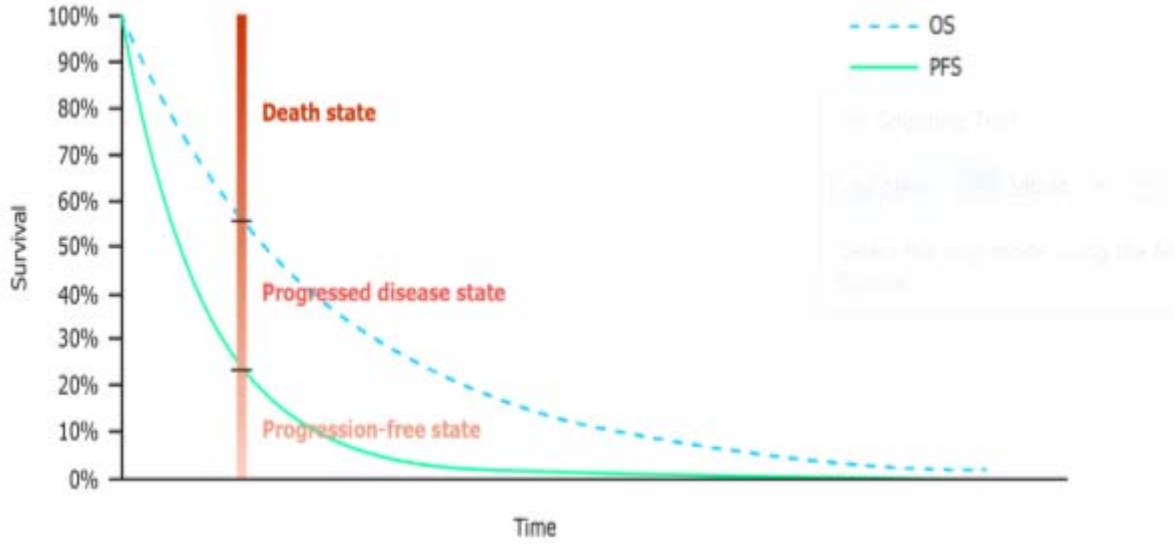


There are three mutually exclusive health states in the model:

- Pre-progression, which is the starting health state, with patients staying in this state until disease progression or death
- Post-progression, which encompasses patients alive after progression and before death
- Death, which is an absorbing health state

Partitioned survival modelling uses an overall survival curve to estimate the proportion of people alive over time- either from a parametric distribution or directly from KM trial data [53]. OS may be further partitioned into different health states to allow these health states to have different HRQoL and cost implications [53]. The model used requires two survival curves to estimate state membership for the model [53]; the area underneath the OS curve represents the proportion of patients that were still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state were identified by the patients located underneath the PFS curve; where progression is defined by the primary censoring rule in KEYNOTE-426 trial [16] [17], i.e. assessment by BICR per RECIST 1.1 [30]. Hence, the area between the PFS and the OS represents the proportion of post-progression patients, i.e. those who were in the 'post-progression' health state. Please see Figure 17 below.

Figure 17. Partitioned survival model structure



Patients enter the model in the pre-progression health state. At the end of each weekly cycle, patients may remain in the state, transition to the post-progression health state or to death; patients who are in the post-progression state may remain in that state or die at the end of each cycle. Patients cannot transition to an improved health state (i.e. from post-progression to pre-progression). The partitioned survival model is unlike a Markov model, in which transition probabilities between health states are needed, as the proportions of patients in each health state at each time point is directly estimated.

For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period for calculating the cumulative costs and cumulative QALYs over the modelled time horizon. Costs and QALYs are discounted with an annual rate of 3.5% in line with NICE reference case [54].

Table 41. Features of the economic analysis

	Previous appraisals				Current appraisal		
Factor	**TA169 [14]**	**TA215 [13]**	**TA512 [12]**	**TA542 [11]**	**TA581 [52]**	**Chosen values**	**Justification**
Appraisal	Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma	Pazopanib for the first-line treatment of advanced renal cell carcinoma	Tivozanib for treating advanced renal cell carcinoma	Cabozantinib for untreated advanced renal cell carcinoma	Nivolumab with ipilimumab for untreated advanced renal cell carcinoma	Pembrolizumab in combination with axitinib for untreated metastatic renal cell carcinoma (RCC)	
Time horizon	10 years	10 years	10 years	20 years	40 years	40 years	Lifetime horizon for the defined population (NICE reference case)
Immunotherapeutic effect	No	No	No	No	Yes- 50 % of patients who are durable responders are expected to receive a curative effect as a result of immune checkpoint inhibitor therapy.	Not explicitly modelled	Consistent with previous NICE TA's for immune checkpoint inhibitors.
Treatment waning effect?	No	No	No	No	Yes- only for patients who are not cured	Explored within scenario analyses	Patients remain on treatment with axitinib after stopping pembrolizumab treatment at 2 years,

							hence maintaining a treatment effect.
Source of utilities	Derived from trial data- 1st line Motzer et al 2007 [28] and 2nd line Motzer et al 2006 [55]; and UK EQ-5D tariffs.	Pre-progression values were based on the mean EQ-5D utility value from patients without AEs in the VEG105192 [56]. In the post-progression state a decrement in utility of 15% was assumed.	Utility values derived from EQ-5D-3L questionnaires from the TIVO-1 study [26] were used for pre and post progression.	The CABOSUN trial [24] did not collect EQ-5D. Hence the utility values derived from the TIVO-1 study as reported in TA512 were used.	A regression model from Checkmate 214 [57] EQ-5D utilities were used.	Utility values collected in KEYNOTE-426 trial [16] [17]	Consistent with NICE reference case
Source of costs	British National Formulary, NHS reference costs, Unit Costs of Health and Social Care 2007 [58]	NHS reference costs, Colosia 2008, British National Formulary, PSSRU	NHS reference costs, PSSRU, British National Formulary, TA169, TA215	British National Formulary, TA215 [13], TA512 [12], NHS reference costs, PSSRU and published literature	TA417 [51], Monthly Index of Medical Specialities, TA215 [13], TA169 [14], NHS reference costs, PSSRU, TA333 [59], ID1029 and published literature	NICE [ID1182], TA169 [14], TA215 [13], TA512 [12], NICE TA542 [11], NHS reference costs, PSSRU, and published literature	Resource use was based on previous NICE TAs in metastatic RCC (TA169 [14], TA215 [13], TA512 [12], TA542 [11] and ID1182) and published literature. Unit costs were taken from recognised databases as per the NICE reference case.

Intervention technology and comparators

The intervention (pembrolizumab in combination with axitinib) was included in the model as per the proposed licensed dosing regimen (i.e. pembrolizumab administered intravenously at a fixed dose of 200 mg over 30 minutes Q3W combined with axitinib 5 mg BID taken orally).
The proposed licence states that pembrolizumab has to be administered until PD or unacceptable toxicities or for a maximum of 35 doses (2 years). If the patient remains progression free after 35 doses of pembrolizumab, treatment with axitinib will be continued as monotherapy until PD or unacceptable toxicity.
In line with the comparator assessed in KEYNOTE-426 [16] [17], sunitinib (based on the trial control arm) was considered as the comparator of relevance in the cost-effectiveness model.

The following comparators were also assessed as per the NICE final scope [50]:

- Tivozanib (TA512) [12]
- Pazopanib (TA215) [13]
- Cabozantinib (TA542) [11] (in the poor/intermediate risk group)

In TA215 [13], TA512 [12], TA542 [11] and TA581 [52] for pazopanib, tivozanib, cabozantinib and nivolumab respectively, each committee noted that pazopanib could be considered clinically equivalent to sunitinib, and in TA512 [12] the committee noted tivozanib could be considered (at best) clinically equivalent to sunitinib and pazopanib. Furthermore, in TA542 [11], the committee preferred the assumption of equal clinical efficacy of pazopanib to sunitinib in their decision making. Hence in the base case analysis of pembrolizumab in combination with axitinib vs tivozanib/pazopanib, the efficacy of tivozanib and pazopanib has been assumed to be equal to that of sunitinib, as seen in the KEYNOTE-426 study [16] [17], for OS, PFS, time on treatment (ToT) and safety profile.

Table 42. Intervention and comparators according to the different types of analyses assessed in de novo cost-effectiveness model

Population	Intervention and comparators Pembrolizumab + axitinib vs.	Clinical evidence derived from:
Base Case		
ITT population	▪ Sunitinib ▪ Pazopanib ▪ Tivozanib	KEYNOTE-426 [16] [17] (assume equal efficacy to Sunitinib)
Subgroups		
Intermediate/poor risk group	▪ Cabozantinib	NMA
	▪ Sunitinib ▪ Pazopanib ▪ Tivozanib	KEYNOTE-426 [16] [17] (assume equal efficacy to Sunitinib)

Please note that nivolumab in combination with ipilimumab is not a comparator of interest within this appraisal following a statement made in January 2019 by NICE [60] whereby products recommended for use in the Cancer Drugs Fund (CDF) after 1 April 2016 should not be considered as comparators in subsequent relevant appraisals.

B.3.3 Clinical parameters and variables

Overall Method of Modelling Effectiveness

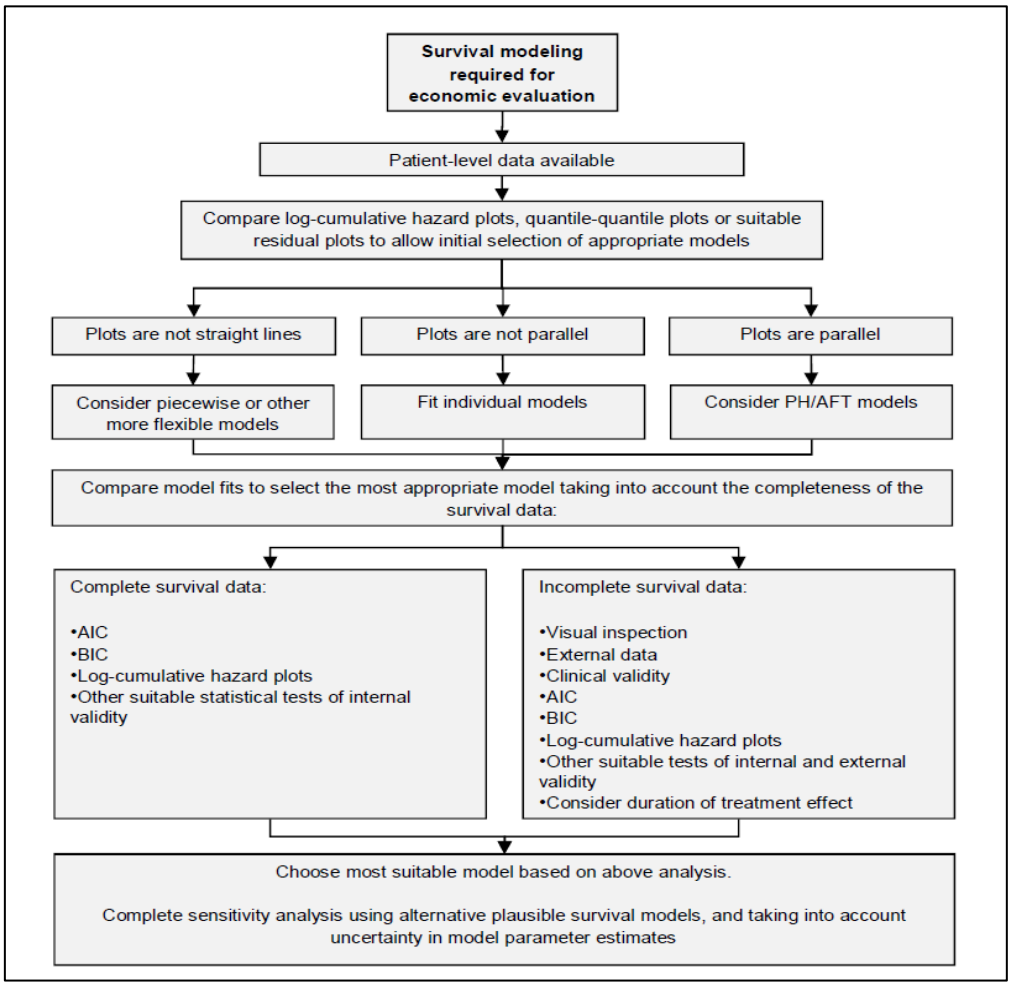
The clinical effectiveness parameters for pembrolizumab in combination with axitinib and sunitinib in the cost-effectiveness model were estimated from the KEYNOTE-426 [16] [17] patient-level data on OS, PFS, ToT and safety profile; with pazopanib and tivozanib [11-13] assumed to be clinically equivalent to sunitinib. This was the primary data source for the economic model, however clinical effectiveness estimates of cabozantinib (in the intermediate/poor risk group) were applied by using constant HRs from the NMA (please see section B.2.9). This was also carried out for scenario analyses of comparison with pazopanib and tivozanib.

The follow-up period in KEYNOTE-426 [16] [17] was much shorter than the time horizon of the economic model. Therefore, extrapolation of OS, PFS and ToT was required for the area-under-the-curve (AUC) partitioned survival approach.
Parametric models were fitted to the KEYNOTE-426 [16] [17] KM data. The survival curve fitting was carried out in line with the NICE DSU guidelines [53]. In summary, the steps that were followed are presented in Figure 18 below.

Consistent with recommendations in the NICE DSU technical support document 14 [61], the selection of base case parametric functions for PFS and OS were informed by:

- Goodness-of-fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and visual inspection to assess the concordance between predicted and observed PFS and OS curves within the trial period; and
- Clinical plausibility of long-term extrapolations beyond the trial period, which was evaluated based on published external sources, clinical expert opinion, and biological plausibility.

Figure 18. Survival Model Selection Process Algorithm [53]



AFT: Accelerated failure time; AIC: Akaike information criterion; BIC: Bayesian information criterion; PH: Proportional hazards Source.

Modelling OS

As KEYNOTE-426 [16] [17] is a comparative phase III trial, patient level data is available for both arms of the study. The cumulative and log cumulative hazard plots can be found in Figure 19 and Figure 20, respectively.

The log-cumulative hazard plots allow an assessment of whether the proportional hazards assumption is reasonable [53]. As seen in Figure 20, the plots of the two arms are not parallel, as the plots cross, suggesting the proportional hazard assumption does not hold; hence a pooled parametric curve was deemed inappropriate.

The log-cumulative hazard plot also shows there were no abrupt changes observed in the hazards of death in either treatment arm based on visual assessment, suggesting the use of fully parametric modelling as most appropriate for extrapolation. This is further supported by the lack of follow-up data from the KEYNOTE-426 trial [16] [17]. Because of this, fitting fully

parametric curves to the limited data is most appropriate in order to use all of the KM data to inform the extrapolated part of the curve.

Figure 19. Cumulative hazard plot of OS for pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 [16] [17]

Figure 20. Log-cumulative hazard plot of OS for pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 [16] [17]

A comprehensive range of individual and piecewise parametric models were fitted to each treatment arm shown in Figure 21 and Figure 22, below.

Figure 21. OS KM curve vs fitted one-piece model for pembrolizumab + axitinib based on KEYNOTE-426 [16] [17]

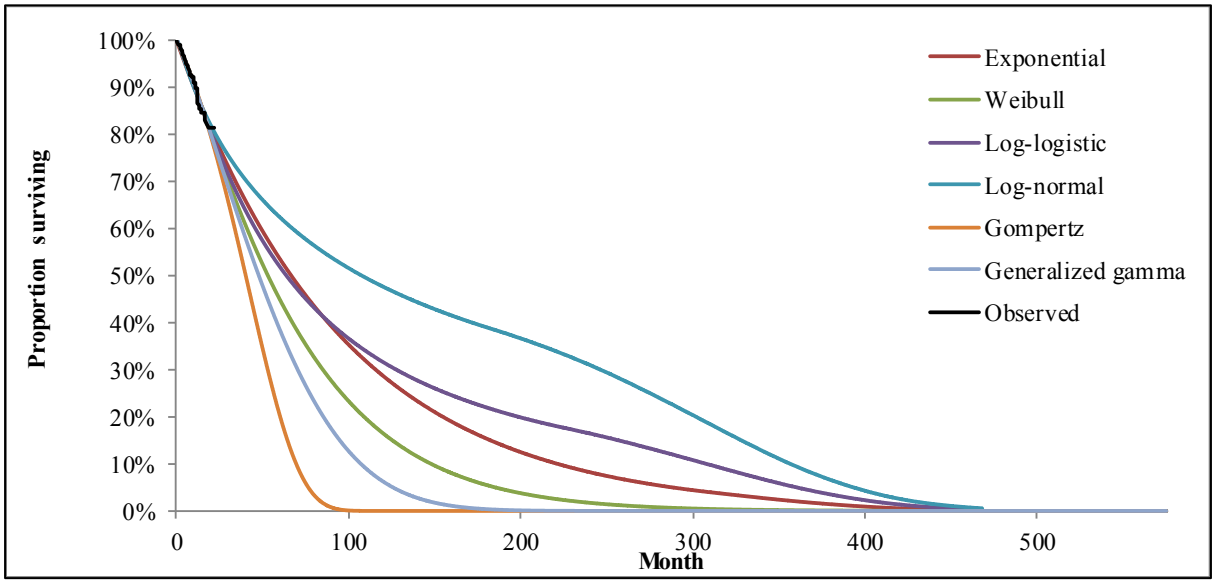
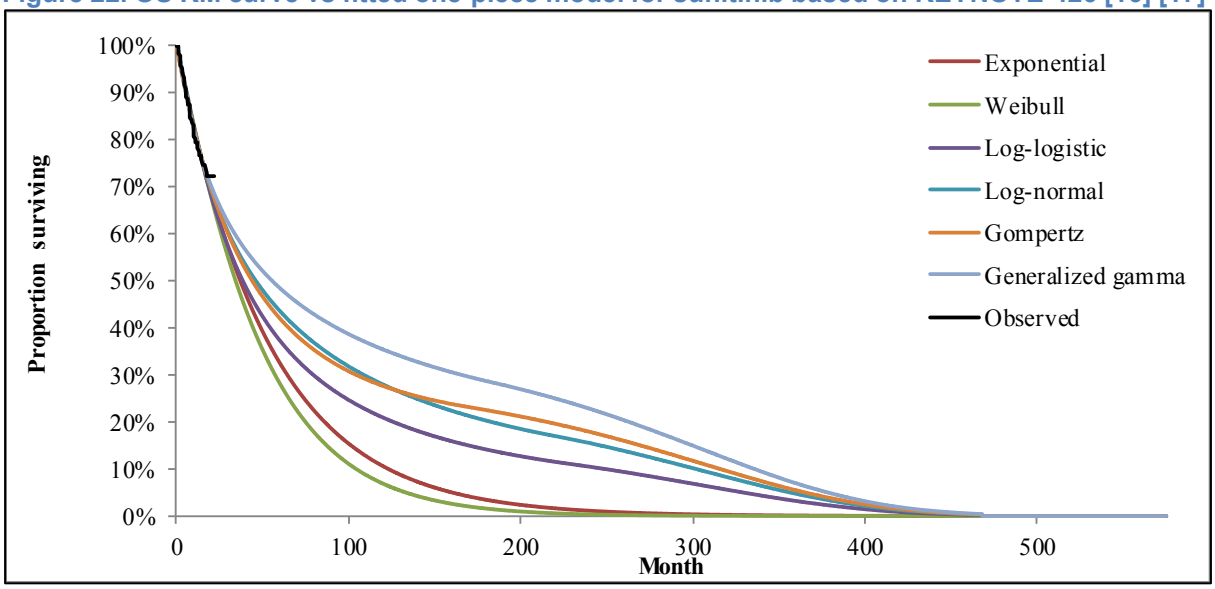


Figure 22. OS KM curve vs fitted one-piece model for sunitinib based on KEYNOTE-426 [16] [17]



Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. However, as the modelled period is much longer than the length of KM data, the external validity was considered most important for parametric curve selection. Furthermore, all six parametric functions achieved a close visual fit to the observed data, within the trial timeframe, and diverged beyond the trial period to yield substantially different long-term extrapolations as depicted in Figure 22. Hence the base-case curve selection for OS was based primarily on the clinical plausibility of long-term survival predictions.

Specifically, the following steps were performed to identify the most plausible base-case distribution of OS in each treatment arm:

1. The set of potentially plausible OS distributions was first refined on the basis of 5-year OS estimates, which were compared with external literature evidence and evaluated through consultations with clinical experts.
2. Of the remaining distributions in each treatment arm, the parametric function demonstrating the most biologically plausible extrapolations over the lifetime horizon was selected for the base-case analysis. Biological plausibility was assessed based on mode of action and clinical expert opinion.

A number of external sources were used to validate the choice of OS curve according to estimated long-term overall survival observed in clinical practice. Input from clinical experts suggested that first-line treatment of sunitinib is associated with 5- and 10-year survival between 20-25% and 10-15%, respectively, and median OS is expected to be 2.5 years or 30

months. Clinical experts suggested that these estimations were in line with longer term follow-up data from CheckMate-025. Previous clinical trials investigating sunitinib report median OS ranging from 29.3 to 37.9 months in the ITT population [25, 57].

Gore et al- a global, expanded-access trial of sunitinib in patients with mRCC- reported median OS in the all comer population as 18.7 months; however, this study included a significant proportion of patients who had received prior systemic treatment and hence underestimates expected survival in untreated advanced RCC patients [49]. Digitised KM data from Gore et al provide approximate 1-, 2- and 5-year OS estimates and are reported in Table 45. Three clinical trials were pooled to validate OS, including: CheckMate 214 [57], Comparz [25] and Javelin Renal 101 [62] and are summarised in Table 44.

Table 43. Summary of goodness-of fit qualities of OS models for pembrolizumab in combination with axitinib and sunitinib

Fitted Function	Pembrolizumab in combination with Axitinib		Sunitinib	
	AIC	BIC	AIC	BIC
Exponential	832.100	836.200	1,253.000	1,257.000
Weibull	832.600	840.700	1,254.300	1,262.400
Llogistic	832.800	840.900	1,252.200	1,260.300
Lnormal	837.200	845.400	1,248.300	1,256.400
Gompertz	832.400	840.600	1,254.600	1,262.800
GenGamma	834.400	846.700	1,249.700	1,261.900
Best fitting	Exponential	Exponential	Lnormal	Lnormal

The AIC/BIC statistics suggested that for pembrolizumab in combination with axitinib the best fitting curve was the exponential curve, followed by the gompertz curve. For the sunitinib arm the best fitting curve was the log-normal curve, followed by the exponential. Notably, the gompertz and generalized gamma distributions leads to clinically implausible outcomes, see Appendix P for more information.

Table 44. Observed and modelled OS estimates for sunitinib at different time points

Time points	Sunitinib				
	Gore et al	Pooled studies [57] [25] [62]	Modelled estimates with Exponential	Modelled estimates with Log-Logistic	KEYNOTE-426 [16] [17]
1 year	~62.5%	76.8%	79.9%	79.7%	78.3%
2 years	~41.3%	60.0%	63.9%	63.6%	-
5 years	~25.9%	~26.73%	32.7%	37.3%	-
10 years	-	-	10.7%	20.9%	-

20 years	-	-	1.1%	10.5%	-
Median OS (months)	18.7	33.5	36.7	38.1	NR

Sunitinib

The exponential distribution was chosen as the most appropriate distribution to extrapolate OS for the sunitinib arm, in terms of internal and external validity:

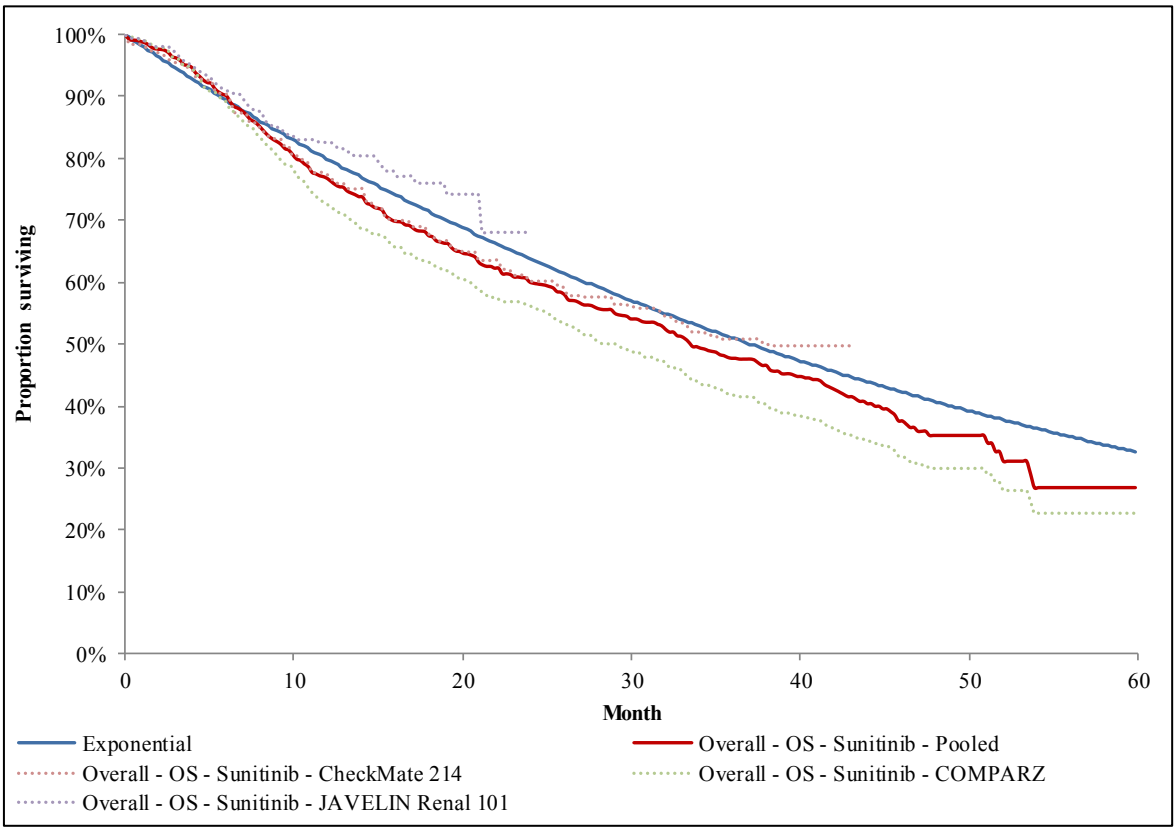
a) Internal validity:

- The log-cumulative hazard plots show a constant hazard over time suggesting the exponential as appropriate.
- The AIC/BIC statistic showing the closest statistical fit for the sunitinib arm is the log-normal distribution, however this estimates implausibly high long-term survival. The second best-fitting distribution according to the AIC/BIC criterion was the generalized gamma and exponential distributions, respectively. As previously noted the generalized gamma distribution provides clinically implausible outcomes.

b) External validity:

- The exponential distribution provides long term OS estimates expected to be seen with first line treatment of sunitinib as per external OS validation, as shown in Table 44 and Figure 23 below. The exponential and weibull curves both predict long term OS closest to seen from external sources, however the exponential curve was selected over the weibull to account for the expanded subsequent treatment landscape.
- As previously mentioned, input from clinical experts suggested 5- and 10-year survival between 20-25% and 10-15%, respectively, suggesting the use of the exponential curve as most appropriate.

Figure 23. Sunitinib OS fully fitted exponential curve vs OS external validation source



Pembrolizumab in combination with axitinib:

The log-logistic distribution was chosen as the most appropriate distribution to extrapolate OS for the pembrolizumab in combination with axitinib arm, in terms of internal and external validity:

a) Internal validity:

- The AIC/BIC statistic showing the closest statistical fit for the pembrolizumab in combination with axitinib arm is the exponential distribution, however this curve does not represent the expected change in hazard rate over time. There is an insignificant increase between AIC/BIC criterion from the best-fitting exponential to the log-logistic, with the log-logistic providing a good visual fit to the KM data.
- Scenario analyses 1 and 2 exploring the use of landmark analysis (see Appendix P) and using a time-constant hazard ratio derived from the NMA for sunitinib, respectively, provide internal validation of the suitability of the base case approach; obtaining similar results for long term survival.

b) External validity:

- Input from clinical experts suggested 5-year OS of approximately 50% when treated with pembrolizumab in combination with axitinib as well as seeing a percentage of patients reaching durable response, existing beyond discontinuation of treatment. While both the log-logistic and exponential OS curves were potentially plausible based on 5-year OS, the tail of the log-logistic curve was considered by clinical experts to be more credible based on the expectation that a percentage of patients would derive a long-term survival benefit from the combination of an immunotherapy with a tyrosine kinase inhibitor. This immunotherapeutic effect would imply a declining rather than constant hazard rate of death over the long term. The log-logistic curve was therefore selected as the base-case model of OS in the pembrolizumab/axitinib arm.

Technical Support Document 14 states that "While fitting separate parametric models to individual treatment arms may be justified, it is important to note that fitting different types of parametric model… to different treatment arms would require substantial justification" [61]. The mode of action of a combination of immunotherapy with a tyrosine kinase inhibitor is not comparable to monotherapy tyrosine kinase inhibitor, and hence the underlying hazard assumption for the choice of parametric curve does not need to be the same. It was also considered that none of the parametric distributions gave clinically plausible long-term OS estimates for both arms simultaneously. Hence the log-logistic distribution was chosen to extrapolate OS for pembrolizumab in combination with axitinib, and the exponential distribution was chosen as the most appropriate distribution to extrapolate OS for the sunitinib arm.

Figure 24 and Figure 25 below show the extrapolated OS over a 5-year period and a lifetime horizon of 40 years.

Figure 24. OS KM curves vs fully fitted parametric distributions for the OS of pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 over a 5-year period

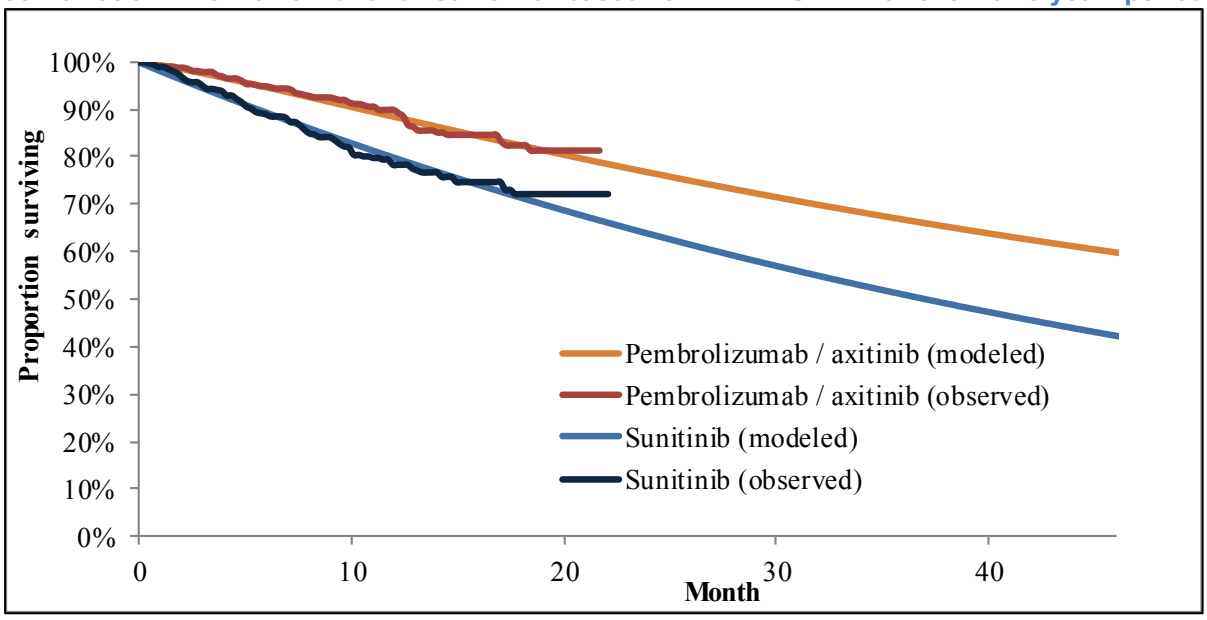
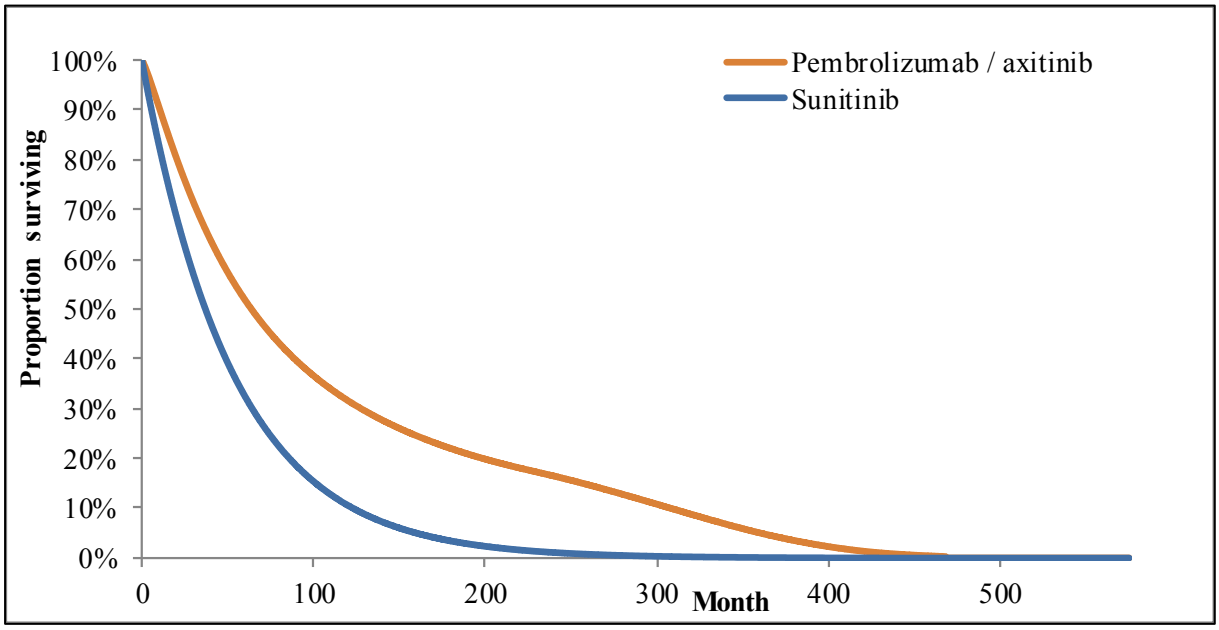


Figure 25. OS KM curves vs fully fitted parametric distributions for the OS of pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 over a lifetime horizon



Modelling PFS

Based on the trial protocol of KEYNOTE-426 [16, 17], the first post-randomisation imaging assessment was performed at week 12, with subsequent imaging being performed every 6 weeks through to week 54 and every 12 weeks thereafter up until progressive disease. Visual inspection of the KM PFS curves revealed a steep drop around week 13 in both arms of KEYNOTE-426 [16, 17], likely reflecting the first protocol-scheduled tumour imaging assessment at 12 weeks (± 1 week) from randomisation; Chow tests and log-cumulative hazard plots similarly suggested a break point in the PFS curves at week 13 (see Appendix P, Figure 26 and Figure 27). Parametric models of PFS were therefore derived using a piecewise approach, in which hazard rates of PFS failure were based on the observed Kaplan-Meier curve up to week 13, followed by parametric models fitted to the post-week 13 data. To identify the most plausible PFS curves among the standard parametric curves, the guidance from the NICE DSU [61] was followed.

Figure 26. Cumulative hazard plot of PFS for pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 [16, 17]

Figure 27. Log-cumulative hazard plot of PFS for pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 [16, 17]

A comprehensive range of individual and piecewise parametric models were fitted to each treatment arm.

Figure 28. PFS KM curve vs. fitted 2-phase piecewise models according to the PFS defined per RECIST v1.1 as assessed by BICR, with cut-off at 13 weeks, for pembrolizumab in combination with axitinib based on KEYNOTE-426 [16, 17]

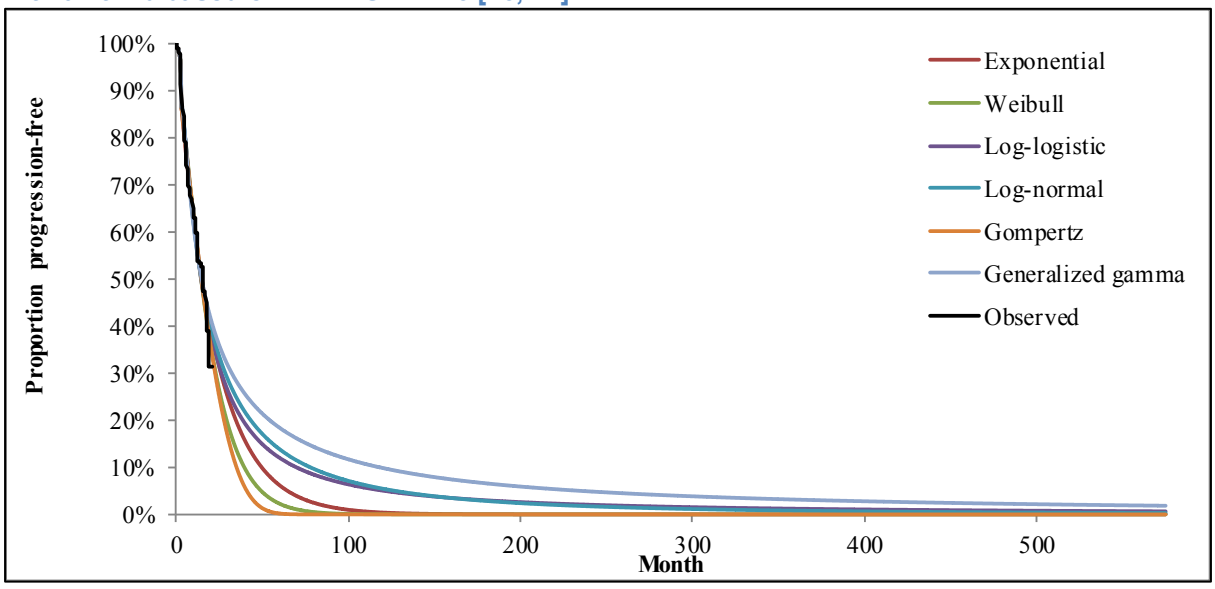
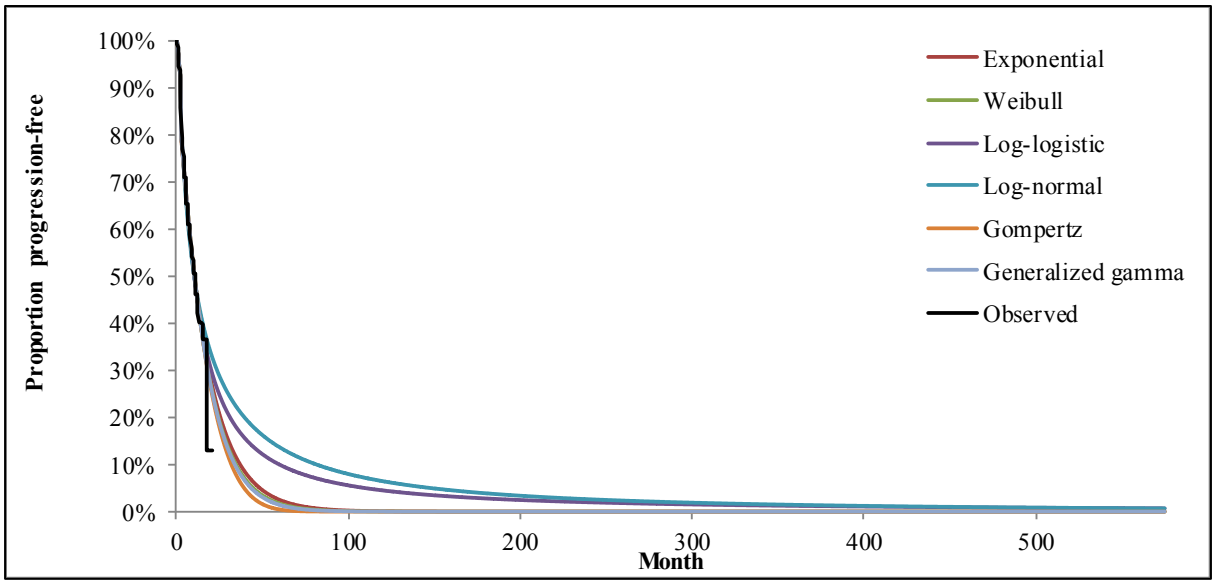


Figure 29. PFS KM curve vs. fitted 2-phase piecewise models according to the PFS defined per RECIST v1.1 as assessed by BICR, with cut-off at 13 weeks, for sunitinib based on KEYNOTE-426 [16, 17]



Statistical tests based on the AIC and the BIC, combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. Table 45 reports the AIC/BIC statistics for the second part of the PFS two-piece fit for pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 [16, 17] PFS data from a 13-week cut-off point.

Table 45. Summary of goodness-of fit qualities of PFS survival models at 13-week cut-off point for pembrolizumab in combination with axitinib and sunitinib

Fitted Function	Pembrolizumab in combination with Axitinib		Sunitinib	
	AIC	BIC	AIC	BIC
Exponential	1,398.800	1,402.700	1,352.000	1,355.800
Weibull	1,396.700	1,404.500	1,353.600	1,361.100
Llogistic	1,395.800	1,403.600	1,355.300	1,362.800
Lnormal	1,390.500	1,398.300	1,366.400	1,373.900
Gompertz	1,399.100	1,406.800	1,353.600	1,361.100
GenGamma	1,391.900	1,403.600	1,355.500	1,366.800
Best fitting	Lnormal	Lnormal	Exponential	Exponential

The best statistical fit according to AIC/BIC criterion for the pembrolizumab in combination with axitinib arm is the log-normal distribution (see Table 45), the second-best fitting model being the generalized gamma distribution. The best statistical fit according to AIC/BIC criterion for the sunitinib arm is the exponential distribution, the second-best fitting model being the Weibull distribution.

The base case for modelling PFS was a piecewise modelling approach; using KM data up to a cut-off of 13 weeks, followed by the exponential distribution. The 13-week cut-off point was determined following review of the log-cumulative hazard plots which showed a significant change in hazard after 12 weeks. In the base case, the piecewise exponential distribution was used to model PFS in both the pembrolizumab/axitinib and sunitinib arms. Piecewise parametric extrapolation generally provided a closer visual fit than one-piece parametric extrapolation due to the observed drop at week 13 in the Kaplan-Meier PFS curves of both treatment arms. Among the six different piecewise parametric functions fitted for PFS, the exponential function was ranked first in the sunitinib arm and second in the pembrolizumab/axitinib arm in terms of BIC. Visual assessment also supported the choice of piecewise exponential as the base-case parametric distribution for PFS.

The modelled PFS curves used in the base case analysis described above are presented in Figure 30 and Figure 31 below.

Figure 30. PFS KM curves vs fitted 2-phase piecewise model, with cut-off at 13 weeks and exponential distribution after, for the PFS of pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 over a 5-year horizon

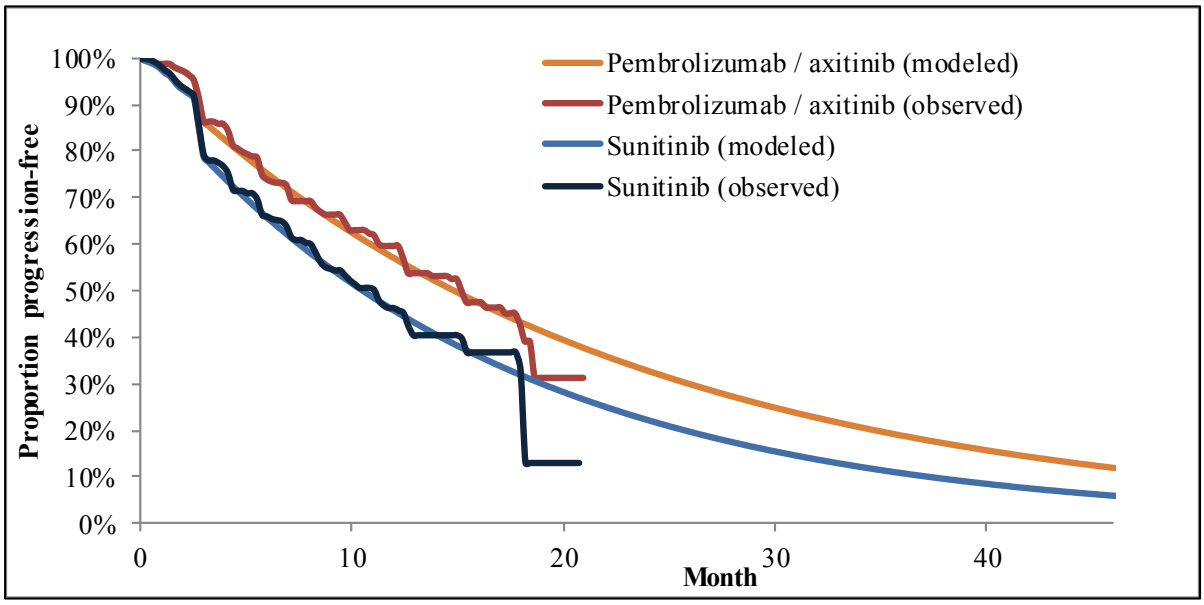
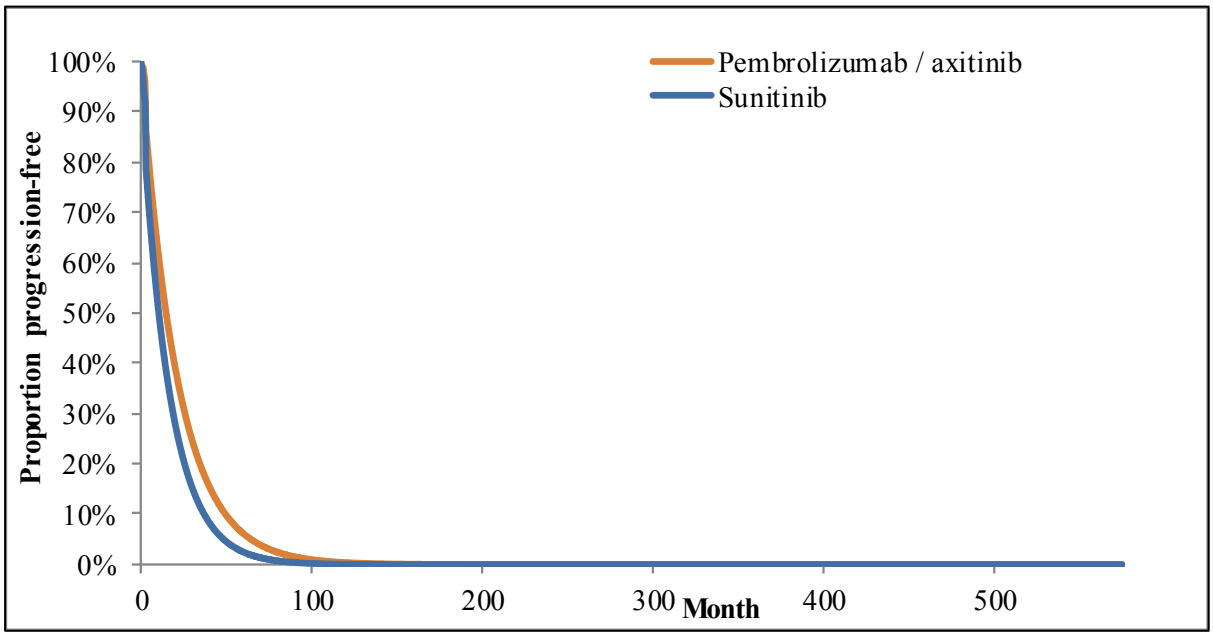


Figure 31. PFS KM curves vs fitted 2-phase piecewise model, with cut-off at 13 weeks and exponential distribution after, for the PFS of pembrolizumab in combination with axitinib and sunitinib based on KEYNOTE-426 over a lifetime horizon



Adverse events

The AEs considered in the economic model include Grade 3+ All-cause Adverse Events, which occurred in at least 5% of patients. The approach to identify the relevant AEs to be included in the economic model has been previously validated by clinical experts.

The incidence of AEs was taken from the KEYNOTE-426 trial [16, 17] (see Table 46). It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since the 5% cut-off is based on AEs of any grade. AE data for the NMA comparator Cabozantinib was obtained from the published literature taken from the respective TAs [11, 13]. In the base case analysis, the safety profile of pazopanib and tivozanib was assumed to be equal to the safety profile of sunitinib (as seen in KEYNOTE-426 [16, 17]). The unit cost and the disutility associated with each individual AEs were assumed to be the same for all treatment arms; therefore, the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 46. This was consistent with the methods used in previous oncology submissions [63] [14] and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm.

Table 46. Grade 3+ AE rates for AEs included in the economic model

Adverse Event	Pembrolizumab + axitnib (% of patients) [16]	Sunitinib, Tivozanib, Pazopanib (% of patients) [16]	Cabozantinib (% of patients in intermediate/poor subgroup) [11]
Alanine aminotransferase increased	13.3%	3.1%	5.1%
Aspartate aminotransferase increased	7.0%	2.4%	2.6%
Decreased appetite	2.8%	0.7%	5.1%
Diarrhea	9.1%	4.7%	10.3%
Fatigue	2.8%	6.6%	6.4%
Hyperglycaemia	2.3%	0.5%	0.0%
Hypertension	22.1%	19.3%	28.2%
Hyponatremia	2.3%	2.6%	0.0%
Lipase level increased	0.5%	0.5%	0.0%
Lymphocytopenia	0.2%	0.5%	0.0%
Neutropenia	0.2%	6.6%	0.0%
Neutrophil count decreased	0.2%	6.8%	0.0%
Palmar-plantar erythrodysaesthesia syndrome	5.1%	3.8%	7.7%
Platelet count decreased	0.2%	7.3%	1.3%

Adverse Event	Pembrolizumab + axitnib (% of patients) [16]	Sunitinib, Tivozanib, Pazopanib (% of patients) [16]	Cabozantinib (% of patients in intermediate/poor subgroup) [11]
Stomatitis	0.0%	5.9%	5.1%
Thrombocytopenia	13.3%	3.1%	0.0%

Inputs from clinical experts

Individual meetings were arranged with clinical oncologists who specialise in RCC to discuss key issues relating to economic modelling. The plausibility of the approach to modelling OS taken in this submission was validated by asking clinicians to estimate 5-year survival percentages for sunitinib. The suggestions were that each extrapolation of sunitinib exaggerated long term-survival, with expected 5-year OS being ~20-25%, hence our modelling approach produces estimates of sunitinib long term OS greater than seen in clinical practice.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

HRQoL was evaluated in the KEYNOTE-426 trial [16, 17] using the EuroQoL EQ-5D-3L. The estimated utilities were used in the cost-effectiveness model as evaluation of HRQoL using EQ-5D directly from patients which is consistent with the NICE reference case [54] [64] [65] . In KEYNOTE-426 [16, 17], for pembrolizumab in combination with axitinib, the EQ-5D questionnaire was administered on day 1 of every cycle from cycle 1 to cycle 9; on day 1 of every other cycle from cycle 9 to cycle 19; and on day 1 of every 4th cycle from cycle 19 (approximately week 54) until treatment discontinuation, as well as at the discontinuation visit, and the 30-day post-treatment discontinuation follow-up visit. Each cycle length was equal to 21 days [30].

In KEYNOTE-426 [16, 17], for sunitinib, the EQ-5D questionnaire was administered on days 1 and 29 of every cycle from cycle 1 to cycle 4; on day 1 of every cycle from cycle 5 to cycle 10; and on day 1 of every other cycle from cycle 10 (approximately week 54) until treatment discontinuation, as well as at the discontinuation visit, and the 30-day post-treatment discontinuation follow-up visit. Each cycle length was equal to 42 days [30].

The analysis of the EQ-5D-3L utilities below is based on the Full Analysis Set (FAS) population (a total of 850 subjects). UK preference-based scores were used for all patients analysed from the KEYNOTE-426 clinical trial [16, 17]. The data cut-off date from IA1 of KEYNOTE-426 [16,

17] used for this analysis is 24 August 2018. The UK scoring functions were developed based on the time trade-off (TTO) technique [66].

When estimating utilities, three approaches were considered:

- Estimation of utilities based on progression-free and progressed disease states.

  This approach, commonly seen in previous oncology economic modelling literature, is to define health states based on time relative to disease progression. This approach generates results to fit the economic model by health state, however there can be a practical issue with the KEYNOTE-426 [16, 17] trial-based utility, where the utility data was collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further. Therefore, limited post-progression utility data is available. Previous NICE committees, when assessing advanced RCC, have preferred utilities to be derived from health-state based regression models, as it considered patients' utility would depend on whether their disease had progressed [51].

  The date of progression was determined via RECIST 1.1 using BICR [16]. To estimate utilities:

    - for the progression-free health state, EQ-5D scores collected at all visits before the progression date were used.
    - for the progressive health state, EQ-5D scores collected at all visits after the progression date were used.

  This was completed using both pooled data, alongside differentiation by treatment.

- Estimation of utilities based on time-to-death

  This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum-based chemotherapy or palliative radiotherapy [67-70] and in advanced melanoma patients [64] [71].

  Based on KEYNOTE-426 EQ-5D data [16, 17], time to death was categorised into the following groups:

    - 360 or more days to death
    - 180 to 360 days to death
    - 30 to 180 days to death
    - Under 30 days to death.

EQ-5D scores collected within each time category was used to estimate mean utility associated with that category. The analyses of the intervals related to time to death lower than 360 days focused on patients with observed death dates. The justification to exclude patients whose death dates were censored was that their EQ-5D values could not be linked to their time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since their EQ-5D data related to a survival of at least 360 days, independent of when the death date was censored.

Collection of EQ-5D questionnaires

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab in combination with axitinib and sunitinib arms), and pooled for both arms. In addition, 95% CIs were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested. The level of EQ-5D compliance through time is presented in Table 47.

Table 47. Compliance of EQ-5D by visit and by treatment (FAS Population)

Treatment Visit	Category	Pembrolizumab + axitinib	Sunitinib
		N = 428	N = 422
Baseline	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 3 /4	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 6	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 9/10	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 12	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 15/16	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 18	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]

Treatment Visit	Category	Pembrolizumab + axitinib	Sunitinib
		N = 428	N = 422
Week 21/22	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 24	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 30	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 36	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 42	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 48	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 54	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 66	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 78	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 90	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		

**Compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete it at each time point (excludes those missing by design).*
Missing by design includes: death, discontinuation, translations not available, and no visit scheduled.
(Database Cut-off Date: 24th August 2018).

The EQ-5D utility values were estimated based on progression status (with or without response and treatment status) or time to death categories adjusting for whether the EQ-5D index was measured during a grade 3+ AE. Since patients could have multiple EQ-5D scores within each time to death or progression status category, linear mixed effects models with random intercept were applied to incorporate the correlation of repeated measures for each

patient. In addition, including AE as a covariate in the mixed-effects models provided estimation for AE disutility, which can be included separately in the cost-effectiveness model. The estimated utilities are presented in Table 48, Table 49 and Table 50 below.

Table 48. EQ-5D health utility scores by progression status (pooled)

	Pooled (N=810), number of observations: 7,119		
	Estimate	SE	95% confidence interval
Progression-free (Intercept)	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

Table 49. EQ-5D health utility scores by progression status (differentiated by treatment)

	Pembrolizumab+axitinib (N=**X**), number of observations:			Sunitinib (N=**X**), number of observations:		
	Estimate	SE	95% confidence interval	Estimate	SE	95% confidence interval
Progression-free (Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]					

Table 50. EQ-5D health utility scores by time-to-death

	Pooled (N=532), number of observations: 2,704		
	Estimate	SE	95% confidence interval
≥360 days	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]
90 to 180 days	[redacted]	[redacted]	[redacted]
30 to 90 days	[redacted]	[redacted]	[redacted]
0 to 30 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

Mapping

Not applicable as HRQoL was derived from the KEYNOTE-426 [16, 17] EQ-5D data. Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-426 trial [16, 17], which is consistent with the NICE reference case [54].

Health-related quality-of-life studies

Please see Appendix H for a list of the studies identified through the SLR.

Adverse reactions

To assess the potential disutility associated with Grade ≥3 AEs, the disutility associated with patients experiencing Grade ≥3 AEs were analysed as a fixed effect in both regression models. For the pooled progression status regression model, this disutility was calculated as [redacted], for the treatment specific progression status regression model this disutility was calculated as [redacted] and for the time-to-death utility regression model, this was calculated as [redacted]. The disutility used in the model is dependent on the utility method selected.

Mean duration of Grade ≥3 AEs was estimated from KEYNOTE-426 [16, 17] which was dependent on the AE and presented in Appendix P. The mean duration of Grade ≥3 AEs was applied together with the disutility associated with Grade ≥3 AE and overall incidence rates of AEs (see section B.3.3) to estimate one-off QALY loss per patient due to AE for each treatment arm ([redacted] for pembrolizumab in combination with axitinib and [redacted] for sunitinib using the time-to-death regression model). The QALY losses were applied on the first cycle of the model for each treatment arm.

Age-related disutility

A study by Ara and Brazier [72] suggests that average utility decreases with age therefore age-adjusted utilities are applied in the model to account for the impact of age on utilities using the formula provided by Ara and Brazier, re-weighted using the starting age of patients in the model, i.e. 73 years of age.

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

Table 51. Summary of utility values for cost effectiveness analysis

	Pooled (N=532), number of observations: 2,704			
	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
≥360 days	[redacted]	[redacted]	Section B.3.4 Health-related quality-of-life data from clinical studies (page 114)	Utility values from KEYNOTE-426 (Data cut: Aug 2018) [16, 17], in line with NICE reference case [54]
180 to 360 days	[redacted]	[redacted]		
90 to 180 days	[redacted]	[redacted]		
30 to 90 days	[redacted]	[redacted]		
0 to 29 days	[redacted]	[redacted]		
AE disutility (scenario analysis)	[redacted]	-	Section B.3.4 Adverse reactions (page 115)	

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

Details of the systematic review conducted as part of the appraisal for the identification of relevant cost and health care resource use data to populate the model can be found in Appendix I.

Intervention and comparators' costs and resource use

Drug costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparators being taken from the British National Formulary (BNF) which provides information about prices for branded drugs.

Pembrolizumab in combination with axitinib

– ***Pembrolizumab***

As per the anticipated licenced dosing regimen for the proposed indication, the model uses a 200 mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion Q3W (which is already the licenced dose of pembrolizumab available in clinical practice for other indications [73]) (see also Appendix C – draft SmPC). The list price of a 100 mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100 mg vials using the list price (3-week cycle length). A commercial access agreement is currently in place for a simple discount of [redacted]

– ***Axitinib***

As per the anticipated licenced dosing regimen for the proposed indication, the model uses a 5 mg orally, twice daily, fixed dose of axitinib (which is already a licensed dose of axitinib available in clinical practice for its existing indication [74]). The list price of a packet of 56 tablets of Inlyta 5 mg is £3,517.00 [75], making the cost of a tablet £62.80 and the cost per day £125.60, at list price. The drug cost for axitinib per administration is £3,517.00 using the list price (4-week cycle length). There is a confidential patient access scheme in place for axitinib.

Comparators

Drug acquisition costs for individual drugs included with the comparison of UK SoC were taken from the BNF, as they are all branded drugs. When multiple vial/package sizes were available, the cheapest price per mg was applied as a conservative assumption.

Sunitinib and pazopanib have known patient access scheme's in place; the first cycle of sunitinib [14] is free to the NHS and pazopanib [13] is provided with a 12.5% discount on the list price - this is in the public domain. However, in line with the ERGs preference, as discussed and agreed during the Decision Problem meeting for this submission, all economic analysis will be presented using list prices for consistency across all therapies.

Dosing for the comparator drugs was based on the KEYNOTE-426 protocol [30] for sunitinib, and respective SmPC's for pazopanib [76], tivozanib [77] and cabozantinib [78]. As a conservative assumption, full vial sharing (i.e. no wastage) is assumed for the administration of all comparator drugs.

Table 52. Dosing, frequency and unit costs per administration for intervention and comparator

Drug	Dosing Schedule	Frequency of administration	Total dose required per admin (mg)	Size of tablet (mg)	Cost per tablet	Cost per administration (assuming no wastage)	Proportion of doses received	Cost per administration (list price)	Reference for dosing	Reference for drug costs
Pembrolizumab	200 mg IV Q3W	Q3W	200	[redacted]	[redacted]	£5260.00	[redacted]	£4,986.48	SmPC [73]	BNF [79]
Axitinib	5 mg BID orally	Q4W	280	5	£62.80	£3,517.00	[redacted]	£2,975.38	SmPC [74]	BNF [75]
Sunitinib	50 mg QD orally for 4 weeks, then 2 weeks off treatment	Q6W	1,400	50	£112.10	£3,138.80	[redacted]	£2,344.68	SmPC [80]	BNF [81]
Pazopanib	800 mg QD orally	Q4W	22,400	400	£37.37	£2,092.53	86.0%	£1,799.58	SmPC [76]	BNF [82]
Tivozanib	1.34 mg QD orally for 3 weeks followed by 1 week without treatment	Q4W	28	1.34	£97.71	£2,052.00	94.0%	£1,928.88	SmPC [77]	BNF [83]
Cabozantinib	20/40/60 mg QD orally	Q4W	1,680	20/40/60	171.43	£4,800.13	94.3%	£4,526.53	SmPC [78]	BNF [84]

Table 53 below shows the distribution of therapies currently used in UK clinical practice.

Table 53. Distribution of the use of TKI's in UK clinical practice [85]

Market Regimen Shares (IPSOS) Stage IV 1st line RCC – ECOG PS 0-1	R3M Dec 18 - Feb 19 N=[redacted]
Sunitinib Malate	[redacted]
Pazopanib	[redacted]
Cabozantinib	[redacted]
Tivozanib	[redacted]
Nivo + Ipi	[redacted]

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the anticipated licensed indication, patients treated with pembrolizumab in combination with axitinib are expected to be treated until disease progression or unacceptable toxicity. In line with the KEYNOTE-426 protocol [30], a stopping rule has been implemented in the model whereby patients do not receive pembrolizumab therapy beyond 24 months. Patients discontinuing pembrolizumab after 24 months may continue treatment with axitinib, as per KEYNOTE-426 protocol [30], until disease progression or unacceptable toxicity. In scenario analysis 13, patients also discontinued treatment with axitinib after a maximum of 24 months. To estimate the duration of treatment of pembrolizumab, time on treatment (ToT) data from KEYNOTE-426 [16, 17] was used to reflect both early discontinuation caused by AEs, alongside other reasons for discontinuing before progression, as well as additional weeks of treatment that some patients may receive awaiting confirmation of progression.

Parametric curves were fitted to the patient level treatment duration data from KEYNOTE-426 [16, 17] to represent ToT in the economic model for pembrolizumab, axitinib and sunitinib separately (see Figure 32, Figure 33, Figure 34, respectively). AIC/BIC based tests combined with visual inspection were used to select the best-fitted parametric distributions. The function with the lowest AIC/BIC is Weibull for pembrolizumab and log-normal for axitinib. The function with the lowest AIC/BIC is log-normal for sunitinib. Input from clinicians suggested that the log-normal distribution exaggerated ToT expected to be seen in clinical practice for sunitinib and axitinib. The log-normal estimates 10-year ToT for sunitinib of ~5%, however clinical expert opinion suggested that 5-10% of patients would be on treatment at 5 years; hence the log-normal was considered inappropriate.

Figure 32. ToT KM curve vs fitted one-piece model for pembrolizumab based on KEYNOTE-426 [16, 17]

Figure 33. ToT KM curve vs fitted one-piece model for axitinib based on KEYNOTE-426 [16, 17]

Figure 34. ToT KM curve vs fitted one-piece model for sunitinib based on KEYNOTE-426 [16, 17]

Table 54. Summary of goodness-of fit qualities of ToT survival models for pembrolizumab, axitinib and sunitinib

Fitted Function	Pembrolizumab		Axitinib		Sunitinib	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	2,219.6	2,223.6	2,197.4	2,201.5	2,483.3	2,487.3
Weibull	2,205.2	2,213.3	2,199.4	2,207.5	2,484.0	2,492.1
Llogistic	2,208.6	2,216.7	2,194.5	2,202.6	2,475.1	2,483.2
Lnormal	2,224.7	2,232.8	2,190.3	2,198.5	2,471.2	2,479.3
Gompertz	2,213.0	2,221.1	2,198.3	2,206.4	2,478.8	2,486.9
GenGamma	2,207.0	2,219.1	2,192.3	2,204.5	2,473.2	2,485.4
Best fitting	Weibull	Weibull	Lnormal	Lnormal	Lnormal	Lnormal

As validated by clinicians, PFS and ToT are closely linked; when patients progress they are often shortly taken off treatment. Hence the exponential distribution was chosen for the extrapolation of ToT, in line with the curve selection for PFS, for both axitinib and sunitinib. For pembrolizumab, the weibull curve was used to extrapolate ToT KM data as it had the best statistical and visual fit. Scenario analysis 6 was conducted to evaluate the choice of ToT distribution.

Administration costs

Pembrolizumab in combination with axitinib

The time required for the administration of pembrolizumab is 30 minutes, as per the SmPC [73]. The National Tariff Chemotherapy Regimens list 2017 - 2018 [86] was used to determine the Health Resource Groups (HRG) code for pembrolizumab in combination with axitinib. The

HRG code SB12Z: *Deliver Simple Parenteral Chemotherapy at First Attendance* based on the latest NHS reference costs 2017-2018 was used to reflect administration costs for pembrolizumab in combination with axitinib. For patients continuing treatment of axitinib after 2 years (when pembrolizumab treatment has stopped), the HRG code SB11Z: *Deliver exclusively oral chemotherapy* was used to reflect administration costs for axitinib monotherapy.

SoC

The administration costs required for comparator therapies were based on the assumption used in TA581 by the Evidence Review Group (ERG) [52], in line with the National Tariff Chemotherapy Regimens list 2017 – 2018 [86], of HRG code SB11Z: *Deliver exclusively oral chemotherapy [87]*.

Table 55. Administration costs of pembrolizumab in combination with axitinib and SoC

	Type of administration required	NHS reference cost code	Setting	Cost [87]
Pembrolizumab in combination with axitinib	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£174.40
Axitinib monotherapy	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Sunitinib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Pazopanib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Tivozanib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Cabozantinib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61

Health-state unit costs and resource use

A comprehensive literature search was conducted and updated on the 20th February 2019, to identify costs and resource use in the treatment of and on-going management of locally advanced or metastatic RCC. Please see Appendix I for details of the search strategy and literature identified.

The main source of resource utilisation per health state used in the submission was from the previous Technology Appraisal for cabozantinib in untreated advanced [11]RCC .

There are three health states included in the model – progression free (PFS), post-progression (PPS) and death (see section 3.2).

Patients incur disease management costs whilst in the progression free and progressed disease health states. Table 56 shows the resource use for monitoring and disease management in the progression free health state and the post-progression health state.

Table 56 presents the unit costs for individual resource use items, which were updated based on the latest NHS reference costs 2017-2018 [87] and the Personal and Social Services Research Unit (PSSRU) 2018 report [58]. The estimated monitoring and disease management costs per cycle were £60.05 for both the pre-progression (PFS) and post-progression periods. A one-off cost of £229.00 was applied in the first cycle of the model for the first attendance outpatient consultation.

Cost of terminal care

A one-off cost is applied to those patients at the point of death to reflect the cost of terminal care. The data for the cost and resource use of RCC patients in terminal care is limited so the resource use has remained consistent with information used and accepted in prior HTA submissions for this disease [11]. The estimated one-off terminal costs were £6,789.76; this value has been inflated to reflect 2017/2018 prices and assumed to be the same for all treatment arms.

Table 56. Resource use and unit costs of progression-free, progressed and terminal health states within the model

	Resource	Resource use (per cycle)	Reference	Unit cost	Reference [87]
PFS	Outpatient consultation (first attendance)	N/A	TA542	£229.00	NHS reference costs 2017-2018 Currency code WF01B, Service code 370, Medical oncology
	Outpatient consultation (follow-up attendance)	0.25		£166.00	NHS reference costs 2017-2018 Currency code WF01A, Service code 370, Medical oncology
	CT Scan	0.08		£110.00	NHS reference costs 2017-2018 Currency code RD25Z Computerised Tomography Scan of three areas, without contrast
	Blood test	0.25		£3.00	NHS reference costs 2017-2018 Currency Code: DAPS05
	Total cost per week	**Cycle 1 - £280.05**		**Subsequent Cycles - £51.05**	
PPS	Outpatient consultation (follow-up attendance)	0.25	TA542	£166.00	NHS reference costs 2017-2018 Currency code WF01A, Service code 370, Medical oncology
	CT Scan	0.08		£110.00	NHS reference costs 2017-2018 Currency code RD25Z Computerised Tomography Scan of three areas, without contrast
	Blood test	0.25		£3.00	NHS reference costs 2017-2018 Currency Code: DAPS05
	Total cost per week		**Every cycle - £51.05**		

Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section B.3.3. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in B.3.4.

The resource use related to the management of AEs was mainly derived from previous technology appraisals for untreated advanced or metastatic RCC [11, 52], or metastatic urothelial carcinoma [63]. All unit costs were taken from the latest NHS Reference Costs 2017/18, and when the codes where not similar, the unit costs were inflated to 2017/18 prices

using the hospital and community health services (HCHS) index published by PSSRU for 2018. Table 57 below presents the unit costs per AE that were applied within the cost-effectiveness model.

Table 57. Unit costs of adverse events

Grade 3+ AE with incidence >5%	Unit Cost	Reference	Rationale
Alanine aminotransferase increased	£0.00	Based on the assumption: Regular blood tests (already considered under health-state management costs)	TA542 [11]
Aspartate aminotransferase increased	£0.00	Based on the assumption: Regular blood tests (already considered under health-state management costs)	TA542 [11]
Decreased appetite	£615.76	Non-elective short stay	TA581 [52]
Diarrhea	£1248.34	Non-elective short stay	TA581 [52]
Fatigue	£657.76	Non-elective short stay, cost of face to face community nurse	TA581 [52]
Hyperglycaemia	£156.00	Based on the assumption of 1 visit to endocrinologists, initiation of therapy with p.o anti-diabetic medication: metformin 500mg o.d for one year	TA542 [11]\
Hypertension	£850.21	Non-elective short stay, consultant medical oncology visit WF01A; *non-admitted face to face attendance, follow-up*, 2 follow up GP visits	TA581 [52]
Hyponatremia	£0.00	Based on the assumption: Regular blood tests (already considered under health-state management costs)	TA542 [11]
Lipase level increased	£357.13	Regular day and night admission SA04J *Iron deficiency Aneamia with CC score 6-9*	TA581 [52]
Lymphocytopenia	£331.90	Assumed that 20% of short stay emergency tariff (weighted average of SA25A-SA35E) and 80% of patients with day case tariff (weighted average of SA35B-SA35E)	TA542 [11]
Neutropenia	£80.50	Assumed that 10% of patients require hospital treatment, each requiring two episodes during therapy. Weighted average of mean costs for HRG code WJ11Z *Other disorders of immunity* across non-elective long- and short-stay episodes and day-case admissions	TA519 [88]
Neutrophil count decreased	£80.50	Assumed to be equal to neutropenia	TA519 [88]
Palmar-plantar erythrodysaesthesia syndrome	£615.76	Non-elective short stay	TA581 [52]
Platelet count decreased	£80.50	Assumed to be equal to neutropenia	TA519 [88]
Stomatitis	£615.76	Non-elective short stay	TA581 [52]
Thrombocytopenia	£357.13	Regular day and night admission SA04J *Iron deficiency Anaemia with CC score 6-9*	TA581 [52]

Miscellaneous unit costs and resource use

Costs associated with subsequent therapies received by patients after treatment discontinuation

There were two options regarding the method of choosing subsequent therapies in the economic model: trial-based distribution of subsequent treatments (as per KEYNOTE-426 trial [16, 17] and respective clinical trials for NMA comparators), or real-world distributions of subsequent treatments expected in UK clinical practice (as per the NHS England submission on the NICE appraisal of the combination of nivolumab and ipilimumab [23]). The real-world distribution of subsequent therapies was used in the base-case analysis, with the trial-based distribution of subsequent therapies explored in scenario analysis 12.

1) Real world-based distribution of subsequent treatments expected to be seen in UK clinical practice

In the base case, upon disease progression patients were assumed to incur the costs of subsequent therapies in line with the NHS England submission in TA581. Within TA581, Peter Clarke (NHS England Chemotherapy Lead and Clinical Lead for the CDF) stated that he expected 50% of patients treated with immunotherapy (in this case nivolumab/ipilimumab) and TKI therapy to receive subsequent therapy [23]. In this approach only one line of subsequent therapy has been modelled. Please see Table 58 for the distribution of subsequent therapies based on UK clinical practice.

Table 58. Type and distribution of second line subsequent chemotherapies used in the base case

		First-Line treatment				
		Pembrolizumab in combination with axitinib	Sunitinib	Pazopanib	Tivozanib	Cabozantinib
Distribution of subsequent :	No active treatment	50.00%	50.00%	50.00%	50.00%	50.00%
	Pazopanib	30.00%	0.00%	0.00%	0.00%	0.00%
	Sunitinib	20.00%	0.00%	0.00%	0.00%	0.00%
	Nivolumab	0.00%	30.00%	30.00%	30.00%	30.00%
	Cabozantinib	0.00%	12.50%	12.50%	12.50%	0.00%
	Axitinib	0.00%	7.50%	7.50%	7.50%	7.50%
	Lenvatinib/ everolimus	0.00%	0.00%	0.00%	0.00%	12.50%*
	Source	NHS England Submission in TA581 [23] *Assumption that the proportion of patients treated with cabozantinib in first-line that are expected to receive second-line treatment with cabozantinib were redistributed to lenvatinib/everolimus				

2) Trial based distributions of subsequent therapies

In scenario analysis 12, upon disease progression patients were assumed to incur the costs of subsequent therapies in line with the proportion of patients receiving subsequent therapy in the KEYNOTE-426 trial [16, 17].

For patients in the sunitinib arm, cross-over adjustment was not implemented in the ITT population since nivolumab monotherapy has a positive recommendation for patients with previously treated advanced RCC; hence UK clinical practice is best reflected without the need for cross-over adjustment.

Some subsequent therapies are not recommended in the UK clinical practice in this population, however as efficacy within the clinical trial was derived from their use, they have been costed appropriately. Please see Table 59 for the distribution of subsequent therapies. Please note that more than one line of subsequent therapy is modelled. As mentioned in Section B.2.6.1, The rate of subsequent therapy use in the sunitinib arm of KEYNOTE-426 was high; in particular there was disproportionately high use of nivolumab in the second-line setting, which exceeds that expected in UK clinical practice [23] (please refer to Table 59 below, and Appendix P).

Table 59. Type and distribution of second line subsequent chemotherapies used in the base case

		First-Line treatment				
		Pembrolizumab in combination with axitinib	Sunitinib	Pazopanib	Tivozanib	Cabozantinib
Distribution of subsequent therapy	No active treatment	[redacted]	[redacted]	74.74%	74.74%	39.24%
	Axitinib	[redacted]	[redacted]	11.45%	11.45%	23.08%
	Cabozantinib	[redacted]	[redacted]	0.00%	0.00%	1.28%
	Everolimus	[redacted]	[redacted]	10.18%	10.18%	8.98%
	Lenvatinib / everolimus	[redacted]	[redacted]	0.00%	0.00%	1.28%
	Nivolumab	[redacted]	[redacted]	0.00%	0.00%	10.77%
	Pembrolizumab	[redacted]	[redacted]	0.00%	0.00%	7.18%
	Sunitinib	[redacted]	[redacted]	0.00%	0.00%	14.11%
	Temsirolimus	[redacted]	[redacted]	0.00%	0.00%	8.98%
	Pazopanib	[redacted]	[redacted]	0.00%	0.00%	17.95%
	Cytokines (interferon)	[redacted]	[redacted]	8.90%	8.90%	3.85%
	Source	**KEYNOTE-426 [16, 17]**	**KEYNOTE-426 [16, 17]**	**Assume equal to Tivozanib**	**Mehta et al. 2014 (TIVO-1) [26]**	**Choueiri et al. 2017 (CABOSUN) [24]**

The costs of each subsequent treatment are detailed in Table 60. In all cases drug costs have been sourced from the BNF [75, 79, 81-84], and applied to dosing regimens as per each therapy's SmPC [73, 74, 76-78, 80].

Table 60. Subsequent therapy- drug formulation, dose, administration, proportion of doses received, mean treatment duration and total drug acquisition cost

Subsequent treatment	Dosing schedule	Dose per admin or pharmacy dispensing (mg or MU)	Strength per unit (mg or MU)	Cost per unit (BNF) (2018 GBP)	Relative dose intensity (mean, %)	Drug acquisition cost per admin (2018 GBP)	Dosing schedule (number per month)	Mean treatment duration (months)	Total drug acquisition cost (2018 GBP)	Source for mean treatment duration
PD1/PD-L1 checkpoint inhibitors										
Nivolumab	480 mg IV Q4W or 240 mg IV Q2W	480	40	439.00	92.0%	4,846.56	1.09	7.9*	41,804.38	Motzer et al. 2015 [89] [90] [CheckMate 025] (Median ToT = 5.5 months)
Pembrolizumab	200 mg IV Q3W	200	100	2,630.00	[redacted]	4,986.48	1.45	7.9	57,348.36	Assume same mean ToT as nivolumab
VEGF/VEGFR inhibitors										
Axitinib	5 mg orally BID	280	5	62.80	102.0%	3,587.34	1.09	11.8*	28,385.41	Motzer et al. (2013) [AXIS] [91] [92, 93]
Cabozantinib	60 mg orally QD	1,680	60	171.43	100.0%	4,800.13	1.09	12.1*	37,981.84	Motzer et al. (2018) [METEOR] [94, 95]
Lenvatinib / everolimus	18 mg orally QD	504	10	47.90	75.0%	1,810.62	1.09	11.0*	14,326.83	Motzer et al. (2015) [89] [NCT01136733]
	5 mg orally QD	140	5	75.00	85.0%	1,785.00	1.09	11.0*	14,124.10	Motzer et al. (2015) [89] [NCT01136733]
Pazopanib	800 mg orally QD	22,400	400	37.37	86.0%**	1,574.63	1.09	10.7*	12,459.53	Sternberg et al. (2013) [VEG105192] [38]

Sunitinib	50 mg orally QD for 4 weeks, then 2 weeks off treatment	1,400	50	112.10	[redacted]	2,344.68	0.72	10.7*	10,023.78	Assume same median ToT as pazopanib
Other treatments										
Everolimus	10 mg orally QD	280	10	89.10	91.8%	2,290.23	1.09	6.3*	15,803.62	Motzer et al. (2018) [METEOR] [94] [96] (Median ToT = 6.3 months)
Temsirolimus	25 mg IV QW	25	25	112.10	92.4%	103.58	4.35	6.3*	2,859.01	Hutson et al. (2014) [INTORSECT] [97] [98] (Median ToT = 6.3 months)
Cytokines (Interferon a2B)	10 MU SC three days per week	120	10	112.10	100.0%***	1,345.20	1.09	4.0*	5,822.14	Rini et al. (2008) [CALGB 90206] [37] (Median ToT = 4.0 months)

** Mean ToT was calculated as a function of median ToT, based on an assumption of constant hazards.*
*** Assume equal to 1L dose intensity*
**** Assumption*
Key: BID, twice daily; IV, intravenous; BNF, British National Formulary; Q2W, once every 2 weeks; MG, milligrams; MU, million units; SC, subcutaneously

Table 61. Administration costs for subsequent therapies

	Type of administration required	NHS reference cost code [87]	Setting	Cost
Nivolumab	Deliver Complex parenteral Chemotherapy, at First Attendance	SB13Z	Outpatient	£309.20
Pembrolizumab	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£174.40
Axitinib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Cabozantinib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Lenvatinib/ everolimus	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Cabozantinib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Pazopanib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Sunitinib	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Everolimus	Deliver Exclusively Oral Chemotherapy	SB11Z	Outpatient	£131.61
Temsirolimus	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£174.40
Cytokines (Interferon a2B)	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£174.40

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The full list of variables used in the cost-effectiveness analysis is presented in Table 62 below.

Table 62. Summary of variables applied in the economic model

Parameters	Mean / Deterministic value	Lower	Upper	Distribution used in PSA	Section in the submission document
General Information					
Model cycle length (weeks)	1			Not varied in SA	See Section B.3.2
Model time horizon (years)	40			Not varied in SA	
Discount rate: Costs	3.5%			Not varied in SA	
Discount rate: Health outcomes	3.5%			Not varied in SA	
Patient Information					
Patient Age	61.50			Not varied in SA	See Section B.3.2
Proportion male	73.5%			Not varied in SA	
Average patient weight (kg)	81.7			Not varied in SA	
Utility Inputs					
Utility by time-to-death					
Utility time to death >=360 days	[redacted]	[redacted]	[redacted]	Beta	See Section B.3.4
Utility time to death days [180,359)	[redacted]	[redacted]	[redacted]	Beta	
Utility time to death days [90,179)	[redacted]	[redacted]	[redacted]	Beta	
Utility time to death days [30,89)	[redacted]	[redacted]	[redacted]	Beta	
Utility time to death <30 days	[redacted]	[redacted]	[redacted]	Beta	
AE-related disutility,	[redacted]	[redacted]	[redacted]	Normal	
Regimen Related Costs					
Drug costs (per administration)					
Pembrolizumab drug cost	£5,260.00			Not varied in SA	See Section B.3.5
Axitinib drug cost	£3,517.00			Not varied in SA	
Sunitinib drug cost	£3,138.80			Not varied in SA	
Tivozanib drug cost	£2,052.00			Not varied in SA	
Pazopanib drug cost	£2,092.53			Not varied in SA	
Cabozantinb drug cost	£4,800.13			Not varied in SA	
Nivolumab drug cost	£5,268.00			Not varied in SA	
Lenvatinib drug cost	£2,414.16			Not varied in SA	
Everolimus 5mg drug cost	£2,100.00			Not varied in SA	
Everolimus 10mg drug cost	£2,494.80			Not varied in SA	
Temsirolimus drug cost	£2,092.53			Not varied in SA	

Interferon a2B drug cost	£3,138.80			Not varied in SA	
Administration cost for IV					
Deliver Simple Parenteral Chemotherapy at First Attendance	£174.40	£156.96	£191.84	Gamma	See Section B.3.5
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£309.20			Not varied in SA	
Deliver Exclusively oral chemotherapy	£131.60	£156.96	£191.84	Gamma	
Disease Management Costs					
Weekly cost in progression-free state (cycle 0)	£280.05	£252.05	£308.06	Gamma	See Section B.3.5
Weekly cost in progression-free state (subsequent cycles)	£60.05	£45.95	£56.16	Gamma	
Weekly cost in progressive disease state	£60.05	£45.95	£56.16	Gamma	
Subsequent treatment cost (following intervention)	£9,100.17			Not varied in SA	
Subsequent treatment cost (following comparator)	£20,480.90			Not varied in SA	
Cost of terminal care (one-off cost)	£6,789.76	£6,110.78	£7,468.74	Normal	
% AE Pembrolizumab					
% Alanine aminotransferase increased	13.3%			Not varied in SA	See Section B.3.3
% Aspartate aminotransferase increased	7.0%			Not varied in SA	
% Decreased appetite	2.8%			Not varied in SA	
% Diarrhea	9.1%			Not varied in SA	
% Fatigue	2.8%			Not varied in SA	
% Hyperglycaemia	2.3%			Not varied in SA	
% Hypertension	22.1%			Not varied in SA	
% Hyponatremia	2.3%			Not varied in SA	
% Lipase level increased	0.5%			Not varied in SA	
% Lymphocytopenia	0.2%			Not varied in SA	
% Neutropenia	0.2%			Not varied in SA	
% Neutrophil count decreased	0.2%			Not varied in SA	
% Palmar-plantar erythrodysaesthesia syndrome	5.1%			Not varied in SA	
% Platelet count decreased	0.2%			Not varied in SA	
% Stomatitis	0.0%			Not varied in SA	
% Thrombocytopenia	13.3%			Not varied in SA	

% AE Sunitnib					
% Alanine aminotransferase increased	3.1%			Not varied in SA	See Section B.3.3
% Aspartate aminotransferase increased	2.4%			Not varied in SA	
% Decreased appetite	0.7%			Not varied in SA	
% Diarrhea	4.7%			Not varied in SA	
% Fatigue	6.6%			Not varied in SA	
% Hyperglycaemia	0.5%			Not varied in SA	
% Hypertension	19.3%			Not varied in SA	
% Hyponatremia	2.6%			Not varied in SA	
% Lipase level increased	0.5%			Not varied in SA	
% Lymphocytopenia	0.5%			Not varied in SA	
% Neutropenia	6.6%			Not varied in SA	
% Neutrophil count decreased	6.8%			Not varied in SA	
% Palmar-plantar erythrodysaesthesia syndrome	3.8%			Not varied in SA	
% Platelet count decreased	7.3%			Not varied in SA	
% Stomatitis	2.1%			Not varied in SA	
% Thrombocytopenia	5.9%			Not varied in SA	
AE Management costs					
Pembrolizumab / axitinib	£379.90	£341.91	£417.89	Gamma	See Section B.3.5
Sunitinib	£348.34	£313.51	£383.17	Gamma	
Tivozanib (assumed equivalent to sunitinib)	£348.34	£313.51	£383.17	Gamma	
Pazopanib (assumed equivalent to sunitinib)	£348.34	£313.51	£383.17	Gamma	
Survival Models					
PFS parametric curve fitting					
Pembrolizumab + axitinib					
PFS - Piecewise exponential Parameter A	0.0106	0.0088	0.0125	Normal	See section B.3.3
Sunitinib					
PFS - Piecewise exponential intercept	0.0139	0.0115	0.0163	Normal	See section B.3.3
OS parametric curve fitting					
Pembrolizumab + axitinib					
OS – Log-logistic Parameter A	-0.2001	-0.4377	0.0374	Multivariate Normal	See section B.3.3
OS - Log-logistic Parameter B	5.6254	5.1950	6.0557	Multivariate Normal	
Sunitinib					
OS - Exponential Parameter A	0.0043	0.0034	0.0052	Normal	See section B.3.3
ToT parametric curve fitting					
Pembrolizumab					
ToT – Weibull Parameter A	0.2463	0.1209	0.3716	Multivariate Normal	See section B.3.3
ToT – Weibull Parameter B	4.6185	4.4190	4.8181	Multivariate Normal	See section B.3.3

Axitinib					
ToT – Exponential Parameter A	0.0109	0.0094	0.0125	Normal	See section B.3.3
Sunitinib					
ToT – Exponential Parameter A	0.0155	0.0135	0.0174	Normal	See section B.3.3

Assumptions

Table 63 summarises the assumptions used in the economic model.

Table 63. List of assumptions used in the economic model

Area	Assumption	Justification
Clinical efficacy of external comparators	The clinical efficacy of pazopanib and tivozanib is equal to the clinical efficacy of sunitinib (as seen in KEYNOTE-426 [16, 17]) for OS, PFS, ToT and safety profile.	As per the FAD for cabozantinib [99], tivozanib [100] and nivolumab in combination with ipilimumab [101], the committee's preferred assumption for analysis between sunitinib, pazopanib and tivozanib was to assume clinical equivalency.
Treatment pathway	Once patients' progress they receive subsequent therapies as is experienced in UK clinical practice.	In order to best reflect the treatment pathway of previously untreated advanced RCC patients, the distribution of subsequent therapies reflects the statement made by the NHS England Chemotherapy Lead and Clinical Lead for the Cancer Drugs Fund in May 2018 in TA581.
PFS efficacy	Use KM data for the first 13 weeks from KEYNOTE-426 trial [16, 17], followed by an exponential distribution to model PFS for pembrolizumab + axitinib and sunitinib.	Based on the trial protocol of KEYNOTE-426, the first tumour assessment was performed at week 12 [30].
OS efficacy	Apply fully parametric log-logistic and exponential distribution fitted to individual treatment arms from KEYNOTE-426 trial [16, 17] to model OS for pembrolizumab + axitinib and sunitnib, respectively.	The fully parametric modelling approach, following guidance from TSD 14, was the most appropriate method for modelling OS [61].
Safety	The incidence of AEs from KEYNOTE-426 [16, 17] and published trials were assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-426 trial [16, 17] (i.e. grade 3-5 AEs (incidence≥5% in one or more treatment groups, considering any grade)) and the published trials on cabozantinib in the intermediate/poor risk group. The same method and criteria were applied in recent NICE oncology appraisals of pembrolizumab [63].

Area	Assumption	Justification
HRQoL	The quality of life of patients is appropriately captured by considering time-to-death utilities	Clinical opinion suggests there is a decline in HRQoL in the final months of life of patients. This may not be accurately captured by using a progression-based health-state approach due to the lack of EQ-5D questionnaires undertaken post-progression. This approach has been previously accepted by NICE committees in other oncology indications [102]. Given the limitations of the progression-based approach to appropriately reflect utilities post-progression, a time to death approach was considered in the base case.
Age-related disutility	Utilities were adjusted by UK general population utility where utility deceases with age	Based on the Ara and Brazier study [72] suggesting the impact of age on HRQoL.
Healthcare resource use costs	Resource use is assumed to be equal between pembrolizumab + axitinib and SoC comparators	Due to paucity of data, resource use was assumed to be equal per treatment arm in the pre- and post- progression health states.
Stopping rule	Pembrolizumab will be administered for a maximum of 35 cycles (24 months), after which axitinib monotherapy will continue until confirmation of PD.	This assumption is in line with the KEYNOTE-426 clinical trial [16, 17]
Vial Sharing	Full vial sharing was assumed for all patients	This is a conservative assumption on the treatment cost of the comparator arm in the cost-effectiveness model

B.3.7 Base-case results

The economic analysis was conducted using the data-cut from IA1 as per section B.2.6.1.

The results of the economic model are presented in Table 64 and Table 65 below. Table 64 presents analysis vs the trial comparator (sunitinib). Table 65 presents analysis vs external comparators (pazopanib and tivozanib), which as per the approach described in Table 63, assumes equivalent efficacy between the external comparators and sunitinib. In the base case analysis vs. the trial comparator sunitinib, the estimated mean overall survival was 6.89 years with pembrolizumab in combination with axitinib and 3.87 years with sunitinib. Patients treated with pembrolizumab in combination with axitinib accrued [redacted] QALYs compared to [redacted] among patients in the sunitinib cohort. This gives an incremental life year gain of 3.02 years and an incremental QALY gain of 2.32. MSD considers this to be an unprecedented expected increase in life years and QALY's regardless of risk-group and to be step-changing in the treatment of untreated advanced RCC.

Base-case incremental cost-effectiveness analysis results

Table 64 and Table 65 below presents the base case incremental cost-effectiveness results for the base case excluding the aforementioned discount. All analyses will be presented with each therapy at list price. This is because the PAS discounts for some therapies are known, and others are not, hence for consistency each therapy will be at list price.

The results show that pembrolizumab in combination with axitinib has the potential to be cost-effective compared to sunitinib when considering a willingness to pay threshold of £30,000 per QALY, taking into account confidential discounts. The corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab in combination with axitinib was compared to sunitinib was £59,292 in the base case, with all therapies at list price.

Table 64. Base-case results versus trial comparator SoC (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Sunitnib	[redacted]	3.864	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	£137,537	2.320	£ 59,292
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 65. Base-case results versus external comparators (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pazopanib	[redacted]	3.864	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	£133,472	2.320	£ 57,540
Tivozanib	[redacted]	3.864	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	£131,402	2.320	£ 56,648
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

The estimates of the clinical outcomes included in the cost-effectiveness analysis (compared with the clinical trial results) and the tabulated, disaggregated results for the base case are presented in Appendix J.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in B.3.6.

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 66, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 35 and Figure 36.

Table 66. Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator sunitinib (list price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Sunitinib	[redacted]	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	[redacted]	£137,352	2.30	£59,726

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The cost-effectiveness acceptability curve shows that, for the base case, there is approximately a 0.3% of chance of pembrolizumab in combination with axitinib being cost-effective when compared to SoC at the £30,000 per QALY threshold. As per the deterministic ICER, list prices have been used for this analysis and hence we expect when confidential discounts are considered there will be a high likelihood that the technology can be deemed cost-effective.

Figure 35. Scatterplot of PSA results (1,000 simulations) versus trial comparator sunitinib (list price)

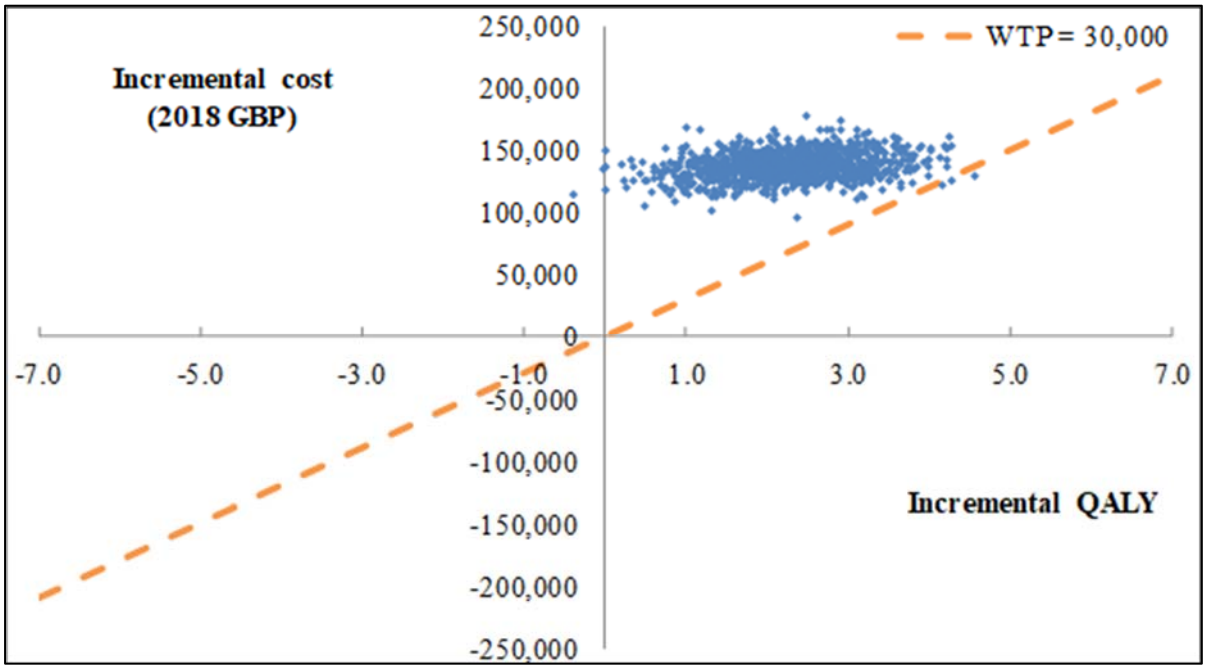
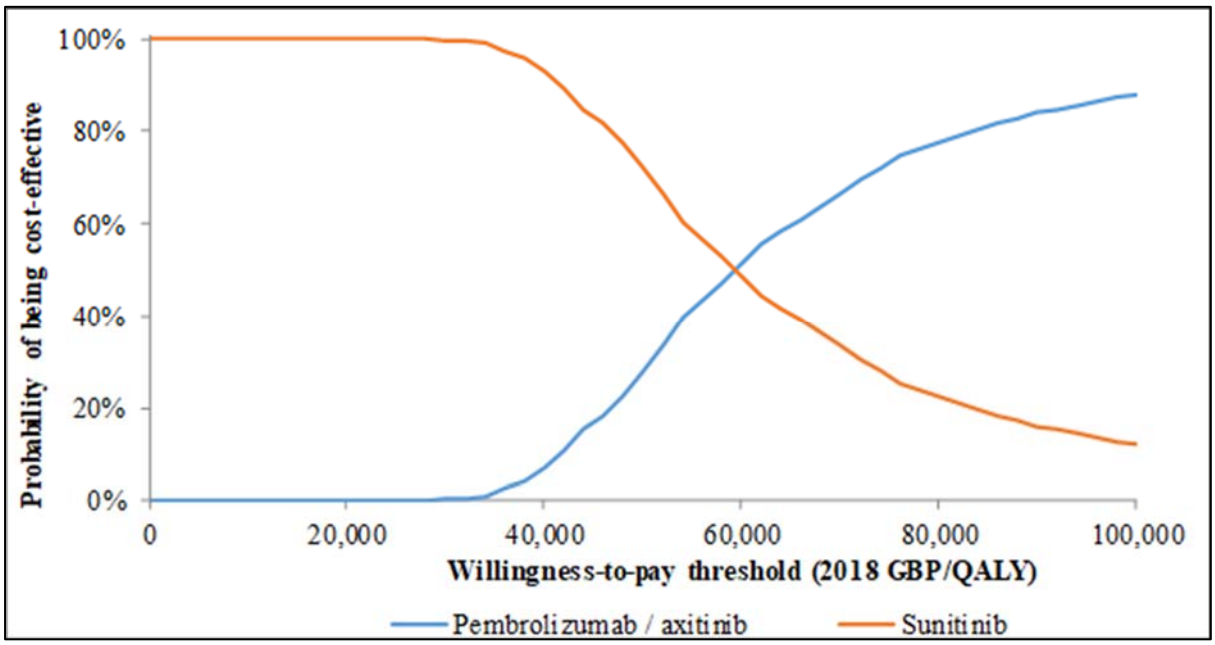


Figure 36. Cost-effectiveness acceptability curve versus trial comparator SoC (list price)



Deterministic sensitivity analysis

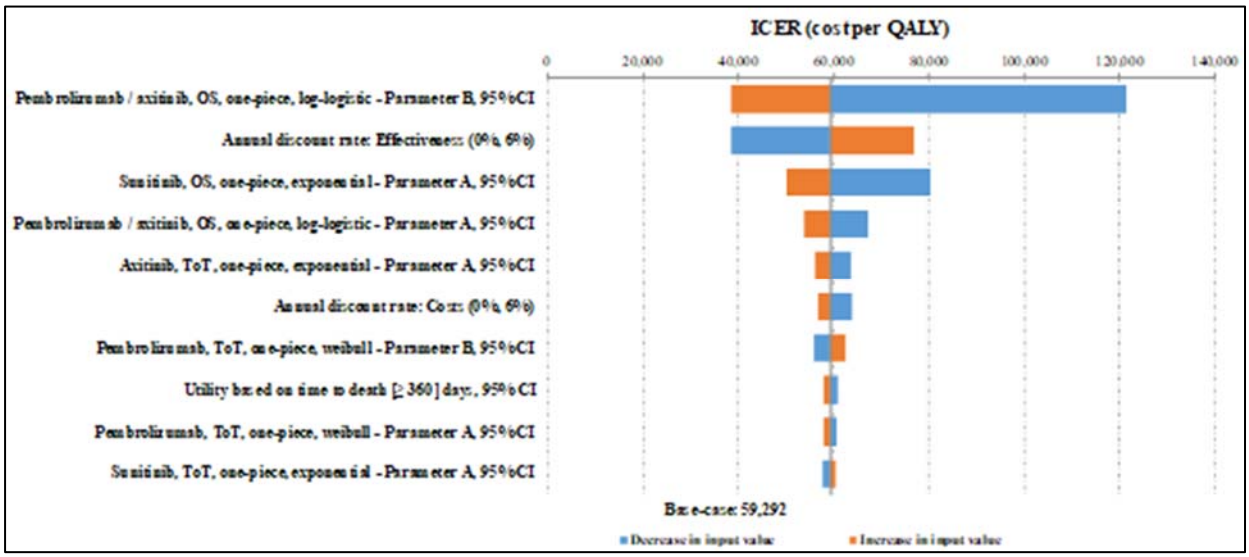
Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- Baseline characteristics (i.e. age, % female)
- Time horizon, discounting, and half-cycle correction
- Drug acquisition and administration costs
- Time on treatment estimation methods
- Resource utilisation
- Subsequent treatment cost
- Health state-based utility and time-to death-based utility
- AE costs and AE-related disutility
- Background mortality
- Parameters of the parametric curves fitted to OS, PFS and ToT.

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab combination vs. SoC are presented in Figure 37 below.

The inputs that most affect the ICERs are those related to the extrapolation of the OS (i.e. the parameters of the log-logistic and exponential distributions used for extrapolation), followed by the annual discount rate of effectiveness (see Figure 37).

Figure 37. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables versus trial comparator SoC (list price)



Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions:

- Using landmark modelling approach- please see Appendix P (Scenario 1).
- Using the fully fitted exponential parametric function to extrapolate OS for both arms (Scenario 2).
- Using the log-logistic parametric function to extrapolate OS for pembrolizumab in combination with axitinib, and time-constant hazard ratio derived from the NMA for sunitinib (Scenario 3).
- Using the log-logistic parametric function to extrapolate OS for pembrolizumab in combination with axitinib, and time-varying hazard ratio derived from the NMA for sunitinib (Scenario 4).
- Assuming that the treatment effect stops at 10 years (Scenario 5), at which point pembrolizumab in combination with axitinib presents the same hazard to that of the sunitinib arm. The cost of axitinib is also stopped after this point.
- Alternative modelling approach of PFS and ToT (Scenario 6):
    - PFS (piecewise approach, parametric distribution selection according to statistical fit): pembrolizumab in combination with axitinib extrapolated using a log-normal distribution, sunitinib extrapolated using an exponential curve.

    - ToT (fully fitted parametric function according to statistical fit for pembrolizumab and consistency with PFS selection for axitinib and sunitinib): pembolizumab extrapolated using weibull curve, axitinib extrapolated using log-normal distribution, sunitinib extrapolated using exponential distribution.

- Using pooled health state-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-426 [16, 17] (Scenario 7).
- Using treatment specific health state-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-426 [16, 17] (Scenario 8).
- Removing the age-related disutilities (Scenario 9).
- Applying dose intensity from TA169 to Sunitinib (Scenario 10).
- Removing AE related disutilities (Scenario 11).
- Using trial-based distribution of subsequent therapies (Scenario 12).
- Introducing a stopping rule for axitinib of 2 years (Scenario 13).
- Assessing the impact of the half-cycle correction (Scenario 14).

Table 67. Results from the scenario analyses versus trial comparator SoC (list price)

Scenario No.	Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 137,537	2.320	£59,292
Scenario 1	Landmark Modelling approach	[redacted]	7.350	[redacted]	[redacted]	4.448	[redacted]	£ 137,249	2.237	£61,341
Scenario 2	Fully parametric exponential OS extrapolation	[redacted]	6.251	[redacted]	[redacted]	3.864	[redacted]	£ 135,994	1.861	£73,094
Scenario 3	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-constant HR for sunitinib	[redacted]	6.887	[redacted]	[redacted]	3.882	[redacted]	£ 137,497	2.318	£59,310
Scenario 4	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-varying HR for sunitinib	[redacted]	6.887	[redacted]	[redacted]	4.654	[redacted]	£ 135,616	1.720	£78,854
Scenario 5	Treatment waning after 10 years	[redacted]	5.836	[redacted]	[redacted]	3.864	[redacted]	£ 134,833	1.555	£86,712
Scenario 6	Alternative modelling approach of PFS and ToT	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 182,710	2.320	£78,767
Scenario 7	Health state-based utilities (pooled)	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 137,537	2.169	£63,400
Scenario 8	Health state-based utilities (treatment specific)	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 137,537	2.259	£60,876
Scenario 9	Removing age-related disutilities	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 137,537	2.499	£55,045
Scenario 10	Sunitinib dose intensity = 86% (TA169) [14]	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 133,690	2.320	£57,634
Scenario 11	Removing AE disutilities	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 137,537	2.319	£59,300
Scenario 12	Trial-based subsequent therapy distribution	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 141,482	2.320	£60,993
Scenario 13	Axitinib 2 year stopping rule	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	£ 116,994	2.320	£50,436
Scenario 14	Remove half-cycle correction	[redacted]	6.896	[redacted]	[redacted]	3.873	[redacted]	£ 137,537	2.320	£59,289

Summary of sensitivity analyses results

The probability of pembrolizumab in combination with axitinib being the most cost-effective treatment at a threshold of £30,000 per gained QALY is 0.3%.
One-way sensitivity analyses showed that the inputs that most affect the ICERs are those related to the extrapolation of the OS (i.e. the parameters of the log-logistic and exponential distributions used for extrapolation), followed by the annual discount rate of effectiveness.

Scenario analyses showed that the most sensitive scenarios relate to the chosen parametric distribution for OS, the introduction of an axitinib stopping rule and the presence of treatment waning. This ranged from £50,436 to £86,712 with one-piece log-normal and piecewise log-normal, respectively.

When the confidential discounts are applied, it is expected most scenario analyses produce ICERs below £30,000/QALY and therefore pembrolizumab in combination with axitinib should be considered a cost-effective strategy when realistic scenarios are considered.

B.3.9 Subgroup analysis

The results of the cost-effectiveness analyses on the intermediate/poor (as defined by the IMDC definition) subgroup of patients with untreated advanced RCC are presented below. The sub-group analysis has been pre-specified in the final scope, due to cabozantinib being recommended in the intermediate/poor risk group only and was also a pre-specified sub-group in the KEYNOTE-426 trial protocol [30]. The subgroups, and relevant comparators, considered are as follows:

- Intermediate/poor risk group
    - Versus sunitinib, pazopanib, tivozanib and cabozantinib

Further detail on the statistical analysis and characteristics of the subgroups can be found in section B.2.

Patients with an intermediate/poor risk score

- OS one-piece exponential distribution for sunitinib (based on clinical plausibility. Log-normal was the best fit for SoC statistically, however when tested gave implausibly high long-term survival at 10 years and so was discarded) and log-logistic distribution for pembrolizumab in combination with axitinib (based on clinical plausibility, see B.3.3 for justification).

- PFS piecewise exponential distribution (based on best statistical fit for sunitinib and second lowest BIC criterion for pembrolizumab in combination with axitinib)
- ToT parametric approach weibull distribution for pembrolizumab (based on visual and statistical fit), exponential distribution for axitinib and sunitinib (for consistency with PFS curve selection).

Table 68. Incremental cost-effectiveness results for pembrolizumab in combination with axitinib vs. sunitinib for patients with intermediate/poor risk score

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Sunitinib	[redacted]	2.936	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	5.878	[redacted]	£135,955	2.275	£59,766
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 69. Incremental cost-effectiveness results for pembrolizumab in combination with axitinib vs. tivozanib, pazopanib (assuming clinical efficacy to sunitinib) for patients with intermediate/poor risk score

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pazopanib	[redacted]	2.936	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	5.878	[redacted]	£132,735	2.275	£58,350
Tivozanib	[redacted]	2.936	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	5.878	[redacted]	£131,054	2.275	£57,611
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 70. Incremental cost-effectiveness results for pembrolizumab in combination with axitinib vs. cabozantinib (NMA comparator; time-constant hazard ratio and time-varying hazard ratio) for patients with intermediate/poor risk score

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Cabozantinib (time-constant HR)	[redacted]	3.885	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	5.878	[redacted]	£33,103	1.543	£21,452
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.10 Validation

Validation of cost-effectiveness analysis

Clinical benefit

The efficacy outcomes of pembrolizumab observed in the KEYNOTE-426 trial [16, 17] have been compared to the outcomes from the cost-effectiveness model. For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J.

Expert validation

The modelling approach has been validated by the University of Sheffield's School of Health And Related Research (SCHARR) with input by 2 external health economists. SCHARR was selected as leading experts in health economic practice and methodology development in the UK. The model structure, selection of appropriate dataset, the survival analysis undertaken and assumption regarding extrapolation and the utility values and healthcare resource use were all discussed within the model review.

The review agreed that the overall model structure was appropriate given the lack of sufficiently granular evidence for all relevant comparators and the assumptions for the model were logical. With regards to extrapolation of clinical efficacy, they have considered the approaches used as in line with TSD 14 [61], however highlighted that there were high levels of uncertainty due to the immaturity of data; this should be explored through scenario analyses.

The model was quality-assured by the internal processes of the economists who produced the economic model in addition to SCHARR who found no major implementation errors or bugs.

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab in combination with axitinib for the treatment of untreated patients with advanced RCC. The economic evaluation reflects patients assessed in KEYNOTE-426 [16, 17] and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

No study assessing the cost-effectiveness of pembrolizumab in combination with axitinib for the target population specified above was identified from the systematic literature review. It

was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the untreated, advanced RCC population eligible for pembrolizumab in combination with axitinib as per the anticipated licence. As mentioned previously, clinical efficacy estimates from the KEYNOTE-426 trial [16, 17], which assessed patients in line with the anticipated licenced indication, were used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab in combination with axitinib in the patient population under consideration.

Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-426 [16, 17] and the de novo economic evaluation are reflective of patients with advanced RCC in the UK.
- The economic model structure is consistent with other oncology models submitted to NICE.
- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab in combination with axitinib.
- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model.

- OS, PFS and ToT data for pembrolizumab were used from the KEYNOTE-426 trial [16, 17], however due to limited follow-up data there is uncertainty surrounding the long term effects of pembrolizumab in combination with axitinib on clinical outcomes.
- OS, PFS and ToT extrapolation: The approaches to OS, PFS and ToT extrapolation were based on statistical and clinical considerations.
- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-426 data [16, 17], in the base case using a time-to-death approach.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 24 months, i.e. 35 cycles, as defined as part of the KEYNOTE-426 protocol [30].
- Resource use and unit costs used in the analysis are reflective of UK clinical practice.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above, which helped in understanding the key variables that could potentially have a major impact on the cost-effectiveness results.

Since the approaches taken for modelling are, mostly conservative, the results presented here support the conclusion that, when confidential discounts are applied, pembrolizumab in combination with axitinib is a cost-effective therapeutic option for the treatment of patients with untreated, advanced RCC.

B.4 References

1. Robert, C., et al., *Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial.* The Lancet, 2014. **384**(9948): p. 1109-1117.
2. UK, K.C. *Kidney Cancer*. [cited 2019 18 July]; Available from: https://www.kidneycareuk.org/about-kidney-health/conditions/kidney-cancer/.
3. UK, C.R. *Kidney cancer: stages, types and grades*. [cited 2019 18 July]; Available from: https://www.cancerresearchuk.org/about-cancer/kidney-cancer/stages-types-grades/types-grades.
4. UK, K.C. *What is Kidney Cancer*. [cited 2019 18 July]; Available from: https://www.kcuk.org.uk/kidneycancer/what-is-kidney-cancer/.
5. NHS. *Overview: Kidney Cancer*. 2016 12 December 2016 [cited 2019 18 July]; Available from: https://www.nhs.uk/conditions/kidney-cancer/.
6. UK, C.R. *Kidney cancer statistics*. [cited 2019 18 July]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer#heading-Zero.
7. UK, K.C. *Kidney Cancer Symptoms and Diagnosis*. [cited 2019 18 July]; Available from: https://www.kcuk.org.uk/kidneycancer/symptoms-and-diagnosis/.
8. NCCN, *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Kidney Cancer*. 2019, NCCN: NCCN website.
9. UK, K.C., *Kidney Cancer factsheet*. --, Kidney Cancer UK: Kidney Cancer UK website.
10. NICE, *Renal cancer overview: NICE pathways*. 2018, NICE: NICE website.
11. NICE, *TA542: Cabozantinib for untreated advanced renal cell carcinoma*. 2018, NICE: NICE website.
12. NICE, *TA512: Tivozanib for treating advanced renal cell carcinoma*. 2018, NICE: NICE website.
13. NICE, *TA215: Pazopanib for the first-line treatment of advanced renal cell carcinoma*. 2011, NICE: NICE website.
14. NICE, *TA169: Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma*. 2009, NICE: NICE website.
15. Albiges, L., et al., *Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma.* European urology, 2019.
16. Rini, B.I., et al., *Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma.* New England Journal of Medicine, 2019. **380**(12): p. 1116-1127.
17. Merck Sharp & Dohme Corp., a.S.o.M.C., *A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426)*. 2018.
18. Heng, D.Y., et al., *Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study.* Journal of clinical oncology, 2009. **27**(34): p. 5794-5799.
19. Heng, D.Y., et al., *External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study.* The lancet oncology, 2013. **14**(2): p. 141-148.
20. Motzer, R.J., et al., *Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma.* New England Journal of Medicine, 2018. **378**(14): p. 1277-1290.
21. Maurer, W. and F. Bretz, *Multiple testing in group sequential trials using graphical approaches.* Statistics in Biopharmaceutical Research, 2013. **5**(4): p. 311-320.

22. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.
23. England, P.P.C.-N., *NHS England submission on the NICE appraisal of the combination of nivolumab and ipilimumab in the treatment of metastatic renal cell adenocarcinoma*. 2018, NICE: NICE website.
24. Choueiri, T.K., et al., *Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial.* Journal of Clinical Oncology, 2017. **35**(6): p. 591.
25. Motzer, R.J., et al., *Pazopanib versus sunitinib in metastatic renal-cell carcinoma.* New England Journal of Medicine, 2013. **369**(8): p. 722-731.
26. Mehta, A., G. Sonpavde, and B. Escudier, *Tivozanib for the treatment of renal cell carcinoma: results and implications of the TIVO-1 trial.* Future oncology, 2014. **10**(11): p. 1819-1826.
27. Escudier, B., et al., *Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma.* Journal of clinical oncology, 2009. **27**(8): p. 1280-1289.
28. Motzer, R.J., et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* New England Journal of Medicine, 2007. **356**(2): p. 115-124.
29. Medicine, U.S.N.L.o. *Study to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Axitinib Versus Sunitinib Monotherapy in Participants With Renal Cell Carcinoma (MK-3475-426/KEYNOTE-426)*. 2016 July 2019 [cited 2019 18 July]; Available from: https://clinicaltrials.gov/ct2/show/NCT02853331.
30. Merck Sharp & Dohme Corp., a.s.o.M.C., *Protocol of A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426)*. 2018.
31. Hutson, T.E., et al., *Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial.* The Lancet Oncology, 2013. **14**(13): p. 1287-1294.
32. eMC. *Inlyta 5 mg film-coated tablets*. 2012 November 2018 [cited 2019 18 July]; Available from: https://www.medicines.org.uk/emc/product/7948/smpc.
33. Wierecky, J., et al., *Immunologic and clinical responses after vaccinations with peptide-pulsed dendritic cells in metastatic renal cancer patients.* Cancer Research, 2006. **66**(11): p. 5910-5918.
34. Medicine, U.S.N.L.o. *KEYNOTE-035: A Dose Finding Study To Evaluate Safety, Drug Interaction, Tumor Markers Of Axitinib In Combination With MK-3475 In Adult Patients With Previously Untreated Advanced Renal Cell Cancer*. 2014 June 2019 [cited 2019 18 July]; Available from: https://www.clinicaltrials.gov/ct2/show/NCT02133742?term=A4061079&rank=1.
35. Escudier, B., et al., *Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial.* The Lancet, 2007. **370**(9605): p. 2103-2111.
36. Motzer, R.J., et al., *Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma.* Journal of clinical oncology, 2009. **27**(22): p. 3584.
37. Rini, B.I., et al., *Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206.* Journal of clinical oncology, 2010. **28**(13): p. 2137.
38. Sternberg, C.N., et al., *A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update.* European journal of cancer, 2013. **49**(6): p. 1287-1296.
39. Motzer, R.J., et al., *Overall survival in renal-cell carcinoma with pazopanib versus sunitinib.* New England Journal of Medicine, 2014. **370**(18): p. 1769-1770.

40. FDA. *CDER Breakthrough Therapy Designation Approvals*. 2018 [cited 2019 22 May]; Available from: https://www.fda.gov/media/95302/download.
41. FDA. *Breakthrough Therapy*. 2018 April 2018 [cited 2019 22 May]; Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.
42. MHRA, *Pembrolizumab (MK-3475): Early Access to Medicines Scientific Opinion - Public Assessment Report*. 2015: assets.publishing.service.gov.uk.
43. Donskov, F., et al., *871P KEYNOTE-427 cohort A: Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (ccRCC).* Annals of Oncology, 2018. **29**(suppl_8): p. mdy283. 080.
44. McDermott, D.F., et al., *Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): Results from cohort A of KEYNOTE-427*. 2018, American Society of Clinical Oncology.
45. FDA. *SUTENT® (sunitinib malate) capsules, oral*. 2006 [cited 2019 18 July]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021938s13s17s18lbl.pdf .
46. FDA. *KEYTRUDA® (pembrolizumab) for injection, for intravenous use*

KEYTRUDA® (pembrolizumab) injection, for intravenous use 2014 [cited 2019 18 July]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf.
47. Hutson, T.E., et al., *Axitinib versus sorafenib in first-line metastatic renal cell carcinoma: overall survival from a randomized phase III trial.* Clinical genitourinary cancer, 2017. **15**(1): p. 72-76.
48. EMA, *Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man*. 2012, EMA: EMA website.
49. Gore, M., et al., *Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma.* British journal of cancer, 2015. **113**(1): p. 12.
50. NICE. *Final scope: Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma ID1426*. 2019 [cited 2019 18 July]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10331/documents.
51. NICE, *TA417: Nivolumab for previously treated advanced renal cell carcinoma*. 2016, NICE: NICE website.
52. NICE, *TA581: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma*. 2019, NICE: NICE website.
53. Woods, B., et al., *NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review.* Sheffield, UK, 2017.
54. NICE, *Guide to the methods of technology appraisal 2013*. 2013, NICE: NICE website.
55. Motzer, R.J., et al., *Sunitinib in patients with metastatic renal cell carcinoma.* Jama, 2006. **295**(21): p. 2516-2524.
56. Sternberg, C., et al., *A randomized, double-blind phase III study (VEG105192) of pazopanib (paz) versus placebo (pbo) in patients with advanced/metastatic renal cell carcinoma (mRCC): Updated safety results.* Journal of Clinical Oncology, 2011. **29**(7_suppl): p. 313-313.
57. Hammers, H.J., et al., *CheckMate 214: A phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma*. 2015, American Society of Clinical Oncology.
58. Curtis, L., *Unit costs of health & social care*. 2007: PSSRU website.
59. NICE, *TA333: Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment*. 2015, NICE: NICE website.
60. NICE, *Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal*

of a new cancer product. 2019, NICE: NICE website.

61. NICE, *NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA* 2013, NICE: NICE website.
62. Motzer, R.J., et al., *Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma.* New England Journal of Medicine, 2019. **380**(12): p. 1103-1115.
63. NICE, *TA522: Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable*. 2018, NICE: NICE website.
64. Batty, A., et al., *PCN148 Estimating Quality of Life in Advanced Melanoma; A Comparison of Standard Gamble, SF-36 Mapped, and Eortc QLQ-C30 Mapped Utilities.* Value in Health, 2011. **14**(7): p. A461-A462.
65. Batty, A., et al. *A comparison of general population and patient utility values for advanced melanoma*. in *ANNALS OF ONCOLOGY*. 2012. OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
66. Dolan, P., *Modeling valuations for EuroQol health states.* Medical care, 1997: p. 1095-1108.
67. Huang, M., J. Pellissier, and J. Liao, *A trial-based EuroQol EQ-5D health utility analysis in patients with previously treated advanced NSCLC.* Value in Health, 2016. **19**(7): p. A744.
68. NICE, *TA366: Pembrolizumab for advanced melanoma not previously treated with ipilimumab*. 2015, NICE: NICE website.
69. NICE, *TA428: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy*. 2017, NICE: NICE website.
70. van den Hout, W.B., et al., *Cost–Utility Analysis of Short-Versus Long-Course Palliative Radiotherapy in Patients With Non–Small-Cell Lung Cancer.* Journal of the National Cancer Institute, 2006. **98**(24): p. 1786-1794.
71. Hatswell, A.J., et al., *Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death.* Health and quality of life outcomes, 2014. **12**(1): p. 140.
72. Ara, R. and J.E. Brazier, *Populating an economic model with health state utility values: moving toward better practice.* Value in Health, 2010. **13**(5): p. 509-518.
73. EMA, *Keytruda SUMMARY OF PRODUCT CHARACTERISTICS*. 2015, EMA: EMA website.
74. EMA, *Inlyta SUMMARY OF PRODUCT CHARACTERISTICS* 2012, EMA: EMA website.
75. BNF. *Axitinib*. 2019 10 April 2019 [cited 2019 22 May 2019]; Available from: https://www.medicinescomplete.com/#/content/bnf/_118443698?hspl=inlyta#DMD21505811000001102.
76. eMC. *Votrient 200 mg film coated tablets*. 2018 25 May 2018 [cited 2019 14 June]; Available from: https://www.medicines.org.uk/emc/product/7861/smpc.
77. eMC. *Fotivda 1340mcg hard capsules SmPC*. 2019 28 March 2019 [cited 2019 14 June]; Available from: https://www.medicines.org.uk/emc/product/8995/smpc.
78. eMC. *Cabometyx 20mg SmPC*. 2019 20 November 2018 [cited 2019 14 May]; Available from: https://www.medicines.org.uk/emc/product/4331/smpc.
79. BNF. *Pembrolizumab*. 2019 6 June 2019 [cited 2019 22 May]; Available from: https://www.medicinescomplete.com/#/content/bnf/_988968089?hspl=keytruda#DMD34349311000001108.
80. eMC. *SUTENT 12.5mg Hard Capsules SmPC*. 2019 22 February 2019 [cited 2019 14 June 2019]; Available from: https://www.medicines.org.uk/emc/product/227/smpc.
81. BNF. *Sunitinib*. 2017 24 July 2017 [cited 2019 22 May]; Available from: https://www.medicinescomplete.com/#/content/bnf/_113004966?hspl=sunitinib.
82. BNF. *Pazopanib*. 2019 27 April 2019 [cited 2019 22 May]; Available from: https://www.medicinescomplete.com/#/content/bnf/_339075720?hspl=pazopanib.
83. BNF. *Tivozanib*. 2018 26 April 2018 [cited 2019 22 May]; Available from: https://www.medicinescomplete.com/#/content/bnf/_553353876?hspl=tivozanib.

84. BNF. *Cabozantinib*. 2017 29 August 2017 [cited 2019 22 May]; Available from: https://www.medicinescomplete.com/#/content/bnf/_844159290?hspl=cabozantinib.
85. Monitor, I.H.G.O., *25 physicians reporting on 105 patients in the UK*. December 2018 - February 2019, Ipsos: Unpublished.
86. NHS, *2017/18 and 2018/19 National Tariff Payment System*. 2019, NHS: NHS website.
87. improvement, N., *Reference costs 2017/18: highlights, analysis and introduction to the data*. 2018, NHS: NHS website.
88. NICE, *TA519: Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy*. 2018, NICE: NICE website.
89. Motzer, R.J., et al., *Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial.* The lancet oncology, 2015. **16**(15): p. 1473-1482.
90. NICE, *TA581: Committee papers*. 2019, NICE: NICE website.
91. Pfizer, *TA333 manufacturer submission : Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment*. 2012, NICE: NICE website.
92. NICE, *TA417 Committee papers: Nivolumab for treated or metastatic renal cell carcinoma [ID853]* 2016, NICE: NICE website.
93. Motzer, R.J., et al., *Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial.* The Lancet Oncology, 2013. **14**(6): p. 552-562.
94. NICE, *TA463 Committe papers: Cabozantinib for previously treated advanced renal cell carcinoma [ID931]* 2017, NICE: NICE website.
95. Motzer, R.J., et al., *Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma.* British journal of cancer, 2018. **118**(9): p. 1176.
96. NICE, *TA432: Everolimus for advanced renal cell carcinoma after previous treatment*. 2014, NICE: NICE website.
97. Hutson, T.E., et al., *Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma.* Journal of Clinical Oncology, 2014. **32**(8): p. 760.
98. Hudes, G., et al., *Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma.* New England Journal of Medicine, 2007. **356**(22): p. 2271-2281.
99. NICE, *TA542 FAD: Cabozantinib for untreated advanced renal cell carcinoma*. 2018, NICE: NICE website.
100. NICE, *TA512 Final appraisal document: Tivozanib for treating advanced renal cell carcinoma*. 2018, NICE: NICE website.
101. NICE, *TA581 FAD: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma*. 2019, NICE: NICE website.
102. NICE, *TA531: Pembrolizumab for untreated PDL1-positive metastatic non-small-cell lung cancer*. 2018, NICE: NICE website.

B.5 Appendices

Appendix C: Summary of product characteristics

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional secondary efficacy results from KEYNOTE-426; IA1 (August 2018 data-cut)

Appendix M: NMA results (Time-varying HRs – 2nd order FP – August 2018 data cut)

Appendix N: NMA results (Time-varying HRs – 2nd order FP – January 2019 data cut)

Appendix O: Additional KEYNOTE-426 data from January 2019 cut-off

Appendix P: Supplementary information on modelling methods

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29 August 2019

Dear Linda,

Re. ID1426: Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

Please find enclosed MSD's responses to the clarification questions from the ERG, concerning the clinical and cost effectiveness data for the above-mentioned submission.

We believe that we have addressed all of the questions but should you or the ERG require any further clarification, please do not hesitate to contact us.

Best regards,

Kalpana D'Oca
Team Lead – HTA & OR

Section A: Clarification on effectiveness data

KEYNOTE-426 trial

A1. How is locally advanced renal cell carcinoma (RCC) defined in the trial? (as distinguished from metastatic RCC).

Company response

The inclusion criteria reported in Section 2.3.1 of the company submission (page 21) specified that locally advanced/metastatic disease includes the following two groups: patients with newly diagnosed stage IV RCC per American Joint Committee on Cancer (AJCC) or those with recurrent disease.

As per AJCC 8th edition [1], stage IV includes patients with T4, any N, M0 and any T, Any N and M1. The first group (T4, any N and M0) is considered as locally advanced as no metastatic disease. For those with recurrent disease, if disease recurred only within the renal fossa or with unresected kidney, this should be considered as locally advanced as well.

A2. In the KEYNOTE-426 trial 54% of the participants had recurrent disease. What stage RCC was their prior treatment for? In the company's submission, table 7 (p33), 305 of the pembrolizumab + axitinib arm and 328 of the sunitinib arm had stage III or IV at initial diagnosis and yet 238 and 231 were reported as having recurrent disease. Does this mean that some of the recurrent cases had previous treatment for stage III and IV disease?

Company response

Please refer to Table A2 for a summary of RCC stage at initial diagnosis for subjects with recurrent disease in the KEYNOTE-426 [2,3] intention to treat (ITT) population.

Table A2. Summary of RCC stage at initial diagnosis for subjects with recurrent disease (ITT population)

RCC Stage of prior treatment for recurrent disease patients	Pembrolizumab + axitinib n (%)	Sunitinib n (%)	Total n (%)
Subjects with recurrent disease	**238**	**231**	**469**
I	68 (28.6%)	62 (26.8%)	130 (27.7%)
II	55 (23.1%)	37 (16.0%)	92 (19.6%)
III	94 (39.5%)	101 (43.7%)	195 (41.6%)
IV	17 (7.1%)	30 (13.0%)	47 (10.0%)
Missing	4 (1.7%)	1 (0.4%)	5 (1.1%)

Among subjects with recurrent disease, only 11 subjects received adjuvant therapy, and none received neo-adjuvant therapy. Only four subjects in the pembrolizumab + axitinib arm had a stage III of RCC at initial diagnosis and received adjuvant therapy. No subjects with recurrent disease and initial diagnosis of stage IV RCC received prior therapy.

A3. Please provide results of adverse events of special interest by grade. The interpretation of the clinical evidence states that most were grade 1 or 2 but no data appear to be presented by grade.

Company response

Please refer to Table A3 for results of adverse events of special interest (AEOSI) by grade in KEYNOTE-426 [2,3].

Table A3 Subjects With AEOSI by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) - (ASaT Population)

	Pembrolizumab + Axitinib		Sunitinib	
	n	(%)	n	(%)
Subjects in population	429		425	
with one or more adverse events	220	(51.3)	154	(36.2)
Grade 1	58	(13.5)	64	(15.1)
Grade 2	116	(27.0)	82	(19.3)
Grade 3	36	(8.4)	7	(1.6)

Grade 4	7	(1.6)	0	(0.0)
Grade 5	3	(0.7)	1	(0.2)
with no adverse events	209	(48.7)	271	(63.8)
Adrenal Insufficiency	**13**	**(3.0)**	**1**	**(0.2)**
Adrenal insufficiency	12	(2.8)	1	(0.2)
Grade 2	9	(2.1)	1	(0.2)
Grade 3	3	(0.7)	0	(0.0)
Secondary adrenocortical insufficiency	1	(0.2)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)
Colitis	**11**	**(2.6)**	**3**	**(0.7)**
Colitis	8	(1.9)	1	(0.2)
Grade 1	1	(0.2)	1	(0.2)
Grade 2	2	(0.5)	0	(0.0)
Grade 3	5	(1.2)	0	(0.0)
Enterocolitis	2	(0.5)	2	(0.5)
Grade 1	0	(0.0)	1	(0.2)
Grade 2	0	(0.0)	1	(0.2)
Grade 3	2	(0.5)	0	(0.0)
Enterocolitis haemorrhagic	1	(0.2)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Hepatitis	**12**	**(2.8)**	**2**	**(0.5)**
Autoimmune hepatitis	3	(0.7)	0	(0.0)
Autoimmune hepatitis	3	(0.7)	0	(0.0)
Grade 1	1	(0.2)	0	(0.0)
Grade 3	2	(0.5)	0	(0.0)
Drug-induced liver injury	1	(0.2)	0	(0.0)
Grade 4	1	(0.2)	0	(0.0)
Hepatitis	7	(1.6)	1	(0.2)
Grade 1	1	(0.2)	1	(0.2)
Grade 3	4	(0.9)	0	(0.0)
Grade 4	2	(0.5)	0	(0.0)
Hepatitis fulminant	0	(0.0)	1	(0.2)
Grade 5	0	(0.0)	1	(0.2)
Immune-mediated hepatitis	1	(0.2)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Hyperthyroidism	**55**	**(12.8)**	**16**	**(3.8)**
Hyperthyroidism	55	(12.8)	16	(3.8)
Grade 1	30	(7.0)	13	(3.1)
Grade 2	20	(4.7)	3	(0.7)
Grade 3	5	(1.2)	0	(0.0)

Hypophysitis	**5**	**(1.2)**	**0**	**(0.0)**
Hypophysitis	5	(1.2)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)
Grade 3	4	(0.9)	0	(0.0)
Hypothyroidism	**152**	**(35.4)**	**134**	**(31.5)**
Hypothyroidism	152	(35.4)	134	(31.5)
Grade 1	49	(11.4)	55	(12.9)
Grade 2	102	(23.8)	78	(18.4)
Grade 3	1	(0.2)	1	(0.2)
Infusion Reactions	**7**	**(1.6)**	**4**	**(0.9)**
Anaphylactic reaction	1	(0.2)	2	(0.5)
Grade 2	0	(0.0)	2	(0.5)
Grade 4	1	(0.2)	0	(0.0)
Drug hypersensitivity	1	(0.2)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)
Hypersensitivity	3	(0.7)	2	(0.5)
Grade 1	3	(0.7)	0	(0.0)
Grade 2	0	(0.0)	1	(0.2)
Grade 3	0	(0.0)	1	(0.2)
Infusion related reaction	2	(0.5)	0	(0.0)
Grade 2	2	(0.5)	0	(0.0)
Myasthenic Syndrome	**4**	**(0.9)**	**0**	**(0.0)**
Myasthenia gravis	4	(0.9)	0	(0.0)
Grade 2	2	(0.5)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Grade 5	1	(0.2)	0	(0.0)
Myocarditis	**2**	**(0.5)**	**0**	**(0.0)**
Myocarditis	2	(0.5)	0	(0.0)
Grade 4	1	(0.2)	0	(0.0)
Grade 5	1	(0.2)	0	(0.0)
Myositis	**4**	**(0.9)**	**0**	**(0.0)**
Myositis	4	(0.9)	0	(0.0)
Grade 1	1	(0.2)	0	(0.0)
Grade 2	2	(0.5)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Nephritis	**6**	**(1.4)**	**1**	**(0.2)**
Autoimmune nephritis	1	(0.2)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)
Nephritis	4	(0.9)	0	(0.0)
Grade 2	3	(0.7)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)

Nephrotic syndrome	0	(0.0)	1	(0.2)
Grade 2	0	(0.0)	1	(0.2)
Tubulointerstitial nephritis	1	(0.2)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)
Pancreatitis	**2**	**(0.5)**	**2**	**(0.5)**
Pancreatitis	2	(0.5)	2	(0.5)
Grade 3	1	(0.2)	2	(0.5)
Grade 4	1	(0.2)	0	(0.0)
Pneumonitis	**12**	**(2.8)**	**1**	**(0.2)**
Interstitial lung disease	1	(0.2)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Pneumonitis	11	(2.6)	1	(0.2)
Grade 1	3	(0.7)	1	(0.2)
Grade 2	7	(1.6)	0	(0.0)
Grade 5	1	(0.2)	0	(0.0)
Severe Skin Reactions	**8**	**(1.9)**	**6**	**(1.4)**
Dermatitis bullous	1	(0.2)	4	(0.9)
Grade 1	0	(0.0)	2	(0.5)
Grade 2	1	(0.2)	1	(0.2)
Grade 3	0	(0.0)	1	(0.2)
Exfoliative rash	2	(0.5)	1	(0.2)
Grade 1	1	(0.2)	1	(0.2)
Grade 2	1	(0.2)	0	(0.0)
Pruritus	1	(0.2)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Rash	1	(0.2)	2	(0.5)
Grade 3	1	(0.2)	2	(0.5)
Rash generalised	1	(0.2)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Rash maculo-papular	2	(0.5)	0	(0.0)
Grade 3	2	(0.5)	0	(0.0)
Thyroiditis	**12**	**(2.8)**	**2**	**(0.5)**
Autoimmune thyroiditis	1	(0.2)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)
Thyroid disorder	0	(0.0)	1	(0.2)
Grade 1	0	(0.0)	1	(0.2)
Thyroiditis	11	(2.6)	1	(0.2)
Grade 1	4	(0.9)	1	(0.2)
Grade 2	6	(1.4)	0	(0.0)
Grade 3	1	(0.2)	0	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.2)**	**0**	**(0.0)**

Diabetic ketoacidosis	1	(0.2)	0	(0.0)
Grade 4	1	(0.2)	0	(0.0)
Uveitis	**2**	**(0.5)**	**0**	**(0.0)**
Uveitis	2	(0.5)	0	(0.0)
Grade 1	1	(0.2)	0	(0.0)
Uveitis	2	(0.5)	0	(0.0)
Grade 2	1	(0.2)	0	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject. Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
AEOSI per ECI guidance excluding Infusion Reactions. Database Cutoff Date: 24Aug2018.

A4. Were any statistical interaction tests performed for the subgroup analyses presented in KEYNOTE-426?

Company response

There were no pre-specified interaction tests performed for subgroup analyses in KEYNOTE-426 [2,3] because at the study design stage, an interaction effect between subgroups was not expected, and the number of subjects within subgroups was expected to be too small to give meaningful results. Therefore, MSD did not pre-specify any interaction tests for subgroups in the statistical analysis plan, and consequently it was not performed or reported in the CSR. However, MSD did conduct statistical interaction analyses to address a request from a regulatory authority. Please see below for further details.

Interaction analyses for OS and PFS on the following subgroups were performed as requested by a regulatory authority:

1) IMDC risk category (favourable, intermediate and poor) versus geographic region (North America, Western Europe and Rest of the World).

2) IMDC risk category (favourable, intermediate and poor) versus PD-L1 status (combined positive score [CPS ≥1] and CPS <1).
3) PD-L1 status (CPS ≥1 and CPS <1) versus geographic region (North America, Western Europe and Rest of the World).

Results of each individual interaction analysis are summarised in Table A4.1 and Table A4.2. For OS analyses, there was remarkable consistency of the HR in most of these subgroups with that of the ITT population. There were only two subgroups, IMDC favourable with CPS <1 and IMDC favourable in Western Europe, with a HR of greater than 1 (1.2 and 1.04, respectively) (Table A4.1); however, there were very few death events in these two subgroups as reflected by the wide confidence intervals (CIs). The size and the number of events for most of these subgroups was small; and the study was not designed to demonstrate statistical significance between the subgroups. Therefore, caution should be used to interpret results from each individual subgroup analysis.

For the PFS analysis, the HR from most of these subgroups were consistent with that of the ITT population. There were only three subgroups with a HR greater than 1: IMDC poor risk patients in North America, participants with IMDC favourable risk and CPS <1, participants from North America with CPS <1 (Table A4.2). As per the OS results, the number of events for most of these subgroups for PFS was relatively small; therefore, caution should be used to interpret results from each individual subgroup analysis.

Table A4.1. Summary of Interaction OS Analysis on Subgroups (ITT Population)

Subgroup 1	Subgroup 2	N (%) of events: Pembrolizumab + Axitinib / Sunitinib	Hazard Ratio‡ (95% CI): Pembrolizumab + Axitinib vs. Sunitinib
IMDC Risk Category vs. Geographic Region			
IMDC Favourable	NA	[redacted]	[redacted]
IMDC Favourable	WEU	[redacted]	[redacted]
IMDC Favourable	ROW	[redacted]	[redacted]
IMDC Intermediate	NA	[redacted]	[redacted]
IMDC Intermediate	WEU	[redacted]	[redacted]
IMDC Intermediate	ROW	[redacted]	[redacted]

IMDC Poor	NA	[redacted]	[redacted]
IMDC Poor	WEU	[redacted]	[redacted]
IMDC Poor	ROW	[redacted]	[redacted]
IMDC Risk Category vs. PD-L1 status			
IMDC Favourable	CPS ≥1	[redacted]	[redacted]
IMDC Favourable	CPS <1	[redacted]	[redacted]
IMDC Intermediate	CPS ≥1	[redacted]	[redacted]
IMDC Intermediate	CPS <1	[redacted]	[redacted]
IMDC Poor	CPS ≥1	[redacted]	[redacted]
IMDC Poor	CPS <1	[redacted]	[redacted]
PD-L1 Status vs. Geographic Region			
CPS ≥1	NA	[redacted]	[redacted]
CPS ≥1	WEU	[redacted]	[redacted]
CPS ≥1	ROW	[redacted]	[redacted]
CPS <1	NA	[redacted]	[redacted]
CPS <1	WEU	[redacted]	[redacted]
CPS <1	ROW	[redacted]	[redacted]

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favourable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).
Abbreviations: NA, North America; WEU, Western Europe; ROW, Rest of the World.
Database Cutoff Date: 24Aug2018.

Table A4.2 Summary of Interaction PFS Analysis on Subgroups (ITT Population)

Comparison	Number (%) of Events: Pembrolizumab + Axitinib / Sunitinib	Median (months) †, (95% CI): Pembrolizumab + Axitinib / Sunitinib	Hazard Ratio‡ (95% CI)
IMDC vs. Region			
IMDC Favourable in NA	[redacted]	[redacted]	[redacted]
IMDC Favourable in WEU	[redacted]	[redacted]	[redacted]
IMDC Favourable in ROW	[redacted]	[redacted]	[redacted]
IMDC Intermediate in NA	[redacted]	[redacted]	[redacted]
IMDC Intermediate in WEU	[redacted]	[redacted]	[redacted]
IMDC Intermediate in ROW	[redacted]	[redacted]	[redacted]
IMDC Poor in NA	[redacted]	[redacted]	[redacted]
IMDC Poor in WEU	[redacted]	[redacted]	[redacted]
IMDC Poor in ROW	[redacted]	[redacted]	[redacted]
IMDC vs. PD-L1			
IMDC Favourable and CPS ≥1	[redacted]	[redacted]	[redacted]

IMDC Favourable and CPS <1	[redacted]	[redacted]	[redacted]
IMDC Intermediate and CPS ≥1	[redacted]	[redacted]	[redacted]
IMDC Intermediate and CPS <1	[redacted]	[redacted]	[redacted]
IMDC Poor and CPS ≥1	[redacted]	[redacted]	[redacted]
IMDC Poor and CPS <1	[redacted]	[redacted]	[redacted]
PD-L1 vs. Region			
CPS ≥1 in NA	[redacted]	[redacted]	[redacted]
CPS ≥1 in WEU	[redacted]	[redacted]	[redacted]
CPS ≥1 in ROW	[redacted]	[redacted]	[redacted]
CPS <1 in NA	[redacted]	[redacted]	[redacted]
CPS <1 in WEU	[redacted]	[redacted]	[redacted]
CPS <1 in ROW	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; CPS = combined positive score; IMDC = International Metastatic RCC Database Consortium; NA = North American; PD-L1 = programmed cell death 1 ligand 1; ROW = Rest of World; WEU = Western European Union

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by International Metastatic RCC Database Consortium (IMDC) risk group (favourable vs. intermediate vs. poor) and geographic region (North America vs. Western Europe vs. Rest of the World).

Database Cutoff Date: 24Aug2018

A5. Were all trial outcomes included in the blinded independent central review results or did any of them have 'further confirmation by the investigator' (as stated for progressive disease, company submission p20)?

Company response

In KEYNOTE-426 [2,3], all trial outcomes were not included in the blinded independent central review (BICR) results or had further confirmation by the investigator. This assessment process was only applied to verify progressive disease (PD) which could impact PFS.

To further explain, KEYNOTE-426 [2,3] study protocol specified that the primary analysis of PFS is based on assessment by blinded independent central review (BICR). In order to reduce censoring on PFS per BICR, the KEYNOTE-426 protocol [4] instituted a process that when the investigator first notified imaging-based progressive disease (PD)

per RECIST 1.1, the site was required to submit an imaging scan immediately to the central imaging company for BICR, to verify evidence of PD. If PD was verified by the BICR, the investigator may have continued to treat patient, if the patient was clinically stable as determined by the investigator, until another scan in > 4 weeks to confirm PD. The rationale to include such PD confirmation step was based on the observation that patients who receive immunotherapy may have pseudo-progression. Therefore, not all patients who had BICR verified PD had further scan at site to confirm PD.

A6. Please clarify the numbers and proportions of participants in KEYNOTE-426 that were from Europe? Page 43 of the company submission reports 55% which ties in with n=475 reported on page 23, but table 7 says 36.8% (n=317).

Company response

The company submission contains figures and proportions which relate to both enrolment and randomisation of the patients for KEYNOTE-426 [2,3].
Specifically, pages 43 and 23 in the company submission report the proportion (55%) and the number of patients (475), respectively, enrolled within KEYNOTE-426 in Europe. In contrast, Table 7 of the company submission (labelled "Subject Characteristics - ITT Population") presents baseline characteristics and related figures and proportion of European patients after randomisation (which equals to 317 (36.8%)). The difference between the enrolled and randomised figures is due to the fact that some of the patients enrolled were not randomised.

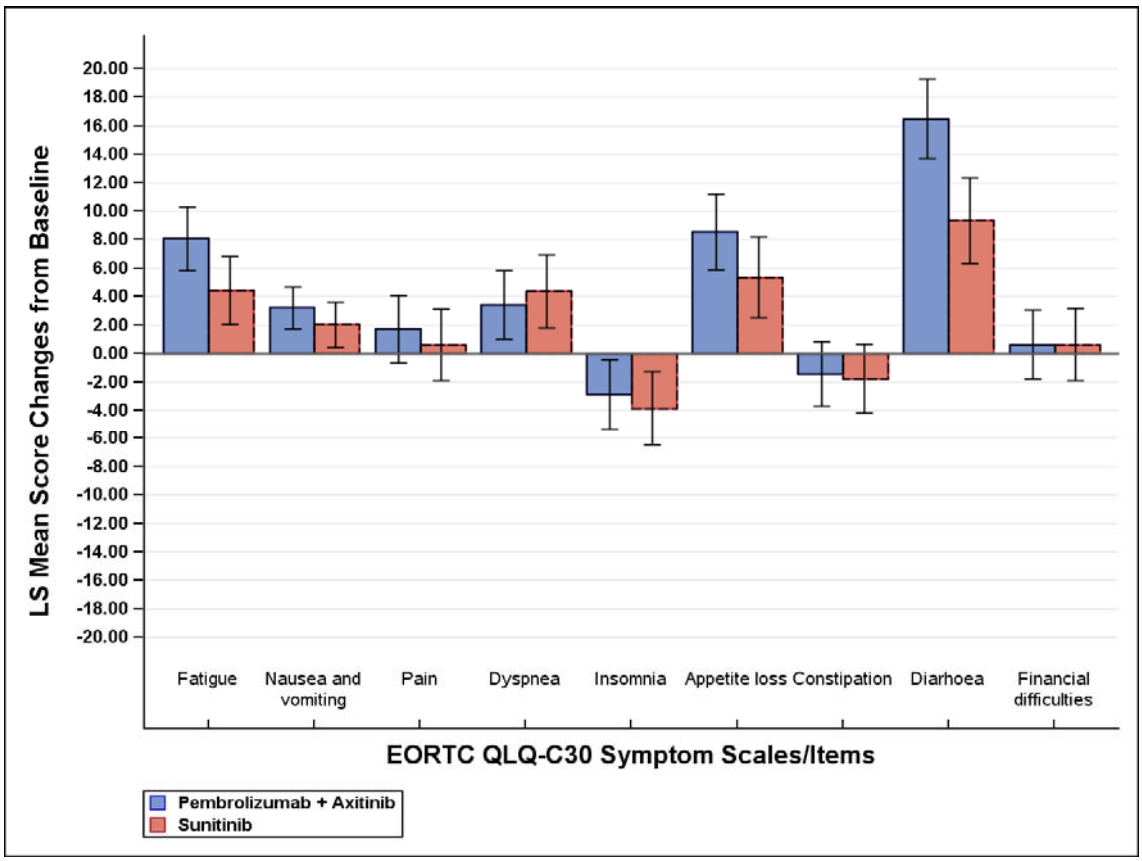
A7. Only selected scales from the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) are presented in the submission (physical functioning, role functioning, nausea/vomiting, diarrhoea). Please provide results for all scales.

Company response

A total of 851 subjects in the FAS population for the EORTC QLQ-C30 questionnaire were used for the analysis. Please find results for the symptom scale, which was not originally provided in the company submission, in Figure A7.1.

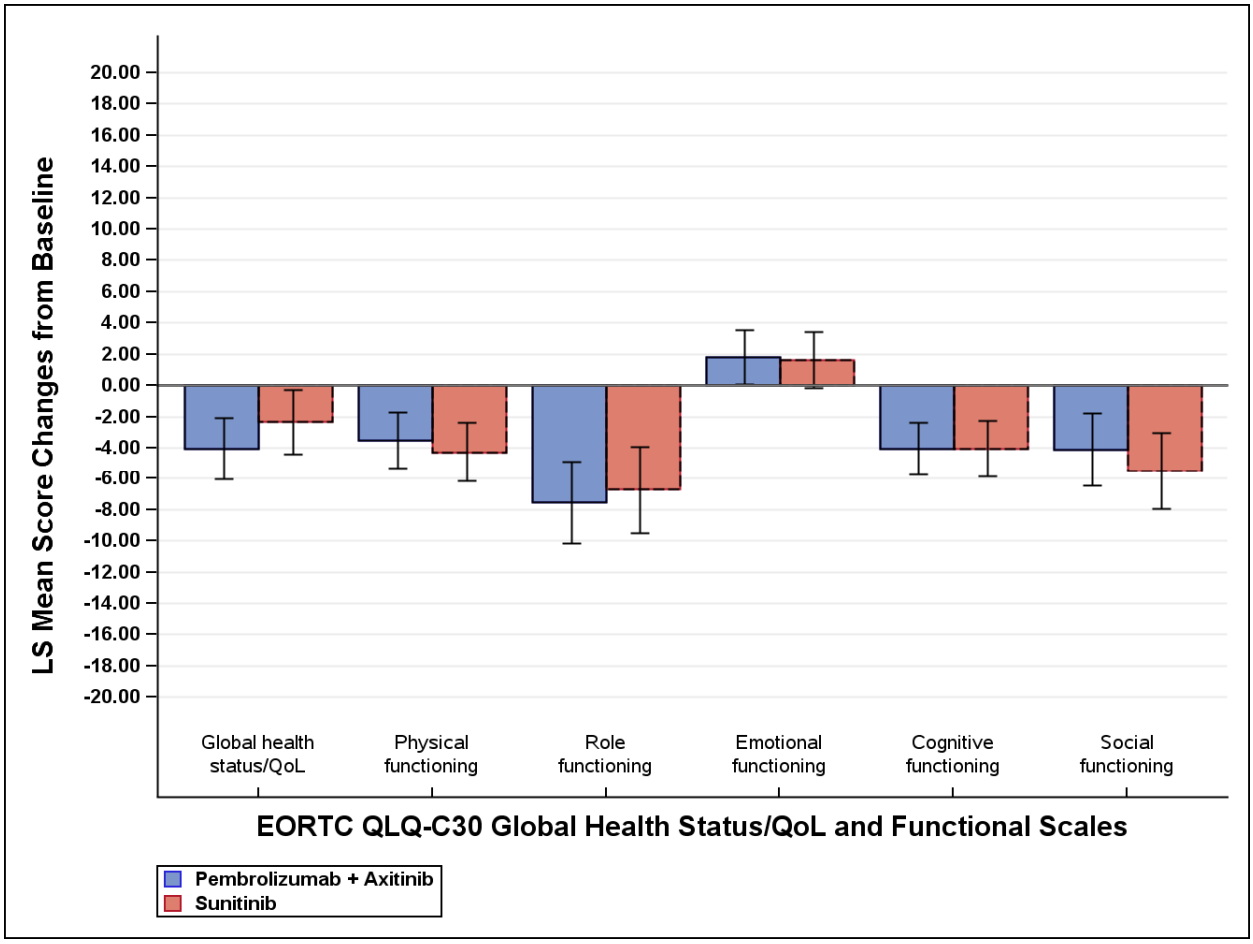
Additionally, Figure A7.2 provides a better resolution graph for the change from baseline for EORTC QLQ-C30 Global Health Status/QoL and Functional Scales at Week 30 as compared to the one provided in the company submission within the Appendices (Appendix L, Figure 6).

Figure A7.1 Change from Baseline for EORTC QLQ-C30 Symptom Scales/Items at Week 30 LS Mean Change and 95% CI (FAS Population)



For symptoms scales: a higher score denotes worse symptoms.
Database Cutoff Date: 24AUG2018.

Figure A7.2 Change from Baseline for EORTC QLQ-C30 Global Health Status/QoL and Functional Scales at Week 30 LS Mean Change and 95% CI (FAS Population)



For global health status/quality of life score and all functional scales: a higher score denotes better health related quality of life (HRQOL) or function.
Database Cutoff Date: 24AUG2018.

A8. Please provide EQ-5D-3L index data at baseline and week 30 for each treatment, and any statistical analysis comparing these.

Company response

Please refer to Table A8 for the EQ-5D-3L index data at baseline and at week 30 for pembrolizumab + axitinib and sunitinib and the results of the pairwise comparison.

Table A8. EQ-5D-3L index data at baseline and at week 30

Treatment	Baseline		Week 30		Change from Baseline at Week 30	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†

Pembrolizumab + Axitinib	390	0.819 (0.2030)	291	0.827 (0.1943)	427	-0.005 (-0.026, 0.016)
Sunitinib	406	0.792 (0.2308)	248	0.819 (0.2070)	421	-0.013 (-0.035, 0.010)
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab + Axitinib vs. Sunitinib					0.007 (-0.022, 0.037)	0.619

† Based on cLDA model with the PRO scores as the response variable, and treatment by timepoint interaction, stratification factors (international metastatic RCC database consortium (IMDC) risk group (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus "Rest of the World")) as covariates.

For baseline and Week 30, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Two-sided p-value.

Database Cutoff Date: 24AUG2018.

The following analysis of mean score change from baseline was applied to EQ-5D UK index score.

To assess the treatment effects on EQ-5D UK, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [5] was used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points.

Based on the cLDA model, group-wise comparisons were performed and the differences in the LS mean change from baseline were reported, together with 95% CI and nominal p-value at the primary analysis time points (Week 30). In addition, model-based LS mean score with 95% CI were provided by treatment group and study visit.

The analysis of mean change is based primarily under the assumption of missing-at-random (MAR) mechanism. The cLDA model implicitly treats missing data as MAR.

Network meta-analysis

A9. Priority question. Two interferon alpha trials (Motzer, 2007; Escudier, 2009) have been used to connect the evidence network to tivozanib. Please clarify how these studies were identified and selected, and whether there are any other relevant studies which could have been used? No study or patient characteristics for these studies are provided in tables 21/22 of the submission or in appendix D, tables 14-17. Please add these studies to the respective tables. We also note that there is a later publication of the Motzer trial which reports updated results. Please confirm whether the updated results are appropriate to use in the network meta-analysis
(NMA), and if so re-run the NMA with these results. (Motzer et al, 2009. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology).

Company response

Motzer, 2007 [6] and Escudier, 2009 [7] studies were selected and identified based on PICOS criteria for a broader systematic literature review (SLR) search, which was designed for global purposes to meet the HTA needs of multiple countries and to identify literature related to three distinct populations:

1) First-line (1L) clear cell mRCC
2) 1L non-clear cell mRCC and,
3) Second-line plus (2L+) clear cell mRCC.

Results from the broader literature search, were then pared down to fit the context relevant to only the 1LCC mRCC population, which included interventions of interest relevant to the global context. Finally, SLR results were further pared down to include interventions only of interest for the UK context. For this reason, Escudier 2009 [7] and Motzer 2007 [6] were originally excluded at the full text review stage (see Appendix D, Table 9 of company submission) due to the interventions not being relevant for the UK.

However, one intervention of interest and relevant to the UK scope, tivozanib, was not connected to the network of evidence. Therefore, interventions that were originally not of interest for the UK, such as IFN-α and sorafenib, were introduced into the UK-specific network of evidence from the global SLR context, to obtain relative treatment effects of tivozanib and competing interventions relevant to the UK. Based on our latest literature search (conducted in February 2019), no other studies were identified that could be used and fit the PICOS criteria; and facilitated a connection of tivozanib to the network of evidence with UK-specific interventions.

Motzer 2009 [8] was identified in the global SLR and provided data for the ITT population, however, did not provide updated subgroup data for risk and age. Updated data from Motzer 2009 was used in base case analyses, however, naming conventions for results consisted of primary author and year of the primary publication even in cases where subsequent publication data was used in the NMA (see additional information provided in response to question A18).

Tables A9.1 - 4 have been updated from the original presented in the company submission (Table 21 of main submission and Tables 14-17 of Appendix D) to reflect the addition of Escudier 2009 [7] and Motzer 2007 [6] as requested. Table 22 of the main submission presents the base case results for constant HRs for PFS and already includes both studies as replicated below in Table A9.5.

Table A9.1. Treatment characteristics of trials included

Trial ID	Treatment	Agent 1	Agent 2
CABOSUN	Cabozantinib	Cabozantinib, PO 60mg, once daily UDP	--
	Sunitinib	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
COMPARZ	Pazopanib	Pazopanib, PO 800mg, once daily UDP	--
	Sunitinib	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
Escudier 2009	Sorafenib	Sorafenib, PO 400mg twice daily UDP	--
	Interferon	Interferon, SC 9 million units, three times weekly UDP	--

Trial ID	Treatment	Agent 1	Agent 2
KEYNOTE-426	Pembrolizumab + axitinib	Pembrolizumab, IV 200mg, every three weeks	Axitinib, PO 5mg, twice daily UDP
	Sunitinib	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
Motzer 2007	Sunitinib	Sunitinib, PO 50mg, D1-28 of 6 week cycle UDP	--
	Interferon alpha	Interferon, SC 9 million units, three times weekly UDP	--
TIVO-1	Tivozanib	Tivozanib, PO 1.5mg, once daily UDP	--
	Sorafenib	Sorafenib, PO 400mg twice daily UDP	--

Table A9.2. Patient characteristics of randomized controlled trials included in the feasibility assessment

Trial ID	Intervention	N	Median age (range)	Female (%)	Caucasian (%)	Asian (%)
CABOSUN	Cabozantinib	79	63 (40-82)	13 (16.5)	70 (88.6)	1 (1.3)
	Sunitinib	78	64 (21-87)	21 (26.9)	75 (96.2)	0 (0.0)
COMPARZ	Pazopanib	557	61 (18-88)	159 (29.0)	--	--
	Sunitinib	553	62 (23-86)	138 (25.0)	--	--
Escudier 2009	Sorafenib	97	62 (34-78)	32 (33.0)	--	--
	Interferon	92	62 (18-80)	40 (43.5)	--	--
KEYNOTE-426	Pembrolizumab + axitinib	432	62 (30-89)	124 (28.7)	343 (79.4)	66 (15.3)
	Sunitinib	429	61 (26-90)	109 (25.4)	341 (79.5)	71 (16.6)
Motzer 2007	Sunitinib	375	62 (27-87)	108 (29.0)	--	--
	Interferon	375	59 (34-85)	106 (28.0)	--	--
TIVO-1	Tivozanib	260	59 (23-83)	75 (29.0)	249 (96.0)	10 (4.0)
	Sorafenib	257	59 (23-85)	68 (26.0)	249 (97.0)	8 (3.0)

Table A9.3. Distribution of performance score and risk score of randomized controlled trials included in feasibility assessment

Trial ID	Intervention	N	ECOG 0 (%)	ECOG 1 (%)	ECOG 2 (%)	MSKCC favourable (%)	MSKCC intermediate (%)	MSKCC poor (%)
CABOSUN	Cabozantinib	79	36 (45.6)	33 (41.8)	10 (12.7)	--	--	--
	Sunitinib	78	36 (46.2)	32 (4.01)	10 (12.8)	--	--	--
COMPARZ	Pazopanib	557	--	--	--	151 (27.0)	322 (58.0)	67 (12.0)
	Sunitinib	553	--	--	--	152 (27.0)	328 (59.0)	52 (9.0)
Escudier 2009	Sorafenib	97	56 (57.7)	41 (42.3)	--	52 (53.6)	44 (45.4)	1 (1.0)
	Interferon	92	49 (53.3)	43 (46.7)	--	47 (51.1)	44 (47.8)	0 (0.0)
KEYNOTE-426*	Pembrolizumab + axitinib	432	--	--	--	138 (31.9)	238 (55.1)	56 (13.0)
	Sunitinib	429	--	--	--	131 (30.5)--	246 (57.3)	52 (12.1)
Motzer 2007	Sunitinib	375	231 (62.0)	144 (38.0)	--	143 (38.0)	209 (56.0)	23 (6.0)
	Interferon	375	229 (61.0)	146 (39.0)	--	121 (34.0)	212 (59.0)	25 (7.0)
	Tivozanib	260	116 (45.0)	144 (55.0)	--	--	--	--

Trial ID	Intervention	N	ECOG 0 (%)	ECOG 1 (%)	ECOG 2 (%)	MSKCC favourable (%)	MSKCC intermediate (%)	MSKCC poor (%)
TIVO-1	Sorafenib	257	139 (54.0)	118 (46.0)	--	--	--	--

**Trial reports IMDC risk score, not MSKCC risk score*

Table A9.4. Distribution of prior non-systemic treatment and metastatic sites of randomized controlled trials included in the feasibility assessment

Trial ID	Intervention	N	Prior nephrectomy (%)	Prior radiotherapy (%)	Lung metastases (%)	Bone metastases (%)	Liver metastases (%)	Lymph node metastases (%)
CABOSUN	Cabozantinib	79	57 (72.2)	6 (7.6)	--	29 (36.7)	--	--
	Sunitinib	78	60 (76.9)	14 (17.9)	--	28 (35.9)	--	--
COMPARZ	Pazopanib	557	459 (82.0)	46 (8.0)	424 (76.0)	110 (20.0)	86 (15.0)	223 (40.0)
	Sunitinib	553	465 (84.0)	42 (8.0)	425 (77.0)	85 (15.0)	110 (20.0)	247 (45.0)
Escudier 2009	Sorafenib	97	95 (97.9)	22 (22.7)	84 (86.6)	31 (32.0)	24 (24.7)	54 (55.7)
	Interferon	92	83 (90.2)	12 (13.0)	74 (80.4)	34 (37.0)	19 (20.7)	43 (46.7)
KEYNOTE-426	Pembrolizumab + axitinib	432	357 (82.6)	41 (9.5)	312 (72.2)	103 (23.8)	66 (15.3)	199 (46.1)
	Sunitinib	429	358 (83.4)	40 (9.3)	309 (72.0)	103 (24.0)	71 (16.6)	197 (45.9)
Motzer 2007	Sunitinib	375	340 (91.0)	53 (14.0)	292 (78.0)	112 (30.0)	99 (26.0)	218 (58.0)
	Interferon	375	335 (89.0)	54 (14.0)	298 (79.0)	112 (30.0)	90 (24.0)	198 (53.0)
TIVO-1	Tivozanib	260	--	--	212 (82.0)	61 (23.0)	67 (26.0)	182 (70.0)
	Sorafenib	257	--	--	204 (79.0)	52 (20.0)	49 (19.0)	166 (65.0)

Table A9.5. From Table 22 of main submission: Constant HRs for PFS; base case

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
COMPARZ	Sunitinib	Pazopanib	[redacted]	[redacted]
Escudier 2009	IFN-α	Sorafenib	[redacted]	[redacted]
KEYNOTE-426 (IA1 Aug 2018 data cut) [16] [17]	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]
Motzer 2007	Sunitinib	IFN-α	[redacted]	[redacted]
TIVO-1* [26]	Sorafenib	Tivozanib	[redacted]	[redacted]

*Note: * denotes trials in grey used subgroup first-line data*
Grey rows represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.

A10. We note the between-study heterogeneity and company's preference for fixed effects given insufficient data to perform a random effects model. Could an informative prior (e.g. Turner, 2015) have been used for the random effects? If so, please re-run the NMA using random effects.

Company response

Although informative prior distributions can be used in cases where few studies are available to connect treatments in a network of evidence, the use of informative priors require either expert opinion or meta-epidemiological data for the specific indication and outcome of interest to determine what informative priors are best. To our knowledge, there is no meta-epidemiological data for 1LCC mRCC data that can be used at this point in time to determine what informative prior distributions are best for OS and PFS outcomes in the ITT and intermediate/poor risk populations. Furthermore, as per the guidelines outlined by Zonderven-Zwijneburg et al., 2017 [9], the search for prior information requires ample time to conduct an SLR or targeted literature search to find literature that encompasses the same outcomes within the same population. Once this is finished, priors are agreed upon by researchers, clinical experts, or confirmed by previous meta-epidemiological studies. Once visualisation and construction of informative priors have been agreed upon, the Bayesian analysis using MCMC methods is conducted along with multiple sensitivity analyses to demonstrate and asses the validity of the chosen informative priors. The process to ensure informative priors are correctly informing the posterior distribution requires time and

resources. Given the time constraint and lack of meta-epidemiological data for this indication and time-to-event outcomes, the use of informative priors to inform between-study heterogeneity is not recommended and is not possible to conduct within the given time frame.

A11. Please explain why you chose to test fractional polynomials with a relatively narrow range of powers (P1 in the range 0,1, and P2 in the range -1 to +1). Did you consider trying other functional forms?

Company response

First order fractional polynomial models with p1=0 and p1=1 correspond to the Weibull and Gompertz survival function, respectively. These models only allow for monotonically increasing or decreasing hazard functions. Adding a second time-related factor with P2 provides more flexibility and allows for (inverted) u-shaped hazard curves as well. As such, the 2nd order fractional polynomials with p1=0 or p1=1 can be considered flexible extensions of the Weibull and Gompertz models. We have generally found that the set of 2nd order fractional polynomial NMA models according to p1= 0 or 1 in combination with p2=0 or 1 were sufficiently flexible to capture the underlying true hazards according to observed data in a variety of tumour types. However, in rare cases the addition of negative powers for p2 (i.e. -1, -0.5) may yield models with meaningful lower DIC values (e.g. 10 points), indicating they are a better fit to data (see A12). The analyses with additional values for p2 (spanning -1 to +1) are included in a separate results document, as requested in A12. Fractional polynomial models with values for p2 outside the range of -1 to +1 (i.e. -2 and 2) were not considered as these models are too sensitive to "outliers" in the observed data and can result in hazard curves not properly reflecting the true underlying hazard rates.

A12. Priority question. The submission states a wide range of fractional polynomial models were run, p1=0,1, p2=-1,0.5,0,0.5,1 (appendix D1.2.3). However, only the p1=0,1 and p2=0,1 model fit results are presented (appendix M). Please confirm these other models were run and present the model fit statistics for all fractional polynomial models.

Company response

Additional fit statistics with the other requested additional 2nd order fractional polynomial NMA models are provided in Appendix 1. The best fitting models, as determined by the lowest DIC, remained the same as selected for the original analyses included in the submission, with one exception. Upon inclusion of p2 powers ranging from -1 to +1, the model for the intermediate/poor risk subgroup for PFS with the lowest DIC, is now the 2nd order fractional polynomial model with p1=0, p2=-1 (DIC: 441.56, Deviance: 431.74) (Appendix 1: Figure 50, Tables 103-104) rather than the model with p1=0, p2=0 (DIC: 455.94, Deviance: 445.86) (Appendix M of the company submission: Figure 6, Tables 8-9) as originally deemed the best fitting. However, given the nearly identical time-varying hazard ratios (HRs) throughout follow-up with these two models (see Figure A12.1-2 and Table A12 below), it can be concluded that the results obtained with the original model (p1=0 and p2=0) are an appropriate reflection of the relative treatment effects over time.

Please note that the addition of cabozantinib to the base case analysis, referred to as the "base case, sensitivity analysis" (requested in question A22), is also provided in Appendix 1 (Figures: 7-8, 31-49, Tables: 11-20, 65-102). All time-varying HR obtained with the additional NMA models (p1= 0 or 1, p2=-1 to +1) are presented in the supplementary document for the base case, sensitivity analysis.

Figure A12.1 Estimated HRs pf PFS; intermediate and poor risk subgroup – treatment effect as HR over time relative to sunitinib (2nd order FP model (p1=0 p2=-1))

Figure A12.2 Estimated HRs pf PFS; intermediate and poor risk subgroup – treatment effect as HR over time relative to sunitinib (2nd order FP model (p1=0 p2=0))

Table A12. Time-varying hazard ratios of progression-free survival at select follow-up times for competing interventions vs sunitinib; intermediate/poor risk subgroup

Mos.	2nd order FP model (p1=0 p2=-1)) HR vs. sunitinib (95% CrI)	Original model: 2nd order FP model (p1=0 p2=0))

			HR vs. sunitinib (95% CrI)	
	Pembrolizumab + axitinib	Cabozantinib	Pembrolizumab + axitinib	Cabozantinib
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]

A13. It appears that the fractional polynomial model with the lowest Deviance Information Criterion (DIC) value was chosen, but were any other considerations taken into account in the choice of model fit? (E.g. the clinical plausibility of the model chosen with respect to progression-free survival (PFS) and overall survival (OS) curves as observed in the trials).

Company response

In general, the best-fitting fractional polynomial model was chosen based on the lowest DIC value; however, clinical plausibility was also considered insofar as checking if time-varying HR results were relatively stable across fractional polynomial models and cross-referencing time-varying HRs with published constant HRs for included studies.

A14. Priority question. Please present time-varying hazard ratio plots and tabulated time-varying hazard ratios for each of the fractional polynomial models fitted for overall survival and progression-free survival. Presently these are only provided for the best fitting model. This will enable the ERG to compare variation in hazard ratios between different order models.

Company response

Results of time-varying hazard ratio plots and tabulated time-varying HRS for each of the fractional polynomial models fitted for OS and PFS are presented in Appendix 1 (Figures: 1-4, 9-30, 50-67 Tables: 1-10, 21-30, 103-138).

A15. Please provide the hazard ratio plots from the fractional polynomial network meta-analyses (in appendix M and N) without the entire plot shaded in blue for

commercial in confidence. On some of the plots it is difficult to observe the colours of the hazard lines and thus which treatment the line represents.

Company response

Please find below the HR plots from the fractional polynomial NMA originally presented in Appendix M and N with the commercial in confidence (CIC) blue shading lifted from the plot. However, these plots should still be considered as CIC, as denoted by the blue highlighting of the figure titles.

Base case, PFS - August 2018 data-cut (Appendix M)

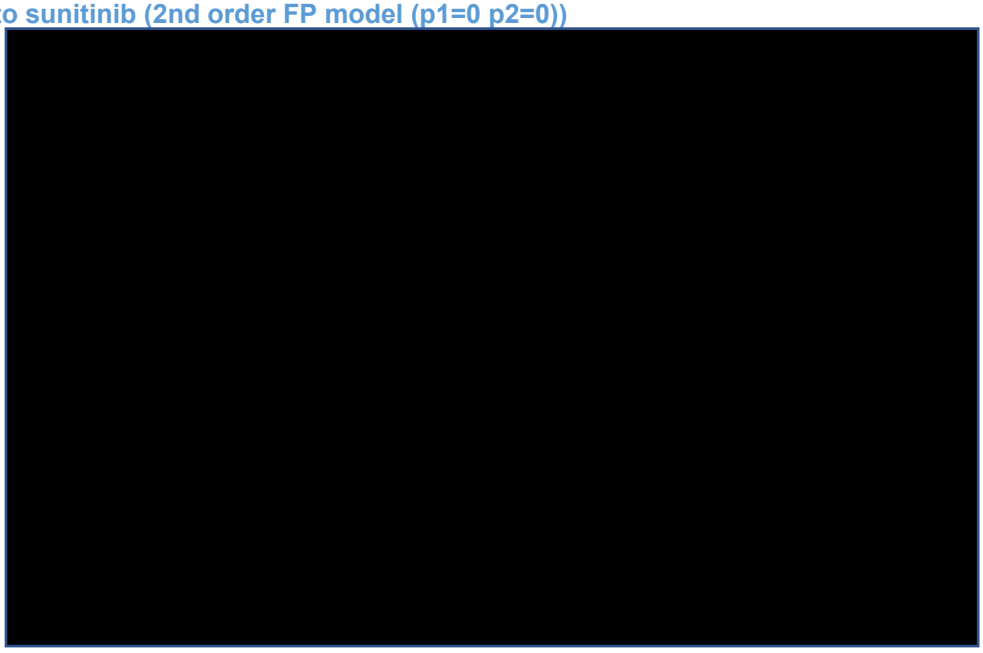
Figure A15.1 From Figure 2 Appendix M - Results of fixed-effects network meta-analysis of progression-free survival; base-case analysis; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=0 p2=0)) without blue shading

Base case, OS - August 2018 data-cut (Appendix M)

Figure A15.2 From Figure 4 Appendix M - Results of fixed-effects network meta-analysis of overall survival; base-case analysis; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=0 p2=0))

PFS intermediate/poor subgroup - August 2018 data-cut (Appendix M)

Figure A15.3 From Figure 6 – Appendix M. Results of fixed-effects network meta-analysis of progression-free survival; intermediate/poor risk; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=0 p2=0))



OS intermediate/poor subgroup - August 2018 data-cut (Appendix M)

Figure A15.4 From Figure 7 – Appendix M. Results of fixed-effects network meta-analysis of overall survival; intermediate/poor risk; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=1, p2=0))

Base case, PFS – January 2019 data-cut (Appendix N)

Figure A15.5 From Figure 7 – Appendix N. Results of fixed-effects network meta-analysis of progression-free survival; base-case analysis; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=0 p2=0))

Base case, OS – January 2019 data-cut (Appendix N)

Figure A15.6 From Figure 8 – Appendix N. Results of fixed-effects network meta-analysis of overall survival; base-case analysis; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=0 p2=0))

PFS intermediate/poor subgroup – January 2019 data-cut (Appendix N)

Figure A15.7 From Figure 9 – Appendix N. Results of fixed-effects network meta-analysis of progression-free survival; intermediate/poor risk; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=0 p2=0))

OS intermediate/poor subgroup – January 2019 data-cut (Appendix N)

Figure A15.8 From Figure 10 – Appendix N. Results of fixed-effects network meta-analysis of overall survival; intermediate/poor risk; treatment effects as hazard ratio over time relative to sunitinib (2nd order FP model (p1=1, p2=0))

A16. Please summarise the evidence in favour of proportional/non-proportional hazards in the NMA. Whilst there is some discussion (section B2.9.4) regarding the intermediate/poor subgroup and figures 19/20 (OS) and 26/27 (PFS) show the proportional hazards assumption is violated for KEYNOTE-426, is there further evidence of non-proportional hazards?

Company response

By visual inspection as well as constructing a 95% credible interval (CrI) around d1, the time-varying parameter estimate of each intervention from the best-fitting fractional polynomial model, there is potential violation of the proportional hazard assumption for the analysis of PFS (tivozanib, sorafenib, and IFN-α versus sunitinib) and the analysis of OS in the intermediate/poor risk subgroup (pembrolizumab versus sunitinib). However, it is important to recognise that in these scenarios, results from constant HR NMAs may still be considered appropriate. Specifically, in scenarios where follow-up is relatively short, such as Escudier 2009 [7], which facilitates the connection of tivozanib to sunitinib, in the base case PFS analysis. Tails of Kaplan-Meier (KM) curves may become unstable due to heavy censoring when follow-up is relatively short, contributing to uncertainty as seen in wider CrIs in the tails of the time-

varying HR NMA. Furthermore, when the sample size of the at-risk population becomes low at the end of follow-up, such as observed in the OS analysis of the intermediate/poor risk subgroup, 2nd order fractional polynomial models are more sensitive and detect "chance" fluctuations in the observed hazard in the tail ends of follow-up. In both of these scenarios, relative treatment effects are extrapolated beyond the provided trial data and may be considered unrealistic. Therefore, we recognise that violations to the proportional hazards' assumption were observed in these two scenarios, but the constant HR NMA results are still considered appropriate given the increased uncertainty due to short follow-up and low numbers of events.

Constant HR analyses were considered appropriate for the base case OS analysis and intermediate/poor risk PFS analysis based on visual inspection as well as constructed 95% CrIs of the d1 estimates for the best-fitting fractional polynomial model.

A17. Priority question. Please provide the R and OpenBUGS code for the best fitting fractional polynomial model for OS and PFS.

Company response

```
# Fixed effects
#p0 FE
Run_Survival_NMA(effect="FE",P1=0,P2=NULL,maxt=maxt,NBURNIN=20
000,NITER=40000,NTHIN=3, parameters = c("d",  "S", "HR1",
"HRmaxtx", "HAZARD", "best", "mu_mean"),CODAsave=T,Npred=0,
diagparams=c("d"),zerods = c(1,1))
#p1 FE
Run_Survival_NMA(effect="FE",P1=1,P2=NULL,maxt=maxt,NBURNIN=20
000,NITER=40000,NTHIN=3, parameters = c("d",  "S", "HR1",
"HRmaxtx", "HAZARD", "best", "mu_mean"),CODAsave=T,Npred=0,
diagparams=c("d"),zerods = c(1,1))
#p0 p0 FE
Run_Survival_NMA(effect="FE",P1=0,P2=0,maxt=maxt,NBURNIN=20000
,NITER=40000,NTHIN=3, parameters = c("d",  "S", "HR1",
"HRmaxtx", "HAZARD", "best", "mu_mean"),CODAsave=T,Npred=0,
diagparams=c("d"),zerods = c(1,1,0))
#p0 p1 FE
Run_Survival_NMA(effect="FE",P1=0,P2=1,maxt=maxt,NBURNIN=20000
,NITER=40000,NTHIN=3, parameters = c("d",  "S", "HR1",
"HRmaxtx", "HAZARD", "best", "mu_mean"),CODAsave=T,Npred=0,
diagparams=c("d"),zerods = c(1,1,0))
#p1 p0 FE
```

```
Run_Survival_NMA(effect="FE",P1=1,P2=0,maxt=maxt,NBURNIN=20000
,NITER=40000,NTHIN=3, parameters = c("d",  "S", "HR1",
"HRmaxtx", "HAZARD", "best", "mu_mean"),CODAsave=T,Npred=0,
diagparams=c("d"),zerods = c(1,1,0))
#p1 p1 FE
Run_Survival_NMA(effect="FE",P1=1,P2=1,maxt=maxt,NBURNIN=20000
,NITER=40000,NTHIN=3, parameters = c("d",  "S", "HR1",
"HRmaxtx", "HAZARD", "best", "mu_mean"),CODAsave=T,Npred=0,
diagparams=c("d"),zerods = c(1,1,0))
# RUN JAGS
jags1 <- suppressWarnings(jags.model(  file = MODELFILE, data
= data, #inits=inits,
                                       n.chains = 2, n.adapt
= NBURNIN)   )
print(paste0('part 1 jags.model( file = MODELFILE, data =
data, n.chains = 2, n.adapt = ',NBURNIN,') complete'))
update(jags1,NBURNIN)
print(paste0('part 2 update(jags1,',NBURNIN,') burn-in
complete'))
monitorparms=parameters
jags.out <- coda.samples(jags1, monitorparms, n.iter = NITER1,
thin = NTHIN)
```

Fixed effects, 1st order fractional polynomial OpenBUGS code:

```
Model{
for (i in 1:N){
timen[i]<-(time[i])     # time is expressed in months
timen1[i]<-(equals(P1,0)*log(timen[i]) + (1-
equals(P1,0))*pow(timen[i],P1)   )

# likelihood
r[i]~dbin(p[i], z[i])
p[i]<-1-exp(-h[i]*dt[i])  # cumulative hazard over interval
[t,t+dt] expressed as success per person-month
#Fixed effects model
log(h[i])<- Beta[s[i],a[i],1]+Beta[s[i],a[i],2]*timen1[i]
}
for (l in 1:Ns){
for (ll in 1:na[l]){
Beta[l,ll,1]<-mu[l,1] + (equals(scaleeffect,1)*(d[t[l,ll],1]-
d[t[l,1],1]))
Beta[l,ll,2]<-mu[l,2] +
(equals(firstshapeeffect,1)*(d[t[l,ll],2]-d[t[l,1],2]))
}
}
#priors
for (j in 1:Ns){
mu[j,1:2] ~ dmnorm(mean[1:2],prec[,])
```

```
}
d[1,1]<-0
d[1,2]<-0

for (k in 2:Ntx){
d[k,1:2] ~ dmnorm(mean2[1:2],prec2[,])
}
#Output
for (m in 1:maxt){
time1[m]<-(equals(P1,0)*log(m) + (1-equals(P1,0))*pow(m,P1)
)
}

for (nn in 2:Ntx){
for (m in 1:maxt){
log(HR1[1,nn,m])<-(equals(scaleeffect,1)*(d[nn,1]-
d[1,1]))+(equals(firstshapeeffect,1)*(d[nn,2]-
d[1,2])*time1[m])
}
}
for (n in 1:(Ntx-1)){
for (m in 1:maxt){
log(HRmaxtx[n,Ntx,m])<-(equals(scaleeffect,1)*(d[Ntx,1]-
d[n,1]))+(equals(firstshapeeffect,1)*(d[Ntx,2]-
d[n,2])*time1[m])
}
}

for (i in 1: Ns){
mu1[i,1] <- mu[i,1]*equals(t[i,1],1)
mu1[i,2] <- mu[i,2]*equals(t[i,1],1)
st1[i] <- equals(t[i,1],1)
}
mu_mean[1]<- (equals(UD,1)*mu[anchortrial,1] + (1-
equals(UD,1))*(sum(mu1[,1])/sum(st1[])))
mu_mean[2]<- (equals(UD,1)*mu[anchortrial,2] + (1-
equals(UD,1))*(sum(mu1[,2])/sum(st1[])))

for (n in 1:Ntx){
beta1[n]<-mu_mean[1]+(equals(scaleeffect,1)*d[n,1])
beta2[n]<-mu_mean[2]+(equals(firstshapeeffect,1)*d[n,2])
}
for (n in 1:Ntx){
for (m in 1:maxt){
log(HAZARD[n,m])<-
(mu_mean[1]+(equals(scaleeffect,1)*d[n,1]))+(mu_mean[2]+(equal
s(firstshapeeffect,1)*d[n,2]))*time1[m]
CUM_H[n,m]<-sum(HAZARD[n,1:m])
T[n,m]<-1-exp(-CUM_H[n,m])
S[n,m]<-1-T[n,m]
```

```
Ssum[n,m]<-sum(S[n,1:m])
rk[n,m]<-Ntx+ 1- rank(Ssum[,m],n)
best[n,m]<-equals(rk[n,m],1)
}}
for (n in 1:Ntx){
Mean_surv[n]<-sum(S[n,])
}
for (n in 1:(Ntx-1)) {
for (nn in (n+1):Ntx) {
Mean_surv_diff[n,nn]<-Mean_surv[nn]-Mean_surv[n]
}}
}
}
```

Fixed-effects, 2nd order fractional polynomial OpenBUGS code:

```
Model{
for (i in 1:N){
timen[i]<-(time[i])    # time is expressed in months
timen1[i]<-(equals(P1,0)*log(timen[i]) + (1-
equals(P1,0))*pow(timen[i],P1)   )
timen2[i]<-(  (1-equals(P2,P1))*(   equals(P2,0)*log(timen[i])
+ (1-equals(P2,0))*pow(timen[i],P2)  ) +
equals(P2,P1)*(   equals(P2,0)*log(timen[i])*log(timen[i])   +
(1-equals(P2,0))*pow(timen[i],P2) *log(timen[i])   )   )
# likelihood
r[i]~ dbin(p[i],z[i])
p[i]<-1-exp(-h[i]*dt[i])  # cumulative hazard over interval
[t,t+dt] expressed as deaths per person-month
#Fixed effects model
log(h[i])<- Beta[s[i],a[i],1]+Beta[s[i],a[i],2]*timen1[i]+
Beta[s[i],a[i],3]*timen2[i]
}
for (l in 1:Ns){
for (ll in 1:na[l]){
Beta[l,ll,1]<-mu[l,1] + (equals(scaleeffect,1)*(d[t[l,ll],1]-
d[t[l,1],1]))
Beta[l,ll,2]<-mu[l,2] +
(equals(firstshapeeffect,1)*(d[t[l,ll],2]-d[t[l,1],2]))
Beta[l,ll,3]<-mu[l,3] +
(equals(secondshapeeffect,1)*(d[t[l,ll],3]-d[t[l,1],3]))
}
}
#priors
for (j in 1:Ns){
mu[j,1:3] ~ dmnorm(mean[1:3],prec[,])
}
d[1,1]<-0
d[1,2]<-0
d[1,3]<-0
```

```
for (k in 2:Ntx){
d[k,1:3] ~ dmnorm(mean2[1:3],prec2[,])
}
#Output
for (m in 1:maxt){
time1[m]<-(equals(P1,0)*log(m) + (1-equals(P1,0))*pow(m,P1)
)
time2[m]<-(  (1-equals(P2,P1))*(   equals(P2,0)*log(m) + (1-
equals(P2,0))*pow(m,P2)  ) +
equals(P2,P1)*(   equals(P2,0)*log(m)*log(m)   +   (1-
equals(P2,0))*pow(m,P2) *log(m)   )   )
}
for (nn in 2:Ntx){
for (m in 1:maxt){
log(HR1[1,nn,m])<-(equals(scaleeffect,1)*(d[nn,1]-
d[1,1]))+(equals(firstshapeeffect,1)*(d[nn,2]-
d[1,2])*time1[m])+(equals(secondshapeeffect,1)*(d[nn,3]-
d[1,3])*time2[m])
}
}
for (n in 1:(Ntx-1)){
for (m in 1:maxt){
log(HRmaxtx[n,Ntx,m])<-(equals(scaleeffect,1)*(d[Ntx,1]-
d[n,1]))+(equals(firstshapeeffect,1)*(d[Ntx,2]-
d[n,2])*time1[m])+(equals(secondshapeeffect,1)*(d[Ntx,3]-
d[n,3])*time2[m])
}
}
for (i in 1: Ns){
mu1[i,1] <- mu[i,1]*equals(t[i,1],1)
mu1[i,2] <- mu[i,2]*equals(t[i,1],1)
mu1[i,3] <- mu[i,3]*equals(t[i,1],1)
st1[i] <- equals(t[i,1],1)
}
mu_mean[1]<- (equals(UD,1)*mu[anchortrial,1] + (1-
equals(UD,1))*(sum(mu1[,1])/sum(st1[])))
mu_mean[2]<- (equals(UD,1)*mu[anchortrial,2] + (1-
equals(UD,1))*(sum(mu1[,2])/sum(st1[])))
mu_mean[3]<- (equals(UD,1)*mu[anchortrial,3] + (1-
equals(UD,1))*(sum(mu1[,3])/sum(st1[])))
for (n in 1:Ntx){
beta1[n]<-mu_mean[1]+(equals(scaleeffect,1)*d[n,1])
beta2[n]<-mu_mean[2]+(equals(firstshapeeffect,1)*d[n,2])
beta3[n]<-mu_mean[3]+(equals(secondshapeeffect,1)*d[n,3])
}
for (n in 1:Ntx){
for (m in 1:maxt){
log(HAZARD[n,m])<-
(mu_mean[1]+(equals(scaleeffect,1)*d[n,1]))+(mu_mean[2]+(equal
```

```
s(firstshapeeffect,1)*d[n,2]))*time1[m]+(mu_mean[3]+(equals(se
condshapeeffect,1)*d[n,3]))*time2[m]
CUM_H[n,m]<-sum(HAZARD[n,1:m])
T[n,m]<-1-exp(-CUM_H[n,m])
S[n,m]<-1-T[n,m]
Ssum[n,m]<-sum(S[n,1:m])
rk[n,m]<-Ntx+ 1- rank(Ssum[,m],n)
best[n,m]<-equals(rk[n,m],1)
}}
for (n in 1:Ntx){
Mean_surv[n]<-sum(S[n,])
}
for (n in 1:(Ntx-1)) {
for (nn in (n+1):Ntx) {
Mean_surv_diff[n,nn]<-Mean_surv[nn]-Mean_surv[n]
}}
}
}
```

A18. Priority question. Please provide the data used in the constant hazard ratio NMA for each of the trials, for OS and PFS outcomes. Likewise, please provide the Kaplan-Meier data used in the fractional polynomial NMA for OS and PFS outcomes.

Company response

Please refer to Table A18 for a summary of the data used in the constant HR NMA for each of the trials, for OS and PFS. Additionally, please see accompanying folder "Digitised Curves", which contains digitised KM curves and a word document, "Kaplan Meier Curve Overlay Plots.docx", with KM overlay plots constructed from the digitised curves included in the folder.

Table A18. Summary of the data used in the constant HR NMA for each trial

Trial	Publications	KM (OS)	KM (PFS)	HR (OS)	HR (PFS)
CABOSUN	Choueiri 2018	Figure 4	Figure 2	Figure 4	Figure 2
COMPARZ	Motzer 2014	Figure 1	--	Page 1769	--
	Motzer 2013	--	Figure 1	--	Page 726
Escudier 2009	Escudier 2009	--	Figure 2A	--	Figure 2A
Motzer 2007	Motzer 2009	Figure 2	--	Page 3587; Figure 2	Page 3587
	Motzer 2007	--	Figure 2	--	--
KEYNOTE-426	Client Provided 2018	--	--	--	--
	Client Provided 2019	--	--	--	--

Trial	Publications	KM (OS)	KM (PFS)	HR (OS)	HR (PFS)
TIVO-1*	Motzer 2013	--	Figure 2B	--	Figure 2B

* denotes trials in grey used subgroup first-line data
Please note that the reference to Figures within the table is related to the main journal publication

A19. We note that 62% of patients in the sorafenib arm of the TIVO-1 trial switched to tivozanib on disease progression. Please confirm whether the data used in the NMA adjusts for this crossover? Please confirm whether there was any patient crossover in any of the other trials in the NMA and if so whether this was adjusted for?

Company response

The data used in the NMA does not account for cross-over, therefore, OS results where TIVO-1 is included is confounded by cross-over. Cross-over was allowed only for patients who progressed on sorafenib to receive tivozanib, which may confound OS, in that, treatment effects may underestimate the treatment effect of tivozanib and reflects that sorafenib has improved OS rather than tivozanib. In addition to TIVO-1, both Escudier 2009 [7] and Motzer 2007 [6] allowed patients to cross-over from IFN-α to the experimental intervention. However, Escudier 2009 [7] estimates from period 1 did not include those who crossed over from IFN-α (52%) to sorafenib. Motzer 2007 [6] provided an OS HR which adjusted for the patients who crossed over from IFN-α (7%) to sunitinib, this HR was used in the base case analysis for OS.

A20. International Metastatic RCC Database Consortium (IMDC) risk status is described as an effect modifier in RCC and separate subgroup NMA networks are constructed for (1) intermediate/poor risk and (2) favourable risk (submission section D1.2.1). Please provide evidence to back up the assertion of effect modification of these risk subgroups.

Company response

Risk status is considered a relevant prognostic factor in mRCC (Okita et al., 2019 [10]), and was therefore considered a potential treatment effect modifier. This was based on studies included in the evidence base (Motzer et al., 2013 [11], Choueiri et al., 2017 [12], and Choueiri et al., 2018 [13]) which observed differences in treatment efficacy based on risk classification, specifically, those classified as intermediate/poor risk compared to those classified as favourable risk. With this knowledge, we sought to

conduct subgroup analyses to maintain homogenous patient populations based on important factors that modify the effect of treatment in mRCC patients.

A21. The CABOSUN trial of cabozantinib (Choueiri, 2017) shows differences in PFS between intermediate and poor risk groups (figure A1 in the trial journal paper). Where data permits, please run separate NMA scenarios for (i) IMDC intermediate risk, and (ii) IMDC poor risk.

Company response

The NMA scenarios for PFS in (i) intermediate risk and (ii) poor risk groups have been conducted as requested. The results are presented in Table A21.1-4. Additionally, time-varying HR NMA analyses could not be run for these subgroup analyses as Choueiri 2018 [13] and Choueiri 2017 [12] did not provide KM curves by risk subgroup, therefore only results for constant HRs are provided.

Table A21.1 Constant HRs for PFS; intermediate risk

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN	Sunitinib	Cabozantinib	[redacted]	[redacted]
KEYNOTE-426	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Table A21.2 HRs estimated from fixed-effects constant HR NMA of PFS; intermediate risk

Sunitinib	[redacted]	[redacted]
[redacted]	**Cabozantinib**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 3.39; Deviance: 1.39

Table A21.3 Constant HRs for PFS; poor risk

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN	Sunitinib	Cabozantinib	[redacted]	[redacted]
KEYNOTE-426	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Table A21.4 HRs estimated from fixed-effects constant HR NMA of PFS; poor risk

Sunitinib	[redacted]	[redacted]

[redacted]	Cabozantinib	[redacted]
[redacted]	[redacted]	Pembrolizumab + axitinib

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 3.41; Deviance: 1.4

Furthermore, subgroup analysis for OS in (i) intermediate risk and (ii) poor risk could not be conducted as Choueiri 2018 [13] (CABOSUN), did not provide OS subgroup data by risk group.

A22. The company's rationale for including the CABOSUN trial of cabozantinib in a separate sub-group NMA is understandable, given that it only included patients at intermediate/poor risk. We note that in the cabozantinib NICE appraisal (TA542) the company combined the CABOSUN trial with the pazopanib trial (COMPARZ). The latter included patients from all risk groups. Therefore, please conduct a scenario analysis in which CABOSUN is included in the same network as all the other interventions (i.e. irrespective of risk status).

Company response

Please find time-varying HR NMA analyses for the requested sensitivity analysis in Appendix 1 (Figures: 5-8, 31-49, Tables: 11-20, 65-102). Constant HR analyses results are presented below.

Table A22.1. Constant HRs for PFS; base case, sensitivity analysis

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN†	Sunitinib	Cabozantinib	[redacted]	[redacted]
COMPARZ	Sunitinib	Pazopanib	[redacted]	[redacted]
Escudier 2009	IFN-α	Sorafenib	[redacted]	[redacted]
KEYNOTE-426	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]
Motzer 2007	Sunitinib	IFN-α	[redacted]	[redacted]
TIVO-1*	Sorafenib	Tivozanib	[redacted]	[redacted]

Note: * denotes trials in grey used subgroup first-line data; † denotes trial was conducted in IMDC intermediate and poor risk patients only
Grey columns represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.

Table A22.2 HRs estimated from fixed-effects constant HR NMA of PFS; base case, sensitivity analysis

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
Grey cells represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 11.33; Deviance: 5.3

Table A22.3 Constant HRs for OS; base case, sensitivity analysis

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN†	Sunitinib	Cabozantinib	[redacted]	[redacted]
COMPARZ	Sunitinib	Pazopanib	[redacted]	[redacted]
KEYNOTE-426	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

† denotes trial was conducted in IMDC intermediate and poor risk patients only

Table A22.4 HRs estimated from fixed-effects constant HR NMA of OS; base case, sensitivity analysis

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 5.36; Deviance: 2.36

A23. Appendix D table 16 provides the distribution of patients according to Memorial Sloan Kettering Cancer Center (MSKCC) risk status across the four trials included in the NMA. However, MSKCC was used in only two of those trials. Please can you provide a tabulation of the risk status for each trial according to the classification system used in that trial.

Company response

Please refer to Table A23 for a summary of the risk status for each trial included in the NMA based on the classification system used.

Table A23. Summary of the risk status for each trial included in the NMA

Trial	Risk Classification	Favourable	Intermediate	Poor
CABOSUN	IMDC	--	127 (81%)	30 (19%)
COMPARZ	MSKCC	303 (27%)	650 (59%)	119 (11%)
Escudier 2009	MSKCC	99 (52%)	88 (47%)	1 (1%)
KEYNOTE-426	IMDC	269 (31%)	484 (56.2%)	108 (13%)
Motzer 2007	MSKCC	264 (36%)	421 (58%)	48 (7%)
TIVO-1*	MSKCC	157 (31%)	333 (65%)	27 (6%)

* denotes trials in grey represent ITT population, which included 1L and 2L+ patients

Section B: Clarification on cost-effectiveness data

B1. The total drug acquisition costs for the subsequent treatments differs between the submission, table 60 and the economic model for all except nivolumab, pembrolizumab and everolimus. Please confirm which values are correct: those in table 60 or those in the economic model.

Company response

The costs used within the economic model are correct, and Table 60 should read as Table B1.1 below.

Table B1.1. (Table 60 from Company submission) Subsequent therapy- drug formulation, dose, administration, proportion of doses received, mean treatment duration and total drug acquisition cost

Subsequent treatment	Dosing schedule	Dose per admin or pharmacy dispensing (mg or MU)	Strength per unit (mg or MU)	Cost per unit (BNF) (2018 GBP)	Relative dose intensity (mean, %)	Drug acquisition cost per admin (2018 GBP)	Dosing schedule (number per month)	Mean treatment duration (months)	Total drug acquisition cost (2018 GBP)	Source for mean treatment duration
PD1/PD-L1 checkpoint inhibitors										
Nivolumab	480 mg IV Q4W or 240 mg IV Q2W	480	40	439.00	92.0%	4,846.56	1.09	7.9*	41,804.38	Motzer et al. 2015 [CheckMate 025] (Median ToT = 5.5 months)
Pembrolizumab	200 mg IV Q3W	200	100	2,630.00	[redacted]	4,986.48	1.45	7.9	57,348.36	Assume same mean ToT as nivolumab
VEGF/VEGFR inhibitors										
Axitinib	5 mg orally BID	280	5	62.80	102.0%	3,587.34	1.09	11.8*	**46,133.02**	Motzer et al. (2013) [AXIS]
Cabozantinib	60 mg orally QD	1,680	60	171.43	100.0%	4,800.13	1.09	12.1*	**63,235.08**	Motzer et al. (2018) [METEOR]
Lenvatinib / everolimus	18 mg orally QD	504	10	47.90	75.0%	1,810.62	1.09	11.0*	**42,856.12**	Motzer et al. (2015) [NCT01136733]
	5 mg orally QD	140	5	75.00	85.0%	1,785.00	1.09	11.0*	**n/a**	Motzer et al. (2015) [NCT01136733]
Pazopanib	800 mg orally QD	22,400	400	37.37	86.0%**	1,574.63	1.09	10.7*	**20,884.69**	Sternberg et al. (2013) [VEG105192]
Sunitinib	50 mg orally QD for 4	1,400	50	112.10	[redacted]	2,344.68	0.72	10.7*	**18,140.54**	Assume same median ToT as pazopanib

	weeks, then 2 weeks off treatment									
Other treatments										
Everolimus	10 mg orally QD	280	10	89.10	91.8%	2,290.23	1.09	6.3*	**15,803.62**	Motzer et al. (2018) [METEOR] (Median ToT = 6.3 months)
Temsirolimus	25 mg IV QW	25	25	112.10	92.4%	103.58	4.35	6.3*	**13,177.12**	Hutson et al. (2014) [INTORSECT] (Median ToT = 6.3 months)
Cytokines (Interferon a2A-Roferon-A)	10 MU SC three days per week	**30**	**3**	**14.2**	**100.0%*** **	**142**	**4.35**	**4.0***	**2,458.35**	Rini et al. (2008) [CALGB 90206] (Median ToT = 4.0 months)

** Mean ToT was calculated as a function of median ToT, based on an assumption of constant hazards.*
*** Assume equal to 1L dose intensity*
**** Assumption*
Key: BID, twice daily; IV, intravenous; BNF, British National Formulary; Q2W, once every 2 weeks; MG, milligrams; MU, million units; SC, subcutaneously

B2. The subsequent treatment cost (following the intervention and comparator), reported in the submission, table 62, differs from the values in the economic model. Please confirm which values are correct.

Company response

The subsequent treatment cost in Table 62 should read as per the economic model. Please see Table B5.1 provided in response to question B5, for a revised Table 62.

B3. It is unclear how the subsequent treatment cost for interferon has been calculated. Please clarify the name of the product used to estimate the cost.

Company response

The product used to estimate the cost of interferon during the development of our submission was IntronA- which has since been discontinued. Hence the updated cost for interferon has been calculated using costs sourced from the BNF for Roferon-A. Please see an updated version of Table 60 from the company submission provided in response to question B1 above (presented as Table B1.1), and the revised Scenario Analysis 12 below (Table B3.1), using the trial-based distribution of subsequent therapy.

Table B3.1. Updated Scenario Analysis 12 according to the change in cost of interferon

Scenario No.	Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	137,537	2.320	59,292
Scenario 12	Trial-based subsequent therapy distribution	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	141,485	2.320	60,994

B4. The proportion of patients with Grade 3+ adverse events shown in the submission table 46 differs to the values in the economic model for stomatitis and thrombocytopenia for pembrolizumab and axitinib and sunitinib. Please confirm which values are correct.

Company response

The incidence of Grade 3+ AEs should read as per Table B4.1 below (replicated from the economic model).

Table B4.1. Grade 3+ AE rates for AEs included in the economic model

Adverse Event	Pembrolizumab + axitnib (% of patients) [16]	Sunitinib, Tivozanib, Pazopanib (% of patients) [16]	Cabozantinib (% of patients in intermediate/poor subgroup) [11]
Alanine aminotransferase increased	13.3%	3.1%	5.1%
Aspartate aminotransferase increased	7.0%	2.4%	2.6%
Decreased appetite	2.8%	0.7%	5.1%
Diarrhea	9.1%	4.7%	10.3%
Fatigue	2.8%	6.6%	6.4%
Hyperglycaemia	2.3%	0.5%	0.0%
Hypertension	22.1%	19.3%	28.2%
Hyponatremia	2.3%	2.6%	0.0%
Lipase level increased	0.5%	0.5%	0.0%
Lymphocytopenia	0.2%	0.5%	0.0%
Neutropenia	0.2%	6.6%	0.0%
Neutrophil count decreased	0.2%	6.8%	0.0%
Palmar-plantar erythrodysaesthesia syndrome	5.1%	3.8%	7.7%
Platelet count decreased	0.2%	7.3%	1.3%
Stomatitis	**0.7%**	**2.1%**	**5.1%**
Thrombocytopenia	**0.0%**	**5.9%**	**0.0%**

B5. The weekly resource cost in the progression-free and progressive state differs in table 62 of the submission to that used in the model and reported in table 56 of the submission. Please confirm which values are correct.

Company response

The costs reported in Table 56 of the company submission and the economic model are correct. Please see Table B5.1 below for a revised version of Table 62 that was presented in the company submission.

Table B5.1. (Table 62 from the company submission) Summary of variables applied in the economic model

Parameters	Mean / Deterministic value	Lower	Upper	Distribution used in PSA	Section in the submission document
General Information					
Model cycle length (weeks)	1			Not varied in SA	See Section B.3.2
Model time horizon (years)	40			Not varied in SA	
Discount rate: Costs	3.5%			Not varied in SA	
Discount rate: Health outcomes	3.5%			Not varied in SA	
Patient Information					
Patient Age	61.50			Not varied in SA	See Section B.3.2
Proportion male	73.5%			Not varied in SA	
Average patient weight (kg)	81.7			Not varied in SA	
Utility Inputs					
Utility by time-to-death					
Utility time to death >=360 days	[redacted]	[redacted]	[redacted]	Beta	See Section B.3.4
Utility time to death days [180,359)	[redacted]	[redacted]	[redacted]	Beta	
Utility time to death days [90,179)	[redacted]	[redacted]	[redacted]	Beta	
Utility time to death days [30,89)	[redacted]	[redacted]	[redacted]	Beta	
Utility time to death <30 days	[redacted]	[redacted]	[redacted]	Beta	
AE-related disutility,	[redacted]	[redacted]	[redacted]	Normal	
Regimen Related Costs					
Drug costs (per administration)					
Pembrolizumab drug cost	£5,260.00			Not varied in SA	See Section B.3.5
Axitinib drug cost	£3,517.00			Not varied in SA	
Sunitinib drug cost	£3,138.80			Not varied in SA	
Tivozanib drug cost	£2,052.00			Not varied in SA	
Pazopanib drug cost	£2,092.53			Not varied in SA	
Cabozantinb drug cost	£4,800.13			Not varied in SA	
Nivolumab drug cost	£5,268.00			Not varied in SA	
Lenvatinib drug cost	£2,414.16			Not varied in SA	
Everolimus 5mg drug cost	£2,100.00			Not varied in SA	
Everolimus 10mg drug cost	£2,494.80			Not varied in SA	
Temsirolimus drug cost	£2,092.53			Not varied in SA	
Interferon a2B drug cost	£3,138.80			Not varied in SA	
Administration cost for IV					
Deliver Simple Parenteral Chemotherapy at First Attendance	£174.40	£156.96	£191.84	Gamma	See Section B.3.5

Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£309.20			Not varied in SA	
Deliver Exclusively oral chemotherapy	£131.60	£156.96	£191.84	Gamma	
Disease Management Costs					
Weekly cost in progression-free state (cycle 0)	£280.05	£252.05	£308.06	Gamma	See Section B.3.5
Weekly cost in progression-free state (subsequent cycles)	**£51.05**	£45.95	£56.16	Gamma	
Weekly cost in progressive disease state	**£51.05**	£45.95	£56.16	Gamma	
Subsequent treatment cost (following intervention)	**£10,352.28**			Not varied in SA	
Subsequent treatment cost (following comparator)	**£24,700.62**			Not varied in SA	
Cost of terminal care (one-off cost)	£6,789.76	£6,110.78	£7,468.74	Normal	
% AE Pembrolizumab					
% Alanine aminotransferase increased	13.3%			Not varied in SA	See Section B.3.3
% Aspartate aminotransferase increased	7.0%			Not varied in SA	
% Decreased appetite	2.8%			Not varied in SA	
% Diarrhea	9.1%			Not varied in SA	
% Fatigue	2.8%			Not varied in SA	
% Hyperglycaemia	2.3%			Not varied in SA	
% Hypertension	22.1%			Not varied in SA	
% Hyponatremia	2.3%			Not varied in SA	
% Lipase level increased	0.5%			Not varied in SA	
% Lymphocytopenia	0.2%			Not varied in SA	
% Neutropenia	0.2%			Not varied in SA	
% Neutrophil count decreased	0.2%			Not varied in SA	
% Palmar-plantar erythrodysaesthesia syndrome	5.1%			Not varied in SA	
% Platelet count decreased	0.2%			Not varied in SA	
% Stomatitis	**0.7%**			Not varied in SA	
% Thrombocytopenia	**0.0%**			Not varied in SA	

% AE Sunitinib					
% Alanine aminotransferase increased	3.1%			Not varied in SA	See Section B.3.3
% Aspartate aminotransferase increased	2.4%			Not varied in SA	
% Decreased appetite	0.7%			Not varied in SA	
% Diarrhea	4.7%			Not varied in SA	
% Fatigue	6.6%			Not varied in SA	
% Hyperglycaemia	0.5%			Not varied in SA	
% Hypertension	19.3%			Not varied in SA	
% Hyponatremia	2.6%			Not varied in SA	
% Lipase level increased	0.5%			Not varied in SA	
% Lymphocytopenia	0.5%			Not varied in SA	
% Neutropenia	6.6%			Not varied in SA	
% Neutrophil count decreased	6.8%			Not varied in SA	
% Palmar-plantar erythrodysaesthesia syndrome	3.8%			Not varied in SA	
% Platelet count decreased	7.3%			Not varied in SA	
% Stomatitis	**2.1%**			Not varied in SA	
% Thrombocytopenia	**5.9%**			Not varied in SA	
AE Management costs					
Pembrolizumab / axitinib	£379.90	£341.91	£417.89	Gamma	See Section B.3.5
Sunitinib	£348.34	£313.51	£383.17	Gamma	
Tivozanib (assumed equivalent to sunitinib)	£348.34	£313.51	£383.17	Gamma	
Pazopanib (assumed equivalent to sunitinib)	£348.34	£313.51	£383.17	Gamma	
Survival Models					
PFS parametric curve fitting					
Pembrolizumab + axitinib					
PFS - Piecewise exponential Parameter A	0.0106	0.0088	0.0125	Normal	See section B.3.3
Sunitinib					
PFS - Piecewise exponential intercept	0.0139	0.0115	0.0163	Normal	See section B.3.3
OS parametric curve fitting					
Pembrolizumab + axitinib					
OS – Log-logistic Parameter A	-0.2001	-0.4377	0.0374	Multivariate Normal	See section B.3.3
OS - Log-logistic Parameter B	5.6254	5.1950	6.0557	Multivariate Normal	
Sunitinib					
OS - Exponential Parameter A	0.0043	0.0034	0.0052	Normal	See section B.3.3
ToT parametric curve fitting					
Pembrolizumab					
ToT – Weibull Parameter A	0.2463	0.1209	0.3716	Multivariate Normal	See section B.3.3
ToT – Weibull Parameter B	4.6185	4.4190	4.8181	Multivariate Normal	See section B.3.3

Axitinib					
ToT – Exponential Parameter A	0.0109	0.0094	0.0125	Normal	See section B.3.3
Sunitinib					
ToT – Exponential Parameter A	0.0155	0.0135	0.0174	Normal	See section B.3.3

B6. Please comment on why the uptake of subsequent treatments was roughly [redacted] for people who had sunitinib first-line than for pembrolizumab with axitinib and whether you would expect a similar uptake for patients who first had sunitinib in UK clinical practice?

Company response

Table 59 in the company submission reports that of those patients who discontinued treatment with pembrolizumab in combination with axitinib, [redacted] receive no active treatment compared to [redacted] of patients who receive sunitinib. Hence the proportion of patients who receive subsequent treatments is [redacted] for patients receiving sunitinib, as discussed and agreed over the clarification teleconference with NICE and ERG on the 16 August 2019.

The major difference is caused by a much higher proportion of patients in the sunitinib receiving a subsequent anti-PD1/PD-L1 inhibitor compared to that from the pembrolizumab in combination with axitinib arm. This is expected as the pembrolizumab in combination with axitinib arm included PD-1 upfront. However, the reasons why patients did not receive subsequent therapy was not collected within KEYNOTE-426 [2,3]. Therefore, the exact reason for the difference in proportion of patients receiving subsequent therapy is unknown.

B7. Please confirm that in the economic model, none of the treatments are eligible for vial sharing.

Company response

MSD confirms that none of the first-line or subsequent-line treatments in the model have weight-based dosing; therefore vial-sharing is not applicable.

B8. Priority question. Please include a deterministic sensitivity analysis for the OS and PFS treatment effect using the hazard ratios for sunitinib and varying these between the 5% and 95% confidence intervals.

Company response

The following additional deterministic sensitivity analyses have been incorporated into the updated Excel model (please refer to updated economic model provided alongside MSD response):

- Apply and vary the time-constant HR of PFS for sunitinib vs. pembrolizumab/axitinib (95% credible interval [CrI]); and
- Apply and vary the time-constant HR of OS for sunitinib vs. pembrolizumab/axitinib (95% CrI).

Under both sensitivity analyses, the time-constant HR approach is applied for the specified outcome in the sunitinib arm regardless of the base-case selections. The time-constant HRs and corresponding 95% CrIs for sunitinib vs. pembrolizumab/axitinib are summarized in Table B8.1 below.

Table B8.1 Time-constant HRs and 95% CrIs for sunitinib vs. pembrolizumab/axitinib

	PFS	OS
Hazard ratio	1.45	1.88
95% CrI	(1.19, 1.76)	(1.36, 2.62)

The ICER range for pembrolizumab/axitinib vs. sunitinib in these sensitivity analyses are displayed within "DSA Results" tab of the model and summarized in Table B8.2 below. The HR of PFS for sunitinib vs. pembrolizumab/axitinib had minimal impact on the ICER, but the ICER ranged from £44,115 to £108,861 when varying the HR of OS for sunitinib vs. pembrolizumab/axitinib to the upper and lower limits of its 95% CrI, respectively.

Table B8.2 Tabulated results from one-way DSAs for pembrolizumab/axitinib vs. sunitinib

	ICER (£ per QALY)	
	Low input value	*High input value*
Base case	59,292	
Apply HR approach and use time-constant HRs of PFS for sunitinib, 95% CrI	59,352	59,193
Apply HR approach and use time-constant HRs of OS for sunitinib, 95% CrI	108,861	44,115

B9. Please explain which parameters in the model have been changed for the intermediate and poor risk group. Please provide more information of the curve fitting for PFS, OS and time on treatment for the intermediate and poor risk group.

Company response

To conduct the subgroup analysis within the intermediate and poor risk group, parameter estimates for PFS, OS, and ToT in the pembrolizumab/axitinib and sunitinib arms were re-estimated using subgroup-specific patient-level data from KEYNOTE-426 [2,3]. Corresponding parameter estimates, goodness-of-fit statistics, and efficacy validation figures for the intermediate/poor risk subgroup are displayed within the Excel model when this subgroup is selected as the target population (please refer to updated economic model provided alongside MSD response). In the intermediate/poor risk subgroup, the relevant comparator set expands to also include cabozantinib. The sections below provide details on the parametric curve selection for each outcome in the pembrolizumab/axitinib and sunitinib arms, and on the estimation of each outcome in the external comparator arms (tivozanib, pazopanib, and cabozantinib).

PFS

For pembrolizumab/axitinib and sunitinib, default parametric functions for PFS in the intermediate/poor risk subgroup were selected based on goodness-of-fit statistics (AIC and BIC), visual inspection of fit, and clinical plausibility of the long-term extrapolations. Parametric curves were also selected with consideration for the consistency of survival projections relative to the overall population (i.e., to ensure that expected PFS associated with pembrolizumab/axitinib and sunitinib were monotonically lower in the intermediate/poor risk subgroup than in the overall population).

Based on these criteria, piecewise exponential curves were used to model PFS in both the pembrolizumab/axitinib and sunitinib arms of the intermediate/poor IMDC risk subgroup; In the intermediate/poor IMDC risk group, the exponential distribution demonstrated the best fit for sunitinib and the second-best fit for pembrolizumab/axitinib according to BIC, similar to the ranking of the exponential PFS function in the overall population.

For tivozanib and pazopanib, PFS was assumed to be equivalent to that estimated for the sunitinib arm. For cabozantinib, PFS was derived by applying the estimated HR of progression or death vs. pembrolizumab/axitinib to the PFS curve for pembrolizumab/axitinib. The time-constant HR was estimated through a fixed-effects NMA of PFS. The NMA within the intermediate/poor risk subgroup was restricted to trials that reported outcomes for this target population. Methodological details and results from the subgroup-specific NMA are provided in Section B2.9.3.2 of the company submission.

Table B9.1 reports the resulting long-term extrapolations of PFS, alongside corresponding extrapolations in the overall target population.

Table B9.1 PFS estimation methods and resulting extrapolations by treatment arm and target population

Target population / comparator	Method for estimating PFS	5-year PFS	10-year PFS	20-year PFS
Overall target population				
Pembrolizumab / axitinib	Piecewise, exponential	6.2%	0.4%	0.0%
Sunitinib (Pazopanib and Tivozanib assumed equivalent)	Piecewise, exponential	2.5%	0.1%	0.0%
Intermediate/poor IMDC risk subgroup				
Pembrolizumab / axitinib	Piecewise, exponential	4.3%	0.2%	0.0%
Sunitinib (Pazopanib and Tivozanib assumed equivalent)	Piecewise, exponential	1.6%	0.0%	0.0%
Cabozantinib	NMA-based HR vs. pembrolizumab/axitinib	10.4%	1.1%	0.0%

Sources: Parametric curves for pembrolizumab/axitinib and sunitinib were fitted to patient-level data for the corresponding target population in KEYNOTE-426 (data cutoff date: 24 Aug 2018). The time-constant HR of progression or death with cabozantinib vs. pembrolizumab/axitinib was estimated through a fixed-effects NMA of trials that reported PFS among intermediate/poor participants (section B2.9.3.2 of the submission).

OS

In the intermediate/poor IMDC risk subgroup, parametric models of OS in the pembrolizumab/axitinib and sunitinib arms were selected using a process similar to that described for the overall population (Section B.3.3 of the submission). As in the overall population, the set of potentially plausible OS distributions was first refined on the basis of 5-year OS estimates. Of the remaining distributions in each treatment arm, the parametric function demonstrating the most biologically plausible long-term extrapolations were selected.

Log-logistic and exponential OS curves were used in the pembrolizumab/axitinib and sunitinib arms, respectively, consistent with the functional forms used in the overall population. In this subgroup, the exponential curve demonstrated the second-best fit to observed OS data (as indicated by BIC) in the sunitinib arm. The resulting 5-year OS projection for sunitinib (21.6%) closely aligned with 5-year OS reported from the global access study of sunitinib (~20%, based on a weighted average of digitised Kaplan-Meier data from the intermediate and poor IMDC risk groups in this study [14]). For tivozanib and pazopanib, OS was assumed to be equivalent to that estimated for the sunitinib arm. For cabozantinib, OS was derived by applying the estimated HR of death vs. pembrolizumab/axitinib to the OS curve for pembrolizumab/axitinib. The time-constant HR was estimated through a fixed-effects NMA of OS within the intermediate/poor risk subgroup (Section B2.9.3.2 of the submission).

The resulting OS extrapolations are summarized in Table B9.2 for each treatment arm within the intermediate/poor risk subgroup.

Table B9.2 OS estimation methods and resulting extrapolations by treatment arm and target population

Target population / comparator	Method for estimating OS	5-year OS	10-year OS	20-year OS
Overall target population				
Pembrolizumab / axitinib	One-piece, log-logistic	51.9%	31.6%	16.5%
Sunitinib (Pazopanib and Tivozanib assumed equivalent)	One-piece, exponential	32.5%	10.6%	1.1%
Intermediate/poor IMDC risk subgroup				
Pembrolizumab / axitinib	One-piece, log-logistic	43.8%	24.9%	12.3%
Sunitinib (Pazopanib and Tivozanib assumed equivalent)	One-piece, exponential	21.6%	4.7%	0.2%
Cabozantinib	NMA-based HR vs. pembrolizumab/axitinib	28.3%	11.9%	4.0%

Sources: Parametric curves for pembrolizumab/axitinib and sunitinib were fitted to patient-level data for the corresponding target population in KEYNOTE-426 (data cutoff date: 24 Aug 2018). The time-constant HR of death with cabozantinib vs. pembrolizumab/axitinib was estimated through a fixed-effects NMA of trials that reported PFS among intermediate/poor participants (section B2.9.3.2 of the submission).

ToT

In the intermediate/poor IMDC risk subgroup, ToT for the pembrolizumab and axitinib components and for sunitinib monotherapy was modelled using parametric functions fitted to subgroup-specific data from KEYNOTE-426 [2,3]. Because treatment duration with the pembrolizumab component of pembrolizumab/axitinib is restricted to a maximum of 24 months, the base-case parametric curve for this component was

selected based on fit with observed ToT data within the trial period. Among patients with intermediate or poor IMDC risk, the log-logistic curve presented the closest fit based on AIC/BIC and visual inspection and was therefore selected to model pembrolizumab ToT in this subgroup (please note the company submission in Section B.3.9 incorrectly stated the Weibull was used to extrapolate ToT).

For both axitinib (as a component of pembrolizumab/axitinib) and sunitinib, all of the fitted curves yielded a close visual fit to observed ToT during the trial period. Given the expected concordance between ToT and PFS, exponential ToT curves were used for the axitinib component and for sunitinib monotherapy in the subgroup, consistent with the functional form used to model PFS in both treatment arms. Although the best-fitting curve based on AIC/BIC was log-normal for both axitinib and sunitinib, the tail of the log-normal distribution was considered implausibly long based on input from clinical experts.

For tivozanib and pazopanib, ToT was assumed to be equivalent to that estimated for the sunitinib arm. For cabozantinib, the proportion of patients remaining on treatment in each cycle was approximated based on the modelled PFS curve for this treatment arm. ToT was modelled based on PFS under the clinically validated expectation that ToT would be approximately equal to the time until disease progression for first-line TKI monotherapies.

B10. Priority question. Please provide deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses for pembrolizumab and axitinib versus cabozantinib in the intermediate and poor risk group.

Company response

Please see the below analysis for the intermediate/poor subgroup vs cabozantinib. All analysis was conducted using the list price of all therapies, and hence it is considered that the ICERs presented do not reflect the true ICERs.

Table B.10.1 below presents the base case deterministic ICER, with all therapies at list price.

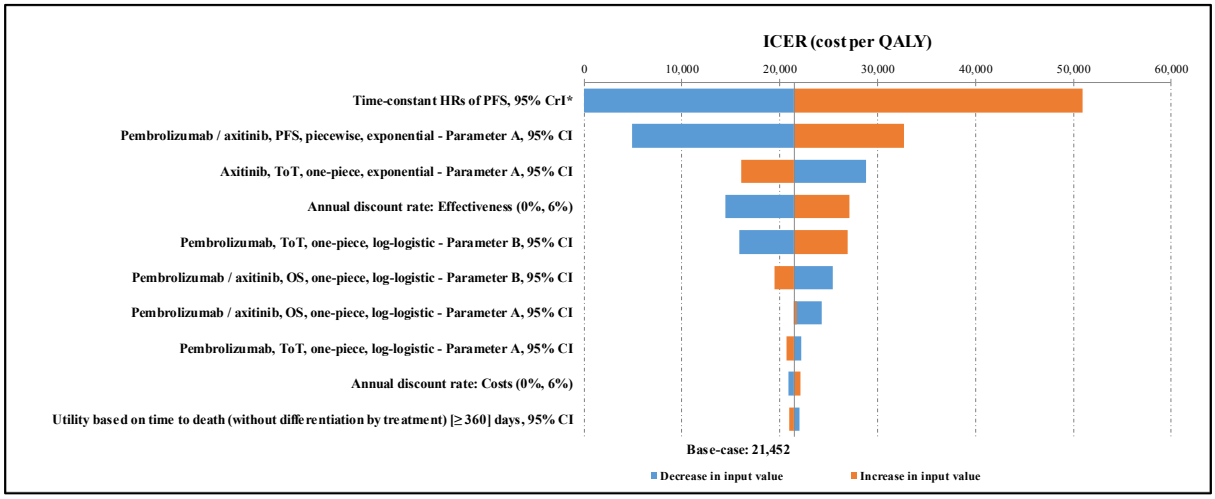
Table B10.1. Incremental cost-effectiveness results for pembrolizumab in combination with axitinib vs. cabozantinib (NMA comparator; time-constant hazard ratio hazard ratio) for patients with intermediate/poor risk score

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Cabozantinib (time-constant HR)	[redacted]	3.885	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	5.878	[redacted]	33,103	1.543	21,452

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure B.10.1 below shows the tornado diagram presenting the results of the deterministic sensitivity analysis. The inputs that most affect the ICERs are the time constant HRs of PFS, and those related to the extrapolation of PFS and ToT (the parameters used for the extrapolation).

Figure B10.11. Tornado diagram presenting the results of the deterministic sensitivity analysis for the intermediate/poor subgroup vs cabozantinib (list price)



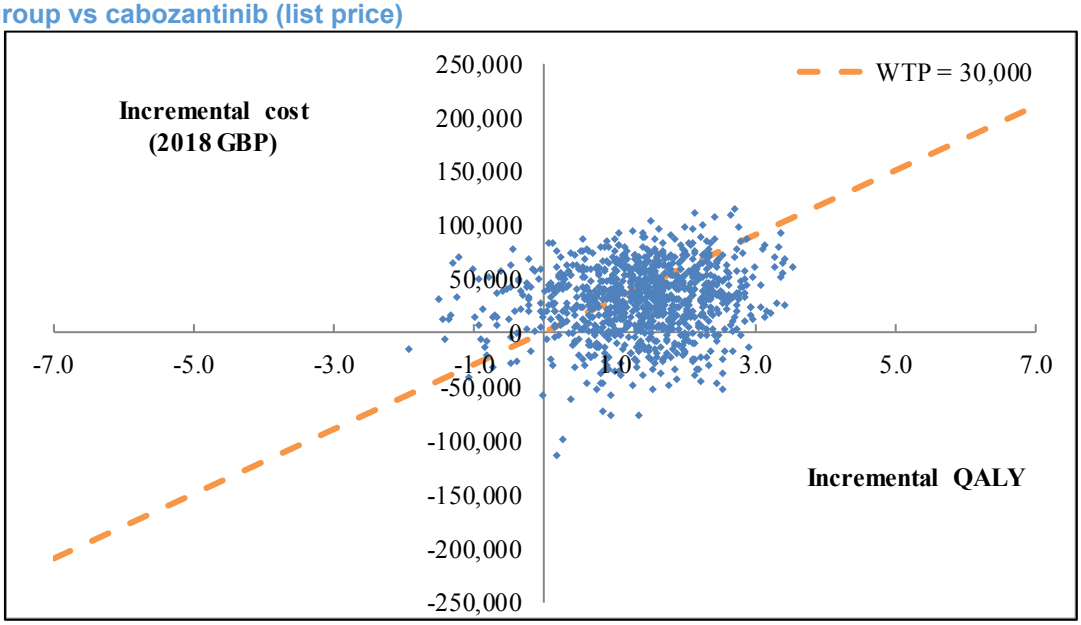
The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table B10.2, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure B10.2 and Figure B10.2.

Table B10.2. Incremental cost-effectiveness results based on probabilistic sensitivity analysis in the intermediate/poor subgroup versus comparator (list price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Cabozantinib	[redacted]	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	[redacted]	29,684	1.39	21,390

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure B10.2. Scatterplot of PSA results (1,000 simulations) for the intermediate/poor subgroup vs cabozantinib (list price)



The cost-effectiveness acceptability curve shows that, in the intermediate/poor subgroup vs cabozantinib, there is approximately a 61.9% of chance of pembrolizumab in combination with axitinib being cost-effective when compared to cabozantinib at the £30,000 per QALY threshold.

Figure B10.3. Cost-effectiveness acceptability curve in the intermediate/poor subgroup vs cabozantinib (list price)

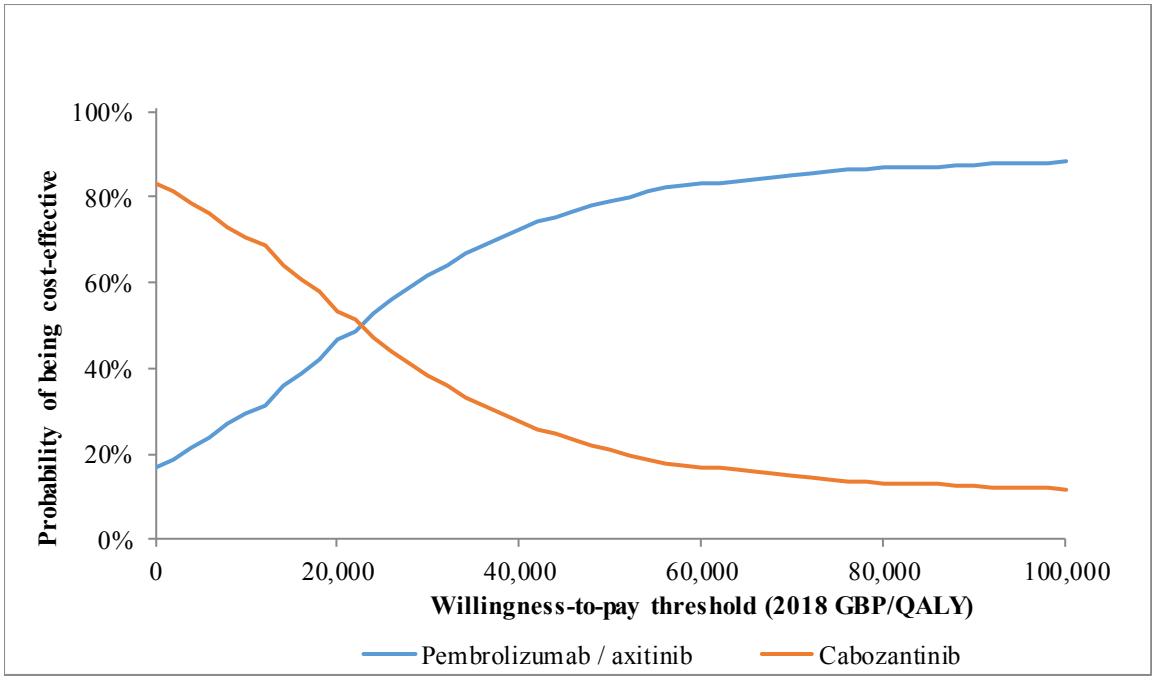


Table B10.3. Results from the scenario analyses in the intermediate/poor subgroup vs cabozantinib (list price)

Scenario No.	Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	33,103	1.543	21,452
Scenario 1	Fully parametric exponential OS extrapolation for pembrolizumab + axitinib, time-constant HR for cabozantinib	[redacted]	5.023	[redacted]	[redacted]	3.496	[redacted]	33,223	1.203	27,608
Scenario 2	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-varying HR for cabozantinib	[redacted]	5.878	[redacted]	[redacted]	5.392	[redacted]	30,305	0.384	78,987
Scenario 3	Treatment waning after 10 years	[redacted]	4.939	[redacted]	[redacted]	3.599	[redacted]	32,416	1.068	30,357
Scenario 4	Alternative modelling approach of ToT for cabozantinib (using HR for PFS)	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	28,368	1.543	18,383
Scenario 5	Health state-based utilities (pooled)	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	33,103	1.418	23,351
Scenario 6	Health state-based utilities (treatment specific)	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	33,103	1.499	22,077
Scenario 7	Removing age-related disutilities	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	33,103	1.651	20,054
Scenario 8	Removing AE disutilities	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	33,103	1.540	21,492
Scenario 9	Trial-based subsequent therapy distribution	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	38,959	1.543	25,247
Scenario 10	Axitinib 2 year stopping rule	[redacted]	5.878	[redacted]	[redacted]	3.885	[redacted]	15,399	1.543	9,979
Scenario 11	Remove half-cycle correction	[redacted]	5.888	[redacted]	[redacted]	3.894	[redacted]	33,103	1.543	21,451

B11. Please calculate how the utilities in the KEYNOTE-426 trial change according to patient age. Please run a scenario analysis where the age-adjusted utility is based upon the relationship seen in the KEYNOTE-426 trial, rather than based on Ara and Brazier.

Company response

Baseline measurements of EQ-5D index scores (scored using the UK algorithm) were analysed to characterize the relationship between patient age and utility within the KEYNOTE-426 trial [2,3]. As an initial exploratory analysis, a non-parametric LOESS function was fitted to the scatterplot of baseline EQ-5D utility by baseline age (Figure B11.1). The fitted curve was approximately horizontal, suggesting the absence of a relationship between age and utility with the trial population. Linear regression models were also fitted to predict baseline EQ-5D utility as a function of age, age^2, and/or male gender (Table B11.1). In all models, the coefficients associated with age and/or age^2 were close to zero and not statistically significant (all $p>0.05$).

Based on these findings, the requested scenario analysis is well-represented by the model scenario in which no age-related disutility is applied (scenario 9 in Table 67 of the submission). In this model scenario, the ICER of pembrolizumab/axitinib vs. sunitinib decreased from £59,292/QALY in the base case to £55,045/QALY.

Figure B11.1 Scatterplot of baseline UK-based EQ-5D-3L index scores by age and the resulting non-parametric LOESS function

Source: KEYNOTE-426 (data cutoff date: 24 Aug 2018)

Table B11.1 Linear regression models of baseline UK-based EQ-5D-3L index scores as a function of age

	Model 1: Age		Model 2: Age and age^2		Model 3: Age, gender, and age^2	
Covariate	Est. (SE)	p-value	Est. (SE)	p-value	Est. (SE)	p-value
Intercept						
Age (years)						
Age^2						
Male						

Source: KEYNOTE-426 (data cutoff date: 24 Aug 2018)

B12. Priority question. Please calculate the time to death-based utilities (including 95% confidence intervals) for each of the treatment groups of the KEYNOTE-426 trial. Please run a scenario analysis where the time to death utilities used are treatment-specific.

Company response

The Excel model has been updated to include the option of applying treatment-specific time to death-based utility values (please refer to updated economic model provided alongside MSD response). To inform this additional scenario analysis, treatment-specific time to death-based utilities and standard errors were estimated through a linear mixed-effects regression model of EQ-5D-3L measurements during the KEYNOTE-426 trial [2,3] (Table B12.1). The model included indicators for time to

death (i.e., 0-29, 30-89, 90-179, 180-359, or ≥360 days until death), randomisation group, and the presence/absence of any grade 3+ AEs, as well as patient-level random effects to account for correlation between repeated measurements of the same patient. For the first-line TKI monotherapies other than sunitinib, time to death-based utilities were assumed to be equal to those estimated for sunitinib.

Table B12.1 Treatment-specific time to death-based utilities in the scenario analysis

Time to death (days)	Pembrolizumab / axitinib				Sunitinib			
	Utility	Standard error	95% CI, Lower	95% CI, Upper	Utility	Standard error	95% CI, Lower	95% CI, Upper
0 to 29 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 to 89 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90 to 179 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
180 to 359 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥360 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: KEYNOTE-426 (data cutoff date: 24 Aug 2018)

The ICERs of pembrolizumab/axitinib vs. comparators from this scenario analysis are reported in the "DSA Results" tab of the Excel model and summarized in Table B12.2. When using this alternative utility approach, the incremental costs per QALY decreased slightly to £58,085/QALY vs. sunitinib, £55,494/QALY vs. tivozanib, and £56,369/QALY vs. pazopanib.

Table B12.2 Results of scenario analysis: treatment-specific time to death-based utilities

Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs SoC		
	Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	137,537	2.320	59,292
Time-to-death utilities (treatment-specific)	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	137,537	2.368	58,085

B13. Priority question. Please complete scenario analyses for PFS, OS and time on treatment where the same parametric distribution is used for each treatment group for all possible distributions.

Company response

The Excel model has been updated to include the following additional scenario analyses in which PFS, OS, and ToT are modelled using the same functional forms in the pembrolizumab/axitinib arm as in the sunitinib arm (please refer to updated economic model provided alongside MSD response):

1. Scenario: Exponential PFS, OS, and ToT in both arms
2. Scenario: Weibull PFS and ToT and exponential OS in both arms
3. Scenario: Log-logistic PFS and ToT and exponential OS in both arms

Each of the above scenarios is specified such that PFS and ToT are modelled using consistent functional forms. As described in section B3.5 of the submission, the log-normal curve demonstrated the lowest AIC/BIC for the axitinib component of pembrolizumab/axitinib and for sunitinib but was considered by clinical experts to present an exaggerated estimate of ToT in clinical practice. For sunitinib, the log-normal ToT curve resulted in ToT projections that exceeded OS projections in the long term. A scenario analysis using log-normal distributions of ToT and PFS therefore was not considered.

Results of the scenario analyses are reported in the "DSA Results" tab of the model and are summarized in Table B13.1. Under the first scenario, ICERs moderately increased to £72,752/QALY vs. sunitinib, £69,455/QALY vs. tivozanib, and £70,568/QALY vs. pazopanib. When the second scenario was applied, ICERs increased to £72,339/QALY vs. sunitinib, £68,877/QALY vs. tivozanib, and £70,042/QALY vs. pazopanib. Under the third scenario, ICERs increased to £86,728/QALY vs. sunitinib, £80,946/QALY vs. tivozanib, and £82,843/QALY vs. pazopanib.

Table B13.1 Results of scenario analyses: alternative extrapolations of PFS, OS, and ToT

Scenario Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs SoC		
	Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	137,537	2.320	59,292
Scenario: Distributions used for pembrolizumab / axitinib and sunitinib: Exponential for PFS, exponential for OS, exponential for ToT	[redacted]	6.251	[redacted]	[redacted]	3.864	[redacted]	135,359	1.861	72,752
Scenario: Distributions used for pembrolizumab / axitinib and sunitinib: Weibull for PFS, exponential for OS, Weibull for ToT	[redacted]	6.251	[redacted]	[redacted]	3.864	[redacted]	134,589	1.861	72,339
Scenario: Distributions used for pembrolizumab / axitinib and sunitinib: Log-logistic for PFS, exponential for OS, log-logistic for ToT	[redacted]	6.251	[redacted]	[redacted]	3.864	[redacted]	161,361	1.861	86,728

B14. Priority question. Despite previous appraisal committees assuming equivalence of pazopanib and tivozanib, the ERG would like to see a scenario analysis where the OS and PFS results of the NMA are used in the economic model. Please run scenarios where the hazard ratio model and best fitting fractional polynomial model are used as scenario analyses in the economic model.

Company response

Results of the requested scenario analyses using the hazard ratio model and best fitting fractional polynomial model are presented in Table B14.1. However, as mentioned in Section B.3.2 of the company submission, within the appraisals of TA215, TA512, TA542 and TA581 for pazopanib, tivozanib, cabozantinib and nivolumab respectively, each committee concluded that pazopanib could be considered clinically equivalent to sunitinib, and in TA512 the committee noted tivozanib could be considered (at best) clinically equivalent to sunitinib and pazopanib. Based on these conclusions reached by the committee, it is MSD's opinion that requested analyses under Question B14 are not appropriate to be considered during decision making. Instead, we maintain that for consistency with approaches agreed in previous appraisals (as mentioned above), the assumption of clinical equivalence between sunitinib, pazopanib and tivozanib, as presented within our company submission (see Table 65 of the company submission) should be considered in the base case.

Table B14.1. Base-case results versus external comparators using NMA results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pazopanib	[redacted]	4.209	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	133,668	2.066	64,695
Tivozanib	[redacted]	4.209	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	141,394	2.060	68,626

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B15. Please provide a scenario analysis where parametric PFS models are derived using the Kaplan Meier curves up to the 54 weeks of post-randomisation imaging assessment.

Company response

The Excel model has been updated with an option to model PFS using parametric curves fitted to patient-level data from the KEYNOTE-426 trial [2,3], up to 54 weeks of post-randomisation imaging assessment (please refer to updated economic model provided alongside MSD response). (Note: Our understanding is that question B15 requests parametric curve fitting based on data up to week 54 only. However, we also examined the feasibility of fitting piecewise parametric models using post-week 54 data only and confirmed that this analysis would not be feasible based on the small number of PFS failure events observed after week 54 as of the August 24, 2018 data cut-off. The results described below therefore focus on the impact of using PFS curves fitted to KEYNOTE-426 data up to week 54 only.)

Efficacy parameters and goodness-of-fit statistics for parametric functions of PFS up to 54 weeks are reported in Table B15.1 for the pembrolizumab/axitinib arm and Table B15.2 for the sunitinib treatment arm in the overall population. Smaller values of AIC and BIC indicate better goodness-of-fit with observed data.

Table B15.1 One-piece parametric functions fitted to PFS in KEYNOTE-426, up to 54 weeks: Pembrolizumab/axitinib (overall population)

Functional form	A	B	C	AIC	BIC
Exponential	0.010	-	-	1,796.5	1,800.5
Weibull	-0.211	4.413	-	1,790.5	1,798.6
Log-logistic	-0.347	4.141	-	1,784.7	1,792.9
Log-normal	0.256	4.209	-	1,784.3	1,792.5
Gompertz	0.006	-4.705	-	1,797.3	1,805.4
Generalized Gamma	4.270	0.160	0.241	1,785.5	1,797.7

Source: KEYNOTE-426 (data cutoff date: 24 Aug 2018)

Table B15.2 One-piece parametric functions fitted to PFS in KEYNOTE-426, up to 54 weeks: Sunitinib (overall population)

Functional form	A	B	C	AIC	BIC
Exponential	0.015	-	-	2,035.6	2,039.7
Weibull	-0.200	4.110	-	2,028.3	2,036.4
Log-logistic	-0.385	3.781	-	2,016.2	2,024.4
Log-normal	0.148	3.799	-	2,005.4	2,013.5

Gompertz	0.003	-4.284	-	2,037.1	2,045.3
Generalized Gamma	3.494	0.256	-0.723	2,002.3	2,014.5

Source: KEYNOTE-426 (data cutoff date: 24 Aug 2018)

Results are reported in the "DSA Results" tab of the Excel model and are summarised in Table B15.3. For consistency with the functional form used in the base-case analysis; the displayed results are based on the exponential PFS curve fitted to data up to week 54 in both arms.

Table B15.3 Results of scenario analysis: One-piece parametric functions fitted to PFS in KEYNOTE-426, up to 54 weeks

Scenario Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs SoC		
	Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	137,537	2.320	59,292
Scenario: One-piece parametric functions fitted to PFS in KEYNOTE-426, up to 54 weeks	[redacted]	6.887	[redacted]	[redacted]	3.864	[redacted]	137,502	2.320	59,277

B16. Please include a scenario analysis where patients whose disease progresses on second line treatment receive third line treatment.

Company response

As stated in Section B.3.5 under Miscellaneous unit costs and resource use, the base case presented analysis using the real-world distribution of subsequent therapies. However, as a scenario analysis (#12), the use of trial-based distribution of subsequent therapies was used. As stated in the company submission, more than one line of subsequent therapy is modelled here, which represents the costs of second- and later-line antineoplastic therapies for advanced RCC.

Under this scenario, the proportions of patients receiving different subsequent treatments after discontinuation were based on the frequencies of subsequent treatments observed in the pembrolizumab/axitinib and sunitinib arms of KEYNOTE-426 [2,3] and in the cabozantinib arm of CABOSUN [13]. Specific subsequent

treatment options were included in the cost estimation if they were received by ≥5% of discontinued patients for at least one first-line treatment; the remaining proportion of patients who received other, less commonly used subsequent treatments were proportionately redistributed to the included treatment options. Table B3.1 presents the results of the scenario analysis in the overall population.

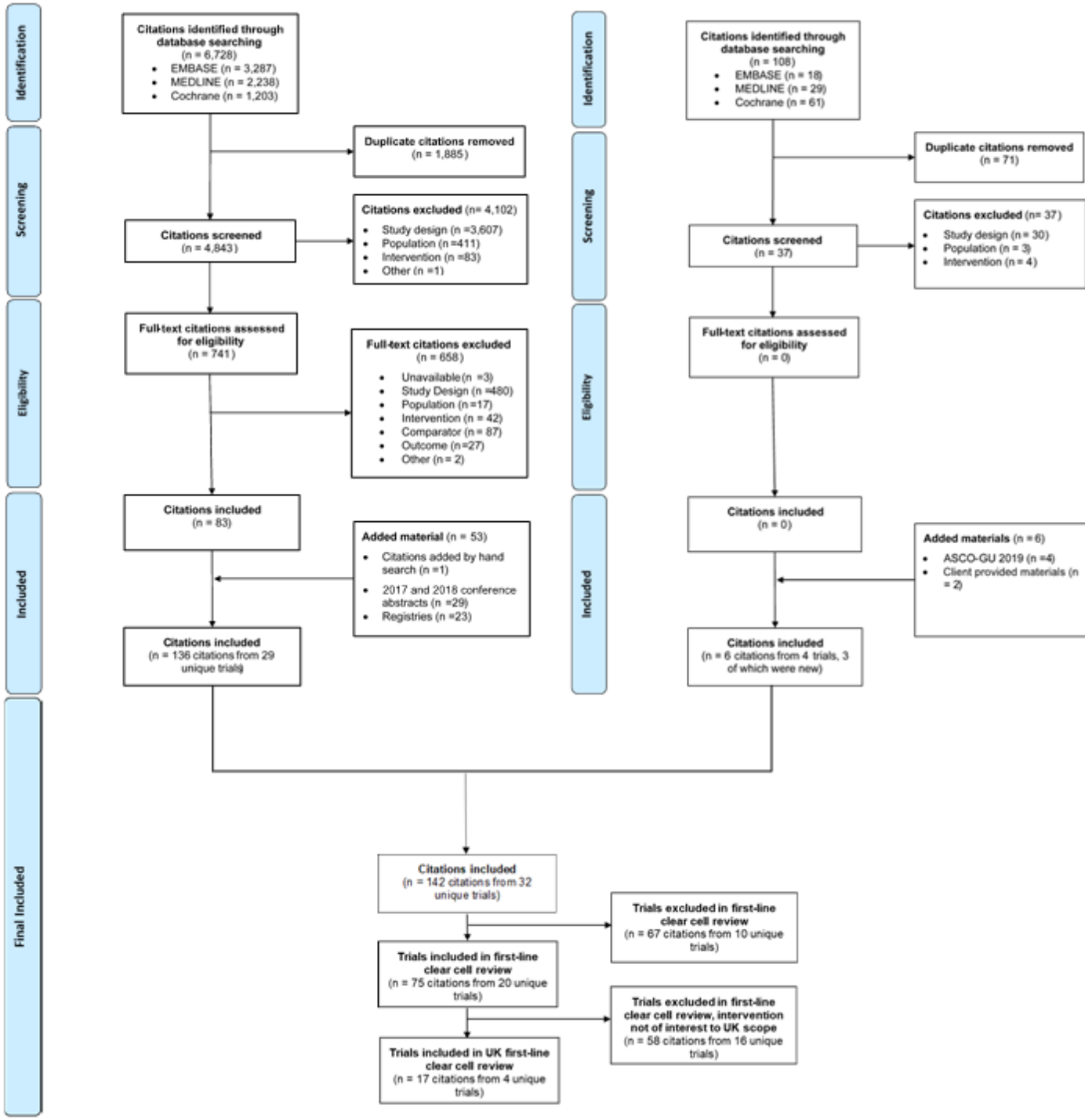
Section C: Textual clarification and additional points

C1. Appendix D1.1.2 figure 1: please provide reasons for exclusion for the step between '142 citations from 32 unique trials' to '20 unique trials'. Please provide the number of citations relating to the 20 unique trials, 16 unique trials and 4 unique trials in the final 3 boxes in the diagram.

Company response

The 32 unique trials originated from trials meeting the criteria for the broader SLR as described in the response to question A9. The broader SLR PICOS criteria encompassed the following populations: 1LCC, 1LNCC, and 2L+CC. The results from the broader SLR (32 unique trials) was pared down to 20 trials upon the removal of trials that were not conducted in 1LCC population or did not provide subgroup data for 1LCC patients. An updated PRISMA diagram with the corresponding number of citations is provided below (Figure C1).

Figure C1. Updated PRISMA diagram



References

1. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA: a cancer journal for clinicians. 2017 Mar;67(2):93-9.

2. Rini, B.I., et al., Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New England Journal of Medicine, 2019. 380(12): p. 1116-1127.

3. Merck Sharp & Dohme Corp., a.S.o.M.C., A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy

4. Merck Sharp & Dohme Corp., a.s.o.M.C., Protocol of A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426). 2018

5. K. Liang and S. Zeger, "Longitudinal data analysis of continuous and discrete responses for pre-post designs," *Sankhyā: The Indian Journal of Statistics,* vol. 62, no. Series B, pp. 134-148, 2000.

6. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007 Jan 11;356(2):115-24.

7. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, Negrier S, Laferriere N, Scheuring UJ, Cella D, Shah S. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. Journal of clinical oncology. 2009 Jan 26;27(8):1280-9.

8. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of clinical oncology. 2009 Aug 1;27(22):3584.

9. Zondervan-Zwijnenburg M, Peeters M, Depaoli S, Van de Schoot R. Where do priors come from? Applying guidelines to construct informative priors in small sample research. Research in Human Development. 2017 Oct 2;14(4):305-20.

10. Okita K, Hatakeyama S, Tanaka T, Ikehata Y, Tanaka T, Fujita N, Ishibashi Y, Yamamoto H, Yoneyama T, Hashimoto Y, Yoshikawa K. Impact of Disagreement Between Two Risk Group Models on Prognosis in Patients With Metastatic Renal-Cell Carcinoma. Clinical genitourinary cancer. 2019 Jun 1;17(3):e440-6.

11. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. New England Journal of Medicine. 2013 Aug 22;369(8):722-31.

12. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, Feldman DR, Olencki T, Picus J, Small EJ, Dakhil S. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. Journal of Clinical Oncology. 2017 Feb 20;35(6):591.

13. Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, Walsh M, Olencki T, Picus J, Small EJ, Dakhil S. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. European Journal of Cancer. 2018 May 1;94:115-25.

14. Gore ME, Szczylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer. 2015;113(1):12-19

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

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 conditions and their treatment that is not typically available from other sources.

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Cancer Support Network
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Cancer Support Network (KCSN) was founded in 2006 by cancer patients/survivors [redacted] and [redacted], who started by providing practical and bespoke support to individual patients for access to life-extending cancer drugs to treat 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 KCSN. Over the years, KCSN has grown considerably, with a membership of over 1300 kidney cancer patients and carers on its confidential social networking sites. KCSN is unique; until recently it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Although KCSN remains patient-led, the group is now a registered charity, which enables it to better meet the growing needs of the kidney cancer community. KCSN is funded by grants from trusts, foundations and the pharmaceutical industry, in addition to donations from patients and fundraising events/activities carried out by the kidney cancer community in the UK.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	When gathering the information for this submission, we specifically asked for patient and carer experience of using the pembrolizumab plus axitinib combination through our closed social media channels. We have a dedicated immunotherapy Facebook group specifically set-up to help us collate experiences from patients using these types of medication. Over 1300 patients and carers use these channels to

carers to include in your submission?	communicate on a regular basis, and we receive in the order of 5-600 posts a day on our closed Facebook group.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	KCSN is a patient-led kidney cancer charity with the largest and most active patient and carer membership across the UK. As such, we feel we are in the strongest position to feedback how metastatic renal cell carcinoma (mRCC) affects the day-to-day lives of people living with this disease. In 2014-16, there were nearly 13,000 new cases of kidney cancer diagnosed annually in the UK (35 cases diagnosed every day) and kidney cancer is the seventh most common cancer affecting British people. Kidney cancer accounts for 3% of all new UK cancer cases (2014-16). In 2014-16, 4,600 people died from the disease and about a third of kidney cancer patients will be diagnosed with late stage disease. In these cases, it is estimated that only 7% of people will survive for five years or more (Cancer Research UK). It is difficult to remain positive in the face of figures like this. Metastatic RCC is a devastating disease and is currently incurable. The majority of mRCC patients are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings enormous financial pressures for the patient and their family (and additional costs to the state), and can precipitate psychological problems; depression, loss of confidence and self-worth. Patients may suffer constant pain from metastatic tumours in the brain, bones, lungs, liver, and other rarer sites. Patients with bone metastases are at risk of bone breaks and spinal cord compression. Metastases in the lungs can lead to breathlessness, and persistent coughing. Spread of the cancer to the brain can lead to severe and debilitating headaches, confusion and, in some cases, paralysis. Kidney function is often compromised, and patients find daily living difficult, often needing periods of rest during the day. Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental as well as physical clinical situation. Sexual function is affected for both male and female patients, and family life suffers as a result. Patients diagnosed with

	hereditary kidney cancer or rare RCC subtypes currently have very limited treatment options, exacerbating feelings of depression, fear and low self-worth. Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period of time. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, a process of elimination is used to select the most effective treatment for individual patients. Clinicians in the UK should have the ability to choose the optimal treatments for individual patients from those available. Without a choice of treatment alternatives, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients need to be able to choose their therapy to continue managing their disease, and to maintain quality of life. An increase in the choice of treatments will eventually lead to more personalised therapy, enabling patients and clinicians to tailor care plans to suite individual patient needs. Kidney cancer cases are rising year-on-year and there is a need for first-line treatment with better overall survival rates than currently exist, especially for difficult-to-treat rare subtypes of RCC. The impact of a terminal diagnosis on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one is diagnosed with a terminal disease.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The current treatment pathway for mRCC is surgery (either radical or partial nephrectomy), followed by either sunitinib, pazopanib or tivozanib in the first-line setting, and axitinib, everolimus, cabozantinib or lenvatinib plus everolimus in the second-line setting, all of which are oral medicines and have similar modes of action (vascular endothelial growth factor receptor (VEGFR) inhibitors or mTOR inhibitors that block angiogenesis). Nivolumab is also recommended for use within NHS England for second- or third-line treatment of mRCC and is the first third-line treatment in use by the NHS. Nivolumab is an immunotherapy (anti-PD-1), which is administered as a biweekly intravenous infusion, requiring outpatient hospital treatment (chemotherapy chair resources), and the associated travel time and expense for the patient and carer.

	We have extracted the following details from statements submitted to the KCSN by patients living with mRCC. Using currently available drugs, many patients suffer with the following side effects, all of which severely affect quality of life: • Extreme fatigue • Rash and itching • Severe hand and foot syndrome which can leave patients unable to walk • Intestinal problems (chronic diarrhoea) • 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-mediated adverse reactions • Muscle pain/joint pain • Constipation • Diarrhoea All the above side effects require additional medicines to help patients manage the drugs and/or tumour pain, which require opioid prescriptions. Costs for additional medicines to mitigate the side effects of these therapies should be taken into account. Other less serious side effects, which still affect the patient's quality of life, are headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment as a result of severe side effects. Patients are aware that these treatments are life-extending drugs, but they continue to look for drugs with different modes of action, which can give improved overall survival with better quality of life. For patients that have been on standard first-line treatment with VEGFR inhibitors and experienced severe side effects, combination immunotherapy and VEGFR inhibitor could see a dramatic change in quality of life:

	"No GI issues at all like I had with Sutent. Some knee and shoulder pain, but I am used to that from arthritis. Food is great, energy is great... I feel cured!! I realise I am not... but I never knew I had kidney cancer until they told me I did... and I never was sick. Start Sutent, and that is all I felt... sick. The surgery to remove my kidney, took me about 8 or 10 months to feel good again... brain met surgery... easy... my hard part was the Sutent side effects." *"When I began treatment I was in a state of helplessness. The abdominal tumour was located in such a position that it was growing so fast and caused so much pain I was unable to function. I was taking very high doses of Opiate pain medication with the result that I had no appetite and combined with side effects of Sutent my weight dropped to 139 pounds from 210 pounds. I lost large amounts of muscle. As a result I was eventually confined to a wheelchair. I was unable to carry out even basic tasks and from being a very physically strong man who was very active and worked on my small ranch, I could do nothing for myself. I was very ill; I was told I had about 12 months to live. Tumours were growing aggressively."* *"I have had three infusions of Nivolumab and I feel great. So far only minor SE. There was some shoulder, neck and headaches at first, but none in the past week after my last infusion. I was on Votrient for almost year and I am so glad to be rid of the GI side effects. My energy is good, my taste buds are back, no more tingling in hands and feet and my hair colour is slowly returning."* For the majority of patients, the most important treatment outcome would be no evidence of disease, i.e., a potential cure for their kidney cancer. The hope of achieving this outcome spurs patients on to continue to take current medication, despite significant toxicity, and to search for alternative, more effective treatments that can extend overall survival. Failing to achieve no evidence of disease, tumour shrinkage or disease stability would be the next best outcome for patients. In addition to treatment outcomes, quality of life is also an important consideration for many patients. Most patients would prefer a treatment that allows them to continue to lead as normal a life as possible, and to contribute both socially and economically to their communities: *"The extra years, which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various ……. enterprises which I manage…….. I'm making a hugely positive contribution to society, and the*

	wider economy, and I wish to be able to carry on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities". *"…….has enabled me to enjoy every day, do 3 or 4 days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths……".* Although less serious than some of the side effects to current first-line treatments available via NHS England, some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and also singles people out as cancer patients. Some of the current first-line treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels. 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. Carers seem to find this even harder, as they live with a guilt of not being able to do all they can for their loved one. Access to a choice of treatments in the first-line would enable patients and their families to know that they had tried their best to beat the cancer, leading to better family relationships and a subsequent improvement in quality of life and wellbeing for the patient. Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities; international discussion forums exist where patients talk to one another daily, and 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 combination treatments is readily available to patients around the world on websites. Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so that patients in England have the same choices as patients in other countries and to improve outcomes.

8. Is there an unmet need for patients with this condition?	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 or rare RCC subtypes, who currently have very limited treatment options.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The pembrolizumab plus axitinib combination has been proven to be a clinically effective and well-tolerated treatment and was granted priority review status by the FDA for the treatment of advanced RCC. As a result, FDA approval for the combination treatment came 2 months earlier than expected. The pembrolizumab plus axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in metastatic RCC. The opinions of patients and carers of the pembrolizumab plus axitinib combination are based on their experience of nivolumab and axitinib monotherapies in the second-line setting. They are hopeful that the combined immunotherapy/VEGFR inhibitor will improve survival compared to current first-line treatments. This is borne out by the results from the KEYNOTE-426 study in which the combination of pembrolizumab plus axitinib significantly improved median progression-free survival by 4 months compared to sunitinib in patients with previously untreated advanced RCC. There was a 31% reduction in the risk of disease progression in patients taking the combination treatment. In addition, 59% of patients had an objective response rate with pembrolizumab plus axitinib, compared with 36% of patients on sunitinib. Overall survival rates were higher at 12- and 18-months with pembrolizumab plus axitinib than with sunitinib, at 89.9% versus 78.3% and 82.3% versus 72.1%, respectively. Survival benefits were irrespective of PD-L1 status or risk group. The improvement in progression-free and overall survival could be as a result of the additive effect of combining an immunotherapy with a VEGFR inhibitor, both of which have different modes of action to currently available treatments. Patients are optimistic that this synergistic effect will result in improved overall survival.

	In addition, the safety profile of the pembrolizumab 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 quotes are taken from patients with advanced RCC being treated with an immunotherapy plus axitinib combination treatment: *"…….my experience of [this combination treatment] has been one of positives. I've been able to live pretty much normally, bearable side effects and until my heart issue (not cancer related we don't think) had shrinkage of 51% over a total of 8 months. Now hoping I can get back on it as post 6 months from my heart op [I have] only been on [pembrolizumab] which on its own has shown 17% growth. These new combinations are looking so promising."* *"I was first diagnosed with a tumour on my right kidney ……. in Summer 2016. A CT scan showed ….. a 4cm tumour that went onto the Vena Cava …… opted for a full Nephrectomy….. October of the same year……March 2017 it was noted to be in my lymph nodes in the renal bed. I was offered standard TKI treatment…….. but the Oncologist offered to refer me to a London cancer centre to explore more options. I volunteered for the [pembrolizumab/axitinib] trial ……. June 2017.* *"……..the side effects of the first [pembrolizumab infusion] was [sic] quite extreme with flu-like symptoms and aches pains, these soon wore off…….I only noted 2 minor side effects of the [axitinib] at this stage and this was spots in my hair and a slight sore throat. However, these were in no way affecting my quality of life. I actually went on a 3-week road trip around Europe without any problems.* *"September 2017 I was put up to 7mg twice a day. This caused some worse side effects with sore mouth, a worse sore throat, sore feet and slight diarrhoea. Again, this did not affect my quality of life too much and I was put [up] to 10mg twice a day in Feb 2018. I have managed to stay on 10mg twice a day, but the side effects can be extreme. I have daily diarrhoea up to 5 times a day, this has led to other connected effects such as ……. haemorrhoids, my feet can be so sore that I*

	cannot walk, I suffer with sore mouth at times, the most unusual side effect is that my muscles can get really tight and make my body ache. I have suffered with breathlessness, headaches, my thyroid has suffered, and I am now on 150mg of Thyroxine daily. However, I have managed to stay on 10mg twice a day and continue to work and lead a normal life (relatively). I don't really experience tiredness, but I have noticed my memory has suffered slightly. *"……..in the summer I have hardly any side effects, the diarrhoea remains but sore feet, mouth, spots in the hair etc. all clear up. As soon as it gets cold again and I come into contact with bugs and viruses the side effects seem to get worse again.* *"The results have been great, so far! [The metastasis in the lymph nodes has reduced from 27mm to 5mm]."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We understand that combination treatments are expensive, and we appreciate the budgetary constraints of the NHS. Nonetheless, NICE and the manufacturer need to work collaboratively to negotiate an acceptable patient access scheme to ensure RCC patients can benefit from this latest clinically effective drug combination; failure to do so would be seen as failure of professional competence. Pembrolizumab is given intravenously over 30 minutes every 3 weeks until disease progression or drug intolerance. This requires hospital visits every 3 weeks and the provision of chemotherapy chairs for the infusion. Axitinib is an oral drug, which can be taken at home. Standard first-line treatment with oral VEGFR inhibitors only require a monthly hospital visit to replenish supplies of medication. Patients will typically be travelling some distance to a regional cancer centre for the pembrolizumab infusions and to collect axitinib supplies. Some patients may need to take time off work, or have a partner travel with them to treatments, the practical aspects of which can impact the quality of life of both patient and carer.

	However, balanced against the extra travel and time is the improved side effect profile and enhanced quality of life. Most patients feel much better able to cope with life, and some return to work. Half a day in hospital is preferable to the debilitating side effects of VEGFR inhibitors.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues	
13. Are there any other issues that you would like the committee to consider?	Pembrolizumab plus axitinib is one of the first combinations of immunotherapy plus VEGFR inhibitor. 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 these novel combinations are made available to patients in order that they have the best possible care. If these combinations 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, and without the pembrolizumab plus axitinib combination, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the first-line, 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 first-line treatment options are not effective for everyone. Undue restrictions in accessing novel combination therapies would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission:	

- The pembrolizumab plus axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in advanced RCC, and has been granted priority review status by the FDA
- The pembrolizumab plus axitinib combination is well tolerated, as well as proven to be more effective at extending progression-free and overall survival, and improving overall response rates compared to standard first-line treatment with sunitinib
- Adding the pembrolizumab 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 and overall survival and relative toxicity of the pembrolizumab plus axitinib combination enhances quality of life and enables patients to contribute socially and economically to society
- The pembrolizumab plus axitinib combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

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 conditions and their treatment that is not typically available from other sources.

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney cancer UK
3. Job title or position	[redacted] – [redacted]
4a. Brief description of the organisation (including who funds it). 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. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We have no links with the tobacco industry.

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 living with kidney cancer days and 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 emailed them questions to help in the submission or talked to them by phone.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of Kidney Cancer can be life changing especially since most tumours are not found at the early stages of the disease. The condition can cause patients and their family considerable anxiety due to delayed and missed diagnosis. Patients are apprehensive and live with uncertainty as they wait for scan results and are fearful of what might come next. A patient stated, “I am constantly on a rollercoaster, emotionally and physically.” Another expressed “It’s like living in limbo.” There is though a real sense of positivity with the community that they are able to have treatment and mostly go on living a normal life. Carers of patients with kidney cancer can find the situation very difficult. One patient describes how his wife constantly worries about him. He states she always wants to be with me when visiting the hospital and likes to be fully aware of my condition and treatment. People living with kidney cancer 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, “There is an overwhelming feeling of helplessness and frustration, with no control over the situation. It is impossible to make any plans.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	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 patient 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. Another patient described how he had Christmas dinner early. "When I am on my two week break I can manage to eat, when I am on treatment this is not a given. I feel nausea, I have diarrhoea and really don't feel like eating. So, we have had our Christmas meal a few weeks early". 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 also comes with specific adverse reactions and 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. Another patient skin problem led him to be admitted due to the severity of the blistering, pain and irritation. 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.
8. Is there an unmet need for patients with this condition?	Kidney cancer is not a homogenous disease and even within the renal clear cell cohort (75 % of all cases), the tumours can be of different grades and characteristics. Some people have very aggressive tumours and treatments fail them quickly. The unmet need within the advanced renal cancer community is an effective first line treatment which would give a durable response whether this is complete or partial. Another other important aspect to patients is a good quality of life whilst they are on treatment, this may be managed side effects. Systemic treatment for brain metastases is also a concern since most treatments do not pass through the blood brain barrier and spread of metastases to the brain is only noticed when patients have symptoms. The standard of care currently is radiotherapy. One more unmet need for this community is psychological and emotional support after initial diagnosis of kidney cancer and whilst they are on treatment to help deal with side effects and the impact of their cancer on their life. As a charity we are trying to address some of these support issues.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages are using the combination of an immune checkpoint inhibitor and a VEGF-targeted antiangiogenic therapy is that they may provide enhanced benefit through complementary mechanisms of action. This is reassuring for patients that as much as possible is being done to stop the spread of the cancer. The analysis of the adverse event profile showed a lower rate of immune side effects than the combination of nivolumab and ipilimumab. The infusion is of short duration and therefore does not mean an extended time in hospital. Patients feel seeing a health care professional to have an infusion is reassuring and they appreciate the help and support they are being given. Another benefit is meeting other patients and carers in the same situation as them, this helps them to so not feel alone It is not as common for patients to discuss the experience of oral treatment in a waiting room of clinic, although there are many who are able use online platforms or attend support groups as available. Patients reported despite having some severe adverse reactions and many manageable side effects; they were able to carry on with daily activities. “I seem to manage quite well to live a normal active life, tiredness occasionally being the only constant.”

	"For me it's entirely tolerable and has no effect on my activities, I do a physical job, I go to the gym most days, I love to walk and enjoy a pint!" The combination of Pembrolizumab and axtinib in the clinical study showed a greater median progression free survival of 15.1 months compared to 11.1 months with sunitinib. This was observed across the international metastatic renal cell carcinoma database consortium risk group; favourable, intermediate and poor risk and regardless of programmed death ligand 1 expression. The objective reason was 59.3% in the pembrolizumab-axtinib group compared to 35.7% in the sunitinib group. A complete response was seen in 5.8% of patients in the pembrolizumab- axtinib group compared to 1.9% in the sunitinib group. This is a great advantage for the kidney cancer population.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The distinct disadvantage of this technology is the adverse events of both drugs in combination. In the clinical trial grade 3 or higher adverse events of any cause occurred in 75.8% of patients in the pembrolizumab-axtinib group compared to 70.6% in the sunitinib group. Although patients we spoke to reported some of these grade 3 adverse reactions; for example, pneumonitis and hepatoxicity toxicity. They felt that their clinical teams managed these promptly and did not cause much disruption to their treatment or quality of life.

	Most persistent adverse events were attributed to the axtinib whilst clinicians titrate the right dose suitable to the individual. Patients suffered a variety of adverse events including diarrhoea, hypertension, skin changes, mucosal inflammation and more. All these interrupted their quality of life making them feel washed up and fatigued and therefore not being able to do their activities of daily living or make reliable arrangements with friends and family. Hypertension was a consistent theme with patients feeling frustrated that they had to come off their medication until this resolved. Diarrhoea was also significant with one lady feeling that she always needed to know where the toilet was in case of an emergency and stopped her from going out. A perceived disadvantage maybe having infusions at the hospital since currently most treatment is oral and is self- administered at home. This maybe a burden on the family who may need to bring the patient to hospital on several occasions, as well as making the day long for the patient. This maybe a temporary barrier until treatment is established. In the current climate cancer services are developing satellite treatment centres, mobile treatment units and home care infusions are seeing more immunotherapies delivered nearer to home.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The technology will benefit all MSKCC/IMDC prognostic groups and specifically favourable who missed out on inclusion of the nivolumab and ipilimumab indication. Patients who maybe needle phobic may struggle with the infusion, although complementary therapy when available could help. Also, a central line or Port may be sited to negate this anxiety. Patients with multiple morbidity and disabilities may find it difficult coming to hospital more frequently due to their complex health issues. This is where home infusions maybe beneficial to accommodate these patients. Geographical location of specialist centres can be an obstacle but most patients we talked to were willing to travel for this treatment. We note that the US food and drug administration has approved pembrolizumab and axitinib in April 2019. This is the first FDA approval for an anti-PD-L1 therapy as part of a combination regimen for patients with advanced RCC.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: ➢ There is an unmet need within the advanced renal cancer community for an effective first line treatment which would give a durable response whether this is complete or partial.	

- The advantages are that using the combination of an immune checkpoint inhibitor and a VEGF-targeted antiangiogenic therapy is that they may provide enhanced benefit through complementary mechanisms of action. This is reassuring for patients that as much as possible is being done to stop the spread of the cancer
- The technology will benefit all MSKCC/IMDC prognostic groups and specifically to those favourable patients who missed out on inclusion of the nivolumab and ipilimumab indication.
- The combination of Pembrolizumab and axtinib in the clinical study showed a greater median progression free survival of 15.1 months compared to 11.1 months with sunitinib

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

Thank you for agreeing to give us your 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.

About you	
1. Your name	**Dr Tom Waddell**
2. Name of organisation	**Christie NHS Foundation Trust, Manchester, UK**

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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ 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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	In the setting of metastatic renal carcinoma (RCC), the primary goals of treatment are to prolong life (improve overall survival), and to ensure that the quality of life is maintained or improved for patients living with this incurable condition. Improvements in quality of life may occur through management of any disease-related symptoms, improvements in the degree of tumour shrinkage (response rate), and delay in the time until tumours start to regrow (progression-free survival). If the above goals can be achieved with advances in the treatment of metastatic RCC then we can be confident that we are both providing more time for patients living with the condition, whilst at the same time ensuring that they can spend this time feeling well, and able to perform most of their normal activities / roles / responsibilities.
8. 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.)	Tumour shrinkage by more than 30% of its original volume is regarded as clinically significant, and is the definition of 'response' within clinical trials. Historically, this level of shrinkage has been difficult to achieve for most RCC patients with standard therapies such as VEGF TKIs. For a new treatment to represent a significant advance, it should bring about this level of clinically significant tumour shrinkages in a greater proportion of patients compared to the standard of care. It should also result in a longer average duration of tumour control, with ideally a 3 month or more improvement in the average progression-free survival. Similarly, it should result in patients living longer on average through improvments in overall survival of at least 3 months or more.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is definitely an ongoing high unmet need for both patients and healthcare professionals in the setting of metastatic RCC. This evidenced by the fact that the average survival of patients with this condition remains somewhere between 2-2.5 years and the majority of these patients will die as a direct result of their RCC diagnosis. Whilst the last few years have seen some improvements in the available treatment options, there is still a long way to go if we are to find ways to cure more patients or turn metastatic RCC into a chronic disease state without threat to life.

	This unmet need is highest in non-clear cell renal cancers where the number of patients (and therefore strength of phase III trials evidence) is less than for clear cell RCC. The non-clear cell group have significantly poorer outcomes in all domains (response rate, progression-free survival and overall survival) and urgently need access to more effective therapeutic options.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Current first-line options approved in the NHS include only single agent VEGF TKI drugs – Sunitinib, Pazopanib, Tivozanib or Cabozantinib. More recently, we have had access to the immunotherapy combination of Ipilimumab and Nivolumab via the CDF for patients with intermediate or poor risk RCC. Whist effective, this combination is associated with a high level of severe immune-related side effects which lead to hospital admission and prolonged courses of steroid treatments.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a number of international clinical guidelines in use for the management of metastatic RCC, though these are currently requiring to be updated very regularly due to positive trial findings and the emergence of novel combinations including the Pembrolizumab plus Axitinib combination. The 2 main guidelines guiding clinical practice are the 'NCCN Guidelines for Kidney Cancer' (in North America) and the 'ESMO Clinical Practice Guidelines for Renal Cell Carcinoma' (in Europe). Within the UK we are also prescribing according to NICE and NHSE guidance regarding funded drug treatments and reimbursement.
• Is the pathway of care well defined? Does it vary or are there differences of opinion	The overall pathway and goals of care are well defined as highlighted in the above international guidelines. However, due to the availability of different VEGF TKI options, there will be subtle differences in the exact medications in use between different NHS professionals. These drugs are regarded as equivalent and

between professionals across the NHS? (Please state if your experience is from outside England.)	therefore these variations according to physician preference do not significantly impact outcomes such as disease control or survival.
• What impact would the technology have on the current pathway of care?	The combination of Pembrolizumab and Axitinib would replace the use of single agent VEGF TKIs as a 1st line of treatment for metastatic RCC. Since the combination of Pembrolizumab and Axitinib is well tolerated and leads to fewer immune-related side-effects requiring hospital admission, it would also be expected to be used in preference to the Ipilimumab and Nivolumab combination in many UK centres. Use of single agent VEGF TKIs would therefore become a standard treatment approach in 2nd line and beyond. Other treatment options such as Everolimus or Everolimus plus Lenvatinib would also remain options in the 2nd line and beyond space (where they are positioned currently).
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – the use of Pembrolizumab plus Axitinib would replace current standards of care in 1st line. The axitinib is used in exactly the same way as other VEGF TKIs. The only addition would be the need for intravenous treatment with Pembrolizumab every 3 weeks. However, use of this drug within a 1st line combination would replace the use of single agent Nivolumab therapy in subsequent treatment lines. CT scan frequencies and clinic reviews would continue at the same frequency alongside the new technology (no change compared to current standard of care).
• How does healthcare resource use differ between the technology and current care?	As above, there would be the need for intravenous treatment administration every 3 weeks. This is the only difference compared to current care provision. 3 weekly intravenous treatment is already in use for those patients receiving Ipilimumab and Nivolumab. For those patients receiving VEGF TKIs, they would normally receive intravenous treatment with Nivolumab in later lines of therapy. This would be substituted by the use of Pembrolizumab in the 1st line combination. There is therefore no significant overall difference in healthcare resource use from a treatment administration perspective.

	Due to the fact that Pembrolizumab and Axitinib would result in fewer hospital admissions for management of toxicity compared to the Ipilimumab and Nivolumab combination, it may be expected to save on healthcare resource in this regard.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This combination should only be used in secondary care and would be overseen by specialist oncologists who treat renal cancer. It would not be prescribed or managed by primary care doctors.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No change compared to current NHS services. Similar drugs are already in routine use and the novel aspect of the new technology is only to combine the use of a VEGF TKI and a checkpoint inhibitor at the same time (normally used sequentially). Physicians, nurses and hospitals are therefore already familiar with the administration and side effect profiles of these drugs.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Definitely. The Keynote-426 data is very clear in demonstrating that the combination of Pembrolizumab and Axitinib is associated with meaningful improvements in response rate, progression free survival and overall survival compared to standard of care Sunitinib.
• Do you expect the technology to increase length of life more than current care?	Yes Due to the relatively short follow-up of Keynote-426 patients to date, the median overall survival is not yet known in either trial arm. However, after a median follow-up of 12.8 months, the percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab–axitinib group and 78.3% in the sunitinib group (HR 0.53; 95% CI, 0.38 to 0.74; P<0.0001). This means that at 1 year the risk of death was reduced by 47% with Pembrolizumab and Axitinib, resulting in 10% more patients still being alive.

	Additionally, due to the mechanism of action of checkpoint inhibitors, it is also observed that more patients achieve deep responses (>80% reduction in tumour volume) or complete responses (disappearance of all visible tumour) with the combination compared to standard of care. Some of these patients will have longterm durable remissions that may even equate to cure. This effect is not seen with use of VEGF TKIs where all patients will eventually progress and die as a result of the disease.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes The side effect profiles of the 2 groups is relatively similar so there will be no overall detrimental effect on quality of life associated with the combination of Pembrolizumab + Axitinib compared to standard of care options. Importantly, quality of life in this patient group is predominantly driven by having good control of the metastatic cancer sites. Therefore, since Pembrolizumab plus Axitinib offers more tumour shrinkage, and prolonged disease control compared to standard of care, patients receiving this combination will maintain a better quality of life for longer. This improved quality of life will allow patients to maintain their normal activities / roles / employment for longer than they are able to currently with standard of care therapies.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No It would be expected that this combination would be more effective than standard of care options for all patients with metastatic RCC. In particular this effect has been confirmed across all prognostic groups (favourable, intermediate and poor) and would be expected regardless of the histological subtype of RCC (clear and non-clear cell patient groups).
The use of the technology	

14. 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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Neutral effect overall – it is no easier or more difficult than current standards. It is combining 2 drugs in combination rather than using a VEGF TKI and an immune checkpoint inhibitor sequentially. No additional tests or monitoring will be needed.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting therapy will be on the basis of a confirmed diagnosis of metastatic RCC. Stopping rules would be according to patient tolerance which is the same as with current standard of care options. If patients have had a very good response then Pembrolizumab and Axitinib could be stopped after 2 years of therapy and it is likely that the treatment effect would continue. There is no need for any additional testing over standard of care to guide starting or stopping.

16. 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?	I would estimate that approximately 15% of patients will achieve longterm durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered. This 'tail of the curve' effect has been seen at a lower % level with single agent Nivolumab in RCC and is well described with immunotherapy in metastatic melanoma. Additionally, in comparison to combination with Ipilimumab and Nivolumab, there will be fewer severe immune-related side-effects with Pembrolizumab and Axitinib. This will lead to fewer hospital admissions for management of toxicity.
17. 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?	Yes This combination is already demonstrating substantial improvements in all measured parameters after relatively short follow-up (1yr OS 90% vs 78%, median PFS extended by 4 months, response rate 59% vs 36% and complete response rate 6% vs 2%). All of the above parameters represent a huge step forwards in the treatment of metastatic RCC compared to using single agent VEGF TKIs such as Sunitinib. The durability of these responses for some patients is completely transformative, and therefore this combination significantly reduces the unmet need for responding patients.
• Is the technology a 'step-change' in the	Definitely – as highlighted in the responses above.

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	With any treatment there will be a group of patients who do not respond at all (so called 'primary progressers'). These patients have the highest unmet need as they have treatment-resistant tumours and have very poor outcomes compared to other patients. From the Keynote-426 data, the % of patients who have primary disease progression on Pembrolizumab plus Axitinib is only 10.9%. This compares to 17% of patients with primary progression on Sunitinib. We can therefore be more confident about the ability of Pembrolizumab and Axitinib to offer control of the cancer for most metastatic RCC patients. In addition, due to the 'tail of the curve' effect with the combination approach, it is likely that Pembrolizumab and Axitinib will result in longterm remissions for some patients. For these patients the threat of dying from their cancer will be almost entirely negated. This does not happen with single agent VEGF TKIs.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No overall difference in side effect profile compared to standard of care therapies. Overall quality of life effect is improved for the reasons outlined in section 12 above.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – except that the phase III evidence is only in those with clear cell RCC. Trials populations will always have the fittest patients compared to the real world population, but the results are definitely representative and applicable to all metastatic RCC patients.
• If not, how could the results be extrapolated to the UK setting?	Inclusion of non-clear RCC histologies as well as clear cell to improve outcomes across all UK RCC patients.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most striking findings of the study are the significantly improved % tumour shrinkage as evidenced by the response rates, and the 47% reduction in the risk of death at 1 year. For patients, the most important outcome is the overall survival and this was the primary outcome being evaluated (and significantly improved) with this technology.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No Neither of these drugs are ‘new’ and the side-effect profiles of both Pembrolizumab and Axitinib are very well known and reported.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA169, TA215, TA512, TA542]?	No
22. How do data on real-world experience compare with the trial data?	We know that in the real world, Sunitinib does not normally perform as well as was seen within the Keynote-426 trial. Therefore, despite Sunitinib performing better than might normally be expected, it is clear that Pembrolizumab and Axitinib was superior across all evaluated endpoints. There is no real world data available yet in relation to Pembrolizumab plus Axitinib as this combination has only just received a European license and is not yet reimbursed for use in the UK. Importantly, it was granted priority review status by the FDA due to the strength of the trial findings.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- The pembrolizumab plus axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in advanced RCC, and has been granted priority review status by the FDA
- The pembrolizumab plus axitinib combination is well tolerated, as well as proven to be more effective at extending overall survival, progression-free survival and response rates compared to standard first-line treatment with sunitinib
- Adding pembrolizumab plus axitinib 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 and overall survival, combined with the low relative toxicity of the pembrolizumab plus axitinib combination, enhances quality of life and enables patients to contribute socially and economically to society
- The pembrolizumab plus axitinib combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

Thank you for agreeing to give us your 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.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Balaji Venugopal
2. Name of organisation	Beatson West of Scotland Cancer Centre

3. Job title or position	Honorary Clinical Senior Lecturer - University of Glasgow Consultant in Medical Oncology
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 this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's	☐ yes, I agree with it ☐ no, I disagree with it

submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ I agree with some of it, but disagree with some of it x other (they didn't submit one, I don't 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
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Advanced renal cell carcinoma (aRCC) is a debilitating condition which causes significant deterioration in patients' quality of life and longevity of life without any option of cure. The aims of treatment are improve the overall survival, treat cancer related symptoms and extend the progression free survival, whilst improving the quality of life.

8. 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.)	Partial response defined as 30% reduction in the burden of disease as measured using Response evaluation criteria in solid tumours (RECIST). In patients with rapidly progressive cancer, stabilisation of disease is also an acceptable clinical end point.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, There is an unmet need for patients and healthcare professionals as the currently approved drugs do not achieve durable clinical response and are associated with significant side effects.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients with advanced renal cell carcinoma (aRCC) can be grouped to three distinct risk groups as per the presence of adverse prognostic factors, with as per International metastatic renal cell carcinoma database consortium (IMDC). Patients in favourable risk group are managed differently to patients with intermediate or poor risk group. Patients with aRCC of favourable prognosis group can be treated with one of the three vascular endothelial growth factor (VEGF) targeted tyrosine kinase inhibitors (VEGF-TKIs) namely pazopanib, sunitinib or tivozanib; patients with aRCC of intermediate or poor risk are treated with nivolumab in combination with ipilimumab (ipilimumab/nivolumab); For patients with aRCC of intermediate or poor risk for whom immunotherapy is contraindicated, one of the four VEGF-TKIs namely cabozantinib, pazopanib, sunitinib or tivozanib is used..

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	European Association of Urology (EAU) guidelines 2019; ESMO guidelines on management of renal cell carcinoma (2019).
• 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.)	There are differences in the preference for ipilimumab/nivolumab or one of the four VEGF TKIs between clinicians. My experience is based on treating patients in NHS Scotland and also through peer to peer interactions with clinicians across NHS England.
• What impact would the technology have on the current pathway of care?	The combination of pembrolizumab and axitinib (technology) could be used as one of the first line treatment options in advanced RCC of all risk categories, and will displace ipilimumab/nivolumab and one of the 4 VEGF TKIs in a proportion of these patients
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Clinician and health care professionals treating aRCC are qualified to use immune checkpoint inhibitors and targeted agents.
• How does healthcare resource use differ	Combination of immuno-oncological agents/immune checkpoint inhibitors administered intravenously and VEGF TKI administered orally is differs from the current care wherein it is either a combination of immuno-oncological agent (ipilimumab/nivolumab) or one of the VEGF TKI (cabozantinib, pazopanib, sunitinib, or tivozanib) dependent upon the prognostic groups.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology would be delivered in specialist clinics with expertise in management of patients on immune checkpoint inhibitors and targeted agents (VEGF TKIs). Treatment can be delivered in an outpatient setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Clinician and health professionals treating aRCC are qualified to use immune checkpoint inhibitors and targeted agents (VEGF TKIs) and no additional training is needed. However as pembrolizumab is administered intravenously, there will be an impact on the service delivery in day bed units administering systemic anticancer therapy (SACT).
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	Yes. The overall survival data based on the first interim analysis indicates a 43% reduction in risk of death in patient treated with the technology compared to patients treated with sunitinib. Although the data is based on the first interim analysis, the statistically significant improvement in overall survival will translate in increasing the length of life than current care. There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as “tail of the curve” in Kaplan Mier survival curves. This effect is proven in melanoma and early evidence with ipilimumab/nivolumab also supports this hypothesis.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, by prolonging the time without worsening of disease (progression free survival), improving overall response rate and manageable adverse event profile, the technology can improve the health-related quality of life more than current care
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The intention to treat analysis of KEYNOTE 426 has demonstrated effective across patients with aRCC irrespective of their prognostic groups, but the magnitude of benefit in overall survival, appears to be less in favourable risk group as the number of events in this group is low.
The use of the technology	
14. 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	Technology is well tolerated and clinicians and health care professional are well trained and qualified to treat patients with this technology. Axitinib has been widely used by renal oncologists who would be able to manage the side effects. There are well established acute oncology guidelines to treat immune checkpoint inhibitors related adverse events but certain centres would need more support. Patients, generally, are willing to attend clinics and SACT administration units for intravenous treatment if the technology results in improved clinical outcomes.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Company has set a stopping rule of administration of pembrolizumab to maximum of 35 infusions, and this will be followed.
16. 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?	This technology can improve the economic productivity of patients, some of whom could be in full time or part time employment, by achieving durable clinical response and these parameters are not captured by QALY calculations. The positive impact on the carers ability to leave the patients independent and carry with their normal employment/day to day activities is also not well elucidated in the QALY calculations.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes. There are a proportion of patients treated with this technology who can achieve durable clinical response and this response does not come with significant adverse events as noticed in the patients

impact on health-related benefits and how might it improve the way that current need is met?	treated with ipilimumab/nivolumab which is now one of the standard of care in aRCC of intermediate or poor risk group.
• Is the technology a 'step-change' in the management of the condition?	This technology would be first of its kind to combine immune checkpoint inhibitor and VEGF TKI, which has shown improvement in all clinical relevant end points of progression free survival, overall survival and overall response rate.
• Does the use of the technology address any particular unmet need of the patient population?	This technology offers the option of durable clinical response without the additional side effects and thereby addresses an unmet need for this patient population.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immune related adverse effects/ and technology related can affect the quality of life and impede the ability of clinicians to continue treatment. However these adverse events can be managed. Axitinib related side effects are reversible and typically short lasting.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	Patients in clinical trials generally are younger and fitter group of patients. The proportion of favourable risk patients in the KEYNOTE 426 trial upon which this technology is evidenced upon, is numerically larger than standard clinical practice. However these variations in current UK clinical practice and clinical trial practice is noted in all clinical trials and patients in standard clinical practice derive clinical benefit.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, improvement in health related quality of life, overall survival. All these end points were measured in KEYNOTE 426 trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Progression free survival is accepted as a surrogate for predicting overall survival.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Nil as this technology is not been used out with clinical trials.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA169, TA215, TA512, TA542]?	Combination of avelumab and axitinib has demonstrated improvement in progression free survival and overall response rates in patients with aRCC of all prognostic groups.
22. How do data on real-world experience compare with the trial data?	There is no real world data on this technology.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Nil

23b. Consider whether these issues are different from issues with current care and why.	Not applicable

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Improvement in overall survival in all patients with aRCC
- Potential for durable clinical response (tail of curve effect)
- Clinically significant improvement on overall response rate
- Clinical and statistical improvement in progression free survival
- ,Manageable adverse event profile

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Michael Robert Lee**

2. Are you (please tick all that apply):	☒ **a patient with the condition**? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Kidney Cancer UK
4. Did your nominating organisation submit a submission?	☒ **yes, they did** ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☒ **I have personal experience of the condition** ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with a Kidney Cancer on my Left Kidney in Mid 2016, which was removed by surgery in September 2016. My scan before and after the operation showed no other cancers present. In January 2017 a scan showed Metastatic Cancers in various organs. They were deemed to be aggressive. I was referred to the Christie Hospital, where I was invited to take part in a trial of the combination of Pembrolizumab with Axitinib, as a 'First Line' treatment, sponsored by Merck, Sharp & Dohme Ltd (MSD). During the trial I experienced only minor side effects due to the treatment, none of which prevented me from leading a normal active life. Regular visits to The Christie to enable the trials team to monitor my general health and condition, were the only minor alteration to my daily life. After the first 12 weeks of the trial I was scanned to appraise the effect of Pembrolizumab with Axitinib on

	my tumours. The result was very pleasing, in that I was verbally told that the 'indicator' tumours had shrunk by 60%. In the previous week, (week 14) to the clinical assessment and results of the scan, I had been feeling a little tired, and had symptoms similar to 'Hay Fever'. I have suffered from Hay Fever, for many years, and had put these symptoms down to the time of year. The blood tests results showed that I had developed a Liver function problem. The trial was suspended for a while, whilst my Liver recovered. I have had no further problems with my Liver function since. Having had this problem my continuance in the trial was restricted. I was then provided with Sunitinib. This was the alternative drug being used for comparison in the trial. Whilst taking Sunitinib I experienced several debilitating side effects, at various stages. The worst of which was mouth ulcers. This at one stage was so bad I was unable to eat / chew. I could only manage supplement drinks, all of which tasted awful, due to my sense of taste also being affected. Also the skin on my hands and feet became very sensitive and hardened which required constant application of creams to enable me to attempt some normality in daily life. An additional side effect was that my hair turned pure white, but this did not have any significant effect on daily life. The results of my following 3 month scans showed that the tumour growth was stable. Throughout all of my treatment my wife has acted as my carer, She has been present at consultations and during treatments. Naturally she helped with my treatment and general care. Her being fully involved, throughout, helped to reduce her natural concern for my condition
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	We believe that the use of **Pembrolizumab with Axitinib** as a 'first line' treatment was of great benefit. Due to the fact I was on a trial, it was not possible to alter the high dosage levels, as we believe that continuation of combination of drugs could have lead to long term remission. I am currently on Nivulumab as a treatment. The only major side effect is skin irritation, which has resulted

	in nasty wheals on the skin. These are very sensitive, and require frequent application of creams to provide a level of comfort. The level of care provided by the NHS cannot be faulted. The monitoring of my condition and the approach of the nursing staff are excellent. As my wife is invited to be present at all times, is critical to both allaying her fears, and understanding what is necessary relating to the treatment and my medical condition.
10. Is there an unmet need for patients with this condition?	My care has been excellent throughout from initial diagnosis to the present time. The only point at which we had difficulty was at the time I was told that I had a Kidney Cancer. This was a great shock as I had had no warning symptoms. We did not know where to turn, and what possibly lay ahead. Although we were given pamphlets, etc, they only tended to give procedures, and technical information. We feel some direct contact with people who have been through the process and treatments would help to give a positive approach to what lay ahead. Giving a list of organisations who can give support does not work. In our case we approached Macmilllan who told us it would be a couple of months before they could talk to us.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The major advantage of the treatment was the dramatic effect in a short period on the cancer growth. There were little side effects. A monthly visit for the infusion, and tablets taken at home, would have only a small impact on daily life, enabling the patient to lead a normal life.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	We see no significant disadvantages in the treatment.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We understand that the combination of Pembrolizumab with Axitinib does not suit all patients, which we have been told verbally, and discussion with others who took part in the trial. We would rely on the consultants evaluations as to the appropriate patients the treatment should be offered too.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None**

Other issues	
15. Are there any other issues that you would like the committee to consider?	Would this combination of Pembrolizumab with Axitinib be considered not only as a 'first line' treatment but also 'second line' treatment provided the patient fits the criteria that indicates they may benefit from it.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- The treatment was very effective.
- Little side effects
- Patient able to live a full and active life.

Thank you for your time.

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NHS England submission on the NICE appraisal of the combination of pembrolizumab plus axitinib in the 1st line treatment of locally advanced/metastatic renal cell adenocarcinoma (RCC)

1. NHS England considers that if NICE recommends the combination of pembrolizumab plus axitinib, there will be patient and clinical enthusiasm for this type of 1st line combination therapy which incorporates both a VEGF inhibitor and a checkpoint inhibitor. Such keenness to use this combination might be tempered in the IMDC poor prognosis group where it may be considered that the data on benefit is more compelling for the use of the combination of nivolumab and ipilimumab (available via the CDF and thus not a comparator).
2. Not only does this combination of pembrolizumab and axitinib join together the 2 key types of systemic therapy in RCC, it does this in the 1st line setting. NHS England considers that the 2nd line treatment rate is currently approximately 50-60% and so a combination of these 2 therapies employed as 1st line treatment removes concern that patients might miss out on one important type of 2nd line therapy if they receive the other important type as 1st line treatment.
3. NHS England does not regard that the current 1st line therapy options of sunitinib or pazopanib or tivozanib have any clinically significant difference in efficacy between them. However, both pazopanib and tivozanib have a superior toxicity profile to sunitinib. Since pazopanib has been recommended by NICE for far longer than tivozanib, it is pazopanib that has the largest market share as a 1st line tyrosine kinase inhibitor that can be potentially used in all IMDC prognostic groups.
4. The Keynote 426 trial with pembrolizumab plus axitinib allowed a maximum initial treatment duration for the pembrolizumab part of the duo of a duration of 35 cycles (in effect after 2 years) although patients in complete remission could stop the pembrolizumab after less than 2 years of treatment. In such patients who stopped at 35 cycles and in those patients who discontinued pembrolizumab because of attaining complete remission, the Keynote 426 trial allowed these patients at subsequent relapse to re-start the pembolizumab for a further 17 cycles. Follow up data in the Keynote 426 trial is too short to have any robust information as to the following: the number of patients completing 2 years of therapy or discontinuing on account of attaining a complete remission; the proportion of these 2 groups that relapse and when they do; and subsequently the response to re-treatment. NHS England would wish such information or at least a range of assumptions which could reflect this information to be incorporated into the economic modelling as at least some patients in Keynote 426 will have had this protocol-specified re-treatment.
5. NHS England also notes that the combination of pembrolizumab plus axitinib could be recommended to go into the CDF. Whist the immaturity of the Keynote 426 trial survival data is clearly apparent, there is a logical mismatch between waiting for the maturation of data from a clinical trial with a re-treatment option and the CDF

collecting data on what constitutes the company's base case which is a capped treatment duration at 2 years.

6. If NICE recommends pembrolizumab plus axitinib on the basis of cost effectiveness with a maximum treatment duration capped at 2 years and no re-treatment at realpse, then a maximum treatment duration at 2 years and no allowed re-treatment are exactly what NHS England will commission. There will be no funding of re-treatment with pembrolizumab plus axitinib and there will be no commissioning of 2nd line therapy with nivolumab in patients previously treated with pembrolizumab plus axitinib.
7. NHS England notes that in previous NICE appraisals of checkpoint inhibitors in which treatment durations were capped at 2 years without there being robust outcome data as to the consequences, NICE committees did not assume lifetime treatment benefit for therapy which has stopped at 2 years. Instead, they examined analyses of treatment benefit waning effects that have benefit waned within 1 year and 3 years of stopping treatment (the '2+1' and '2+3' analyses in terms of time since starting treatment). Such assumptions of treatment waning effect durations have usually been very important in the difference they make to the ICERs.
8. Clinical expert opinion to NHS England remains clear that in the absence of any robust outcome data as to the impact of a 2 year stopping rule of at least checkpoint inhibitor therapy in RCC, an open treatment duration is currently preferred. However, if the only option to patients and clinicians were to be a capped treatment duration for pembrolizumab and no re-starts were commissioned, then clinicians would still wish to use the combination of a VEGF inhibitor and a checkpoint inhibitor as 1st line treatment (with the caveat expressed in paragraph 1 above).
9. If NICE recommends the combination of pembrolizumab plus axitinib in the treatment of all risk categories (favourable, intermediate and poor) of locally advanced/metastatic renal cell adenocarcinoma, this will have a substantial effect on the treatment pathway. Whilst displacement of current 1st line tyrosine kinase inhibitor (TKI) options to 2nd line would be possible, it is more likely that 2nd line treatment options would be considered from a combination of displaced current 1st line options and current 2nd line options. Of the current 2nd line treatment options, 2nd line nivolumab and 2nd line axitinib would not be commissioned as patients have been previously treated with a checkpoint inhibitor and axitinib. NHS England considers that after failure of pembrolizumab plus axitinib, most 2nd line treatment would be with a 'dirty' TKI (one which has many potential modes of action) such as cabozantinib. Other treatment options which NHS England would commission would be the other current NICE-recommended 2nd line options (lenvatinib plus everolimus, everolimus monotherapy) as well as allowing use of displaced current 1st line sunitinib (on label) or pazopanib (off label). NHS England does not consider tivozanib (off label) as such an appropriate displaced current 1st line option after failure of pembrolizumab plus axitinib as tivozanib's mode of action is 'cleaner'.

10. NHS England notes the two pembrolizumab plus axitinib and avelumab plus axitinib combinations when compared with the same sunitinib comparator look very similar. Any clinically significant difference between pembrolizumab (anti-PD-1 mode of action) vs avelumab (anti-PD-L1 mode of action) in RCC is highly speculative without at least longer term follow up data of these 2 trials.
11. NHS England notes that the IMDC poor prognosis group are underrepresented in the Keynote 426 trial (13% of patients rather than the expected 25%, this being probably due to use of the nivolumab/ipilimumab combination).
12. NHS England notes that the Keynote 426 trial was only performed in patients with RCC with a clear cell component. Expert opinion to NHS England is that patients with papillary RCC should also benefit from checkpoint inhibitor therapy and thus if pembrolizumab plus axitinib is recommended by NICE, then NHS England would commission its 1st line use in patients with locally advanced or metastatic papillary RCC.

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

January 2020

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

(Erratum – errors corrected following factual accuracy check of ERG report)

Pembrolizumab in combination with axitinib for untreated advanced renal cell carcinoma

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

None

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Declared competing interests of the authors and clinical advisors

The authors declare no competing interests. Professor Robert Hawkins declares receiving speaker fees from the following companies (treatments): EUSA Pharma (tivozaninb); Ipsen (cabozantinib); Novartis (pazopanib); Pfizer (sunitinib and axitinib). Dr Matthew Wheater declares receiving support from Merck Sharpe & Dohme for conference attendance in June 2019, in which he participated in a general discussion with the company about treatment for renal cell carcinoma (not specifically related to the company's evidence submission to NICE on pembrolizumab plus axitinib). Dr Wheater also declares receiving speaker fees from Pfizer.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Keith Cooper critically appraised the economic evaluation, and drafted the report. Emma Loveman critically appraised the clinical effectiveness review and drafted the report. Olu Onyimadu critically appraised the economic evaluation, and drafted the report. David Scott critically appraised the indirect treatment comparison clinical and drafted the report. Jill Colquitt critically appraised the clinical effectiveness review and drafted the report. Jonathan Shepherd critically appraised the clinical effectiveness review, drafted the report, project managed the report and is the project guarantor.

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Commercial in confidence (CIC) information in blue
Academic in confidence (AIC) information in yellow.

LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Academic in confidence
AJCC	American Joint Committee on Cancer
BICR	Blinded independent central review
CIC	Commercial in confidence
CPS	Combined Positive Score
CR	Complete Response
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
DCR	Disease Control Rate
DIC	Deviance information criteria
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EPAR	European Public Assessment Report
ERG	Evidence Review Group
FDA	Food and Drug Administration
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health related quality of life
IFN-α	Interferon alpha
ICER	Incremental cost effectiveness ratio
IMDC	International Metastatic RCC Database Consortium
IRC	Independent radiology committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
MCMC	Memorial Sloan-Kettering Cancer Center
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
ORR	Objective response rate
PAS	Patient access scheme
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PF	Progression free

PFS	Progression free survival
PH	Proportional hazards
PR	Partial Response
QALY	Quality adjusted life year
QoL	Quality of life
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumours
RTKs	Receptor tyrosine kinases
SAE	Serious adverse event
SD	Stable Disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse events
TOT	Time on treatment
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
TTD	Time to treatment discontinuation
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor (VEGF)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY

Scope of the company submission

The company's decision problem is as follows:

- Population: Adults with untreated advanced RCC
- Intervention: Pembrolizumab in combination with axitinib
- Comparators: Tivozanib; pazopanib; sunitinib; cabozantinib (for disease that is defined as intermediate or poor risk)
- Outcomes: overall survival (OS); progression-free survival (PFS); objective response rate (ORR); adverse events (AE); health-related quality-of-life (HRQoL).

The company's decision problem is largely consistent with the NICE scope.

Summary of submitted clinical effectiveness evidence

The company conducted a broad literature review to meet the needs of multiple countries. Studies providing direct and indirect evidence relevant to the target population for the current scope were selected during the final stages of the review.

One randomised controlled trial (RCT) of pembrolizumab plus axitinib versus one of the scoped comparators, sunitinib, was identified (KEYNOTE-426). Pembrolizumab 200mg was administered every three weeks by IV infusion for up to 35 doses (about 24 months) and axitinib 5 mg was administered twice daily orally. Sunitinib 50mg was administered daily orally, four weeks on, two weeks off. Treatments were continued until progressive disease was confirmed or unacceptable adverse events. A total of 861 participants with previously untreated locally advanced/metastatic clear cell renal cell carcinoma (RCC) were included. The trial was undertaken in 16 countries and 37% of participants were from Europe. The number randomised in the UK is unclear. The ERG notes there is a risk of performance bias in the trial but risk of bias from other sources is low.

The main results presented in the CS and used in the economic model are from the first planned interim analysis (August 2018 data-cut), after a median follow-up of 13.2 months in the intervention arm and 12.1 months in the comparator arm. Efficacy testing was stopped when this analysis showed statistically significant improvement in both co-primary endpoints [progression-free survival (PFS) and overall survival (OS)] and the key secondary endpoint [objective response rate (ORR)]. Results from a second (unplanned) data-cut in January 2019

for US Food and Drug Administration (FDA) with an additional four months follow-up are presented in appendices. Overall survival follow-up of the trial is ongoing. The ERG notes that early stopping of trials can sometimes results in over-estimation of treatment effect. Based on the number of events, the ERG considers that PFS is unlikely to have been overestimated, but OS at the interim analysis is potentially overestimated and should be interpreted with caution due to data immaturity.

KEYNOTE-426 trial results

- Median OS was not reached in either arm, HR 0.53 (95% CI 0.38 to 0.74), p=0.00005. Results from the January 2019 data cut [redacted].
- Median PFS based on blinded independent central review (BICR) was 15.1 months with pembrolizumab plus axitinib and 11.1 months with sunitinib, HR 0.69 (95% CI 0.57 to 0.84, p=0.00014). Results from the January 2019 data cut [redacted].
- Objective response rate (ORR) was 59.3% in the pembrolizumab plus axitinib arm and 35.7% in the sunitinib arm based on BICR according to RECIST 1.1 criteria, a difference of 23.6% (95% CI 17.2 to 29.9, p<0.0001). [redacted].
- Median duration of response (DOR) based on BICR in people with a complete response or partial response was not reached in the pembrolizumab plus axitinib arm and was 15.2 months in the sunitinib arm. Median DOR based on investigator assessment was 18.0 months (range 1.3+ to 18.2+) and 15.2 months (range 1.2+ to 15.4+), respectively ('+' indicates there was no progressive disease by the time of last disease assessment).
- There were no significant differences between treatments for the EQ-5D-3L index, EQ-5D visual analogue scale (VAS) or most functional and symptom scales of the EORTC-QLQ-30 instrument. The exception was a greater worsening of the EORTC-QLQ-30 diarrhoea symptom scale in the pembrolizumab plus axitinib group.
- Subgroup analyses of OS and PFS were consistent with the effect seen in the overall trial population [redacted].
  [redacted].The overall rate of adverse events

(AEs) was similar across both arms of the trial. The rate of serious adverse events (SAEs) was higher in the pembrolizumab plus axitinib group; 40.3% of participants reported SAEs in the pembrolizumab plus axitinib arm compared with 31.3% in the sunitinib arm. For drug-related grade 3 to 5 AEs, pembrolizumab plus axitinib had a higher risk of increased ALT, increased AST and diarrhoea. Sunitinib had a higher risk of fatigue, thrombocytopenia and neutropenia among others. The rates are in line with those of axitinib as monotherapy.

Network meta-analysis results

The CS reports two types of Bayesian approaches for indirect comparison of pembrolizumab plus axitinib with other treatments:

- Network meta-analysis (NMA) assuming constant hazards
- NMA assuming time-varying hazards based on fractional polynomials.

These NMAs were reported for OS and PFS outcomes. The NMA assuming constant hazards appears to be the 'primary' indirect comparison method reported in the CS.

The networks are presented as a base case analysis, which included all patients irrespective of baseline RCC risk status, and subgroup analyses for patients at intermediate/poor RCC risk, and patients at favourable RCC risk. The ERG agrees with the decision to conduct a separate NMA for the intermediate/poor RCC risk group, as inclusion in the CABOSUN trial of cabozantinib was restricted to patients in these risk groups, and cabozantinib is recommended by NICE only for patients at intermediate/poor risk (as defined by the IMDC criteria).

The NMA does not inform the economic model for the base case analysis (all patients irrespective of baseline RCC risk status). The NMA informs the economic model for the subgroup analysis comparing pembrolizumab plus axitinib versus cabozantinib.

The trials (n=6) included in the NMA were generally similar in terms of key patient characteristics, and were assessed by the company and the ERG to be at low risk of bias, with the exception of blinding (trials were open-label).

Overall, the ERG considers the methods and assumptions used to conduct the NMAs to have been appropriately exercised, though with some uncertainties due to relatively small data sets, and potential heterogeneity.

The following results are from the constant hazard NMA

- In the base case NMA, pembrolizumab plus axitinib resulted in [redacted] in the duration of PFS compared to all relevant competing interventions: [redacted]).
- In the intermediate/poor risk subgroup NMA, both cabozantinib and pembrolizumab plus axitinib were associated with [redacted] HRs compared to sunitinib ([redacted] indicating [redacted] PFS.
- In the base case NMA, pembrolizumab plus axitinib was associated with [redacted] in the duration of OS compared to pazopanib ([redacted]) and sunitinib ([redacted]). Tivozanib was omitted from this NMA due to lack of data.
- In the intermediate/poor risk subgroup NMA, pembrolizumab plus axitinib was associated with [redacted] in OS compared to sunitinib [redacted] and compared to cabozantinib [redacted]
- Results from the NMA using the January 2019 KEYNOTE-426 data-cut show [redacted] results to the above.

Summary of submitted cost effectiveness evidence

The CS includes:

- a review of published economic evaluations of comparator therapies to pembrolizumab in treating patients with advanced renal cell carcinoma.
- a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of pembrolizumab in combination with axitinib is compared with sunitinib, tivozanib, pazopanib and cabozantinib for adults with untreated advanced RCC.

The company conducted a systematic search of the literature to identify economic evaluations of comparator treatments to pembrolizumab in untreated advanced RCC. The search identified 10 published cost-effectiveness studies, of which nine were conducted from an English, Welsh or British perspective. None of the studies included pembrolizumab plus axitinib, however the ERG identified a cost-utility study by Chen et al. that compared pembrolizumab plus axitinib to sunitinib in patients with RCC in China.

The company developed a model to evaluate the cost-effectiveness of pembrolizumab plus axitinib as first-line treatment for advanced RCC. The model is a partitioned-survival model,

containing three mutually-exclusive health states: progression free (PF); progressed disease (PD) and death. Patients start in the PF state, and at disease progression, transition to the PD state, which is irreversible. Patients in PF and PD states die from cancer or other causes.

The distribution of the cohort between the health states and treatment states at each time point was estimated using a partitioned survival approach, based on PFS, and OS curves. Patients enter the PF state on initiation of first-line treatment but may stop treatment at any time due to adverse effects or when their disease progresses. The proportion of patients on first-line treatment is determined by the time to treatment discontinuation (TTD) curves. Some patients then progress to a subsequent treatment with one of the drugs suitable for second-line treatment. The duration of second-line treatment was taken from the clinical trials for each drug, after which patients are assumed to receive supportive care until death.

The submitted model includes analyses for two patient populations:

- The overall population of KEYNOTE-426;
- Subgroup population of patients with intermediate/poor RCC risk status, as defined by IMDC criteria, in the KEYNOTE-426 population.

The PFS, OS and TTD curves for pembrolizumab plus axitinib, and sunitinib were based upon survival data from the KEYNOTE-426 trial. The CS assumes that sunitinib is clinically equivalent to tivozanib and pazopanib, based on similar assumptions made in previous NICE appraisals for this indication. For the subgroup population at intermediate / poor risk, pembrolizumab plus axitinib is compared to cabozantinib using the company's NMA, as no head-to-head comparison was available.

Other key features and assumptions of the model are listed below:

- **Cycle length**: 1 week with half cycle correction implemented.
- **Time horizon**: 40 years in the base case
- **Discounting**: 3.5% per year for costs and QALYs
- **Duration of treatment effects**: based on extrapolation of PFS and OS curves fitted to trial data and based on model fit statistics and clinical expert judgement. The persistence of treatment effect throughout the model time horizon was assumed in the company's base case. Treatment waning after 10 years was tested in a scenario.

- **Adverse events**: includes grade 3 and above all-cause adverse events which occur in at least 5% of patients for all first-line treatments. Adverse events related to subsequent treatments are not explicitly modelled.
- **Utility and QALY calculations**: HRQoL estimates evaluated from the KEYNOTE-426 trial are used in the model. Three approaches where used to estimate HRQoL: estimation of utilities based on progression-free and progressed disease states (with or without differentiation by treatment) and the estimation of utilities based on time to death. These approaches are discussed in detail in section 4.3.6. An age-based utility decrement is also applied.
- **Health resource use and costs**: The model estimates costs associated with: acquisition and administration of first-line and subsequent treatments, with adjustment for dose intensity; monitoring and disease management in PF and PD states; treatment of included TEAEs for first-line treatments; and terminal care costs in the last cycle before death.
- **Uncertainty**: the model incorporates macros to conduct: deterministic sensitivity analysis (DSA) with results presented in a tornado diagram; scenario analyses varying selected model assumptions; and probabilistic sensitivity analysis (PSA), producing a cost-effectiveness scatterplot and cost-effectiveness acceptability curve.

Parametric survival curves were fitted to PFS, OS and TTD data from the KEYNOTE-426 trial. The survival curves used in the company's base case and scenario analyses are summarised in the table below.

Table 1 Survival curves used in the company's economic analyses

Curve	Treatment	CS Base case	CS scenarios
PFS	Pembrolizumab + axitinib Sunitinib	Exponential	Lognormal for P+A, Exponential for S
OS	Pembrolizumab + axitinib Sunitinib	Log-logistic Exponential	Exponential Time varying hazard ratio
TTD	Pembrolizumab + axitinib Sunitinib	Weibull Exponential Exponential	Weibull for P, Log-normal for A, Exponential for S.

PFS, progression free survival; OS, overall survival; TTD, time to treatment discontinuation; ITC, indirect treatment comparison; RE, random effects; FP, fractional polynomial

Base case utility estimates were taken from the company's KEYNOTE–426 trial using the time-to-death approach. Adverse event disutilities were estimated according to the EQ-5D values collected in the KEYNOTE-426 trial for pembrolizumab plus axitinib versus sunitinib.

The company conducted a systematic literature review to identify published resource use and cost data relevant to the cost-effectiveness analysis. The costs included in the economic model are acquisition and administration of first-line and subsequent treatments, with adjustment for dose intensity; monitoring and disease management in PF and PD states; treatment of AEs for first-line treatments; and end of life care.

The results of the economic model are presented below using list prices for all drugs as incremental cost effectiveness ratios (ICERs). (NB. cost-effectiveness results based on patient access scheme discount prices for comparator treatments and treatments used in subsequent treatment lines are presented in a separate confidential appendix to this report).

- For the company base case, an ICER of £59,292 per QALY gained is reported for pembrolizumab plus axitinib versus sunitinib.
- For the intermediate/poor risk subgroup analysis, an ICER of £21,452 per QALY gained is reported for pembrolizumab plus axitinib versus cabozantinib.

The company conducted one-way deterministic sensitivity analyses and concluded that the key drivers of the cost-effectiveness results were changes to the distribution used for extrapolating OS and the discount rates for QALYs. The company's scenario analyses found cost-effectiveness results to be most sensitive to the choice of OS curve used in the model. The company's base case probabilistic sensitivity analysis gave an ICER of £59,726 per QALY gained and estimated a 0.3% chance of pembrolizumab plus axitinib is cost-effective at the £30,000 per QALY threshold compared to sunitinib.

End of life criteria and innovation

- The ERG agrees with the company that pembrolizumab plus axitinib does not meet the first end of life criterion in the overall RCC population ("treatment is indicated in patients with a short life expectancy, normally less than 24 months").
- The ERG disagrees with the company that pembrolizumab plus axitinib meets the first end of life criterion in the poor RCC risk subgroup. We consider cabozantinib to be the

NICE recommended treatment for this group rather than sunitinib as referenced in the CS. The company does not provide an explicit rationale for singling out the poor risk group, as opposed to the intermediate / poor risk subgroup. Estimates of cost-effectiveness are not provided in the CS for the poor risk group.

- The ERG is in agreement with the company that pembrolizumab plus axitinib meets the second end of life criterion ("treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment").
- We are therefore of the opinion that pembrolizumab plus axitinib does not fully meet the NICE criteria for being considered as a life-extending treatment for people with a short life expectancy.

The company considers that the innovative immuno-oncology combination regimen of pembrolizumab plus axitinib represents a "step-change" in the management of RCC as it targets both angiogenesis and immune-checkpoint pathways. The CS states that pembrolizumab should be considered innovative by its potential to make a significant and substantial impact in an area of high unmet need. The ERG clinical advisors agree there does remain an element of unmet need and that the rationale for the treatment combination in RCC is made. However, there are other potential treatments that should be considered in relation to pembrolizumab and axitinib, such as avelumab plus axitinib, currently the subject of a separate NICE technology appraisal.

Commentary on the robustness of submitted evidence

Strengths

- The company conducted a reasonable quality systematic review and it is unlikely that any relevant trials have been omitted.
- The evidence for the clinical effectiveness of pembrolizumab plus axitinib is from a large multinational RCT (KEYNOTE-426) comparing the treatment with one of the NICE scoped comparators, sunitinib. The open-label design of the trial means there is a risk of performance bias, but the risk of bias from other sources is low. Outcomes of the trial are appropriate and relevant to the scope.
- The methods and assumptions of the company's NMA are generally appropriate, although uncertainties remain due to the relatively small datasets in subgroup analyses.

- The comparator trials included in the NMA have a low risk of bias, other than that due to their open-label design.
- The structure of the company's economic model reflects the nature of disease progression and the clinical pathway for people with untreated locally advanced or metastatic RCC. The methods used for the economic evaluation are consistent with NICE methodological guidelines and other technology appraisals for treatment for this population.
- EQ-5D utility values were collected in the KEYNOTE-426 trial. These utility values meet the NICE reference case and are suitable for inclusion in the model. Costing methods and sources are also generally of good standard with reasonable assumptions.

Weaknesses and areas of uncertainty

- KEYNOTE-426 restricted inclusion to clear cell RCC. It is not clear whether results are generalisable to all types of RCC. However, this is in line with the pivotal phase III trials of comparator treatments which have been the subject of previous NICE appraisals in this indication.
- The majority of participants in KEYNOTE-426 (63%) were not randomised in Europe. The exact number of UK participants is unclear, but was less than 6% of the total randomised.
- Although typical of a phase III trial, the participants are generally younger and fitter than the general population with adults with untreated locally advanced or metastatic RCC.
- Efficacy testing was stopped early at the first interim analysis. Early stopping can sometimes result in over-estimation of treatment effect, in this case it is unlikely that PFS has been over-estimated, but OS results should be viewed with caution.
- There is significant uncertainty over the extrapolation of OS due to OS immaturity of survival data from the KEYNOTE-426 trial. ICERs are sensitive to this uncertainty. We consider that the Weibull distribution is more plausible for the extrapolation of OS and has more conservative survival predictions. We do not agree with the company's use of different survival curves for the extrapolation of the pembrolizumab plus axitinib and sunitinib arms.

Summary of additional work undertaken by the ERG

The ERG's preferred set of assumptions included the following key differences from the company base case:

- **Method of fitting OS curves**. The ERG considers that the Weibull distribution should be used for the OS curves for pembrolizumab plus axitinib and sunitinib. We note that the OS survival data is immature and therefore the long-term survival of patients treated with pembrolizumab plus axitinib is uncertain. The ERG considers that the same distribution should be used for both treatment arms and that the Weibull provides the best fit to five year survival data for sunitinib.
- **Time on treatment curves (ToT)**. The ERG considers that the same distribution should be used for all treatment arms and that the Weibull provides the best visual fit to the ToT data.
- **Age-adjusted utility.** The company found that there was no relationship between age and utility with the KEYNOTE-426 trial population (Clarification question B11). There was therefore no need to include age-adjusted utility.
- **Subsequent treatment costs.** Based on clinical advice to the ERG, we have modified the proportion of patients receiving subsequent treatments. For the pembrolizumab plus axitinib arm, more patients (20%) would receive cabozantinib.
- **Administration costs.** The cost of the administration of oral treatments was assumed to be £0, as in previous technology appraisals.
- **Terminal care costs.** The cost of terminal care was assumed to be £8,073, rather than £6,789.76, using the costs from the cabozantinib STA and updating to 2017/8.

The ERG preferred base case analysis gave an estimated ICER of £120,455 per QALY for based on list prices (Table 2).

Table 2 ERG base case cost-effectiveness for pembrolizumab + axitinib versus comparators in the overall population (pairwise comparisons)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Pembrolizumab + axitinib	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	£140,895	1.170	£120,455
Tivozanib	[redacted]	[redacted]	£135,168	1.170	£115,558
Pazopanib	[redacted]	[redacted]	£137,335	1.170	£117,411

Subgroup analysis: intermediate / poor risk group

The ERG used the same set of preferred assumptions to estimate the ICERs for the intermediate / poor risk subgroup. The ERG preferred analysis gave an estimated ICER of £48,424 per QALY for pembrolizumab plus axitinib compared with cabozantinib (Table 3).

Table 3 ERG base case cost-effectiveness for pembrolizumab + axitinib versus comparators in the intermediate/poor risk subgroup (Pairwise comparisons)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Pembrolizumab + axitinib	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	£141,941	1.010	£140,481
Tivozanib	[redacted]	[redacted]	£137,480	1.010	£136,065
Pazopanib	[redacted]	[redacted]	£139,200	1.010	£137,768
Cabozantinib	[redacted]	[redacted]	£44,012	0.909	£48,424

The ERG completed scenario analyses varying key assumptions in the model. For the overall patient population, the results vary between £72,591 - £162,424 per QALY gained for pembrolizumab plus axitinib compared to sunitinib. Those scenarios which have the largest effect on model results are changes to the distributions used for OS, using the log-logistic curve for ToT, including a waning effect and changes to the utility values.

For the intermediate/poor risk subgroup, the results vary between £27,892 - £149,347 per QALY gained for pembrolizumab plus axitinib compared to cabozantinib. Those scenarios which have the largest effect on model results are changes to the distributions used for PFS, using the log-logistic curve for ToT, including a waning effect, using time varying hazards (FP) and changes to the utility values.

1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Merck Sharpe & Dohme on the clinical effectiveness and cost effectiveness of pembrolizumab in combination with axitinib for untreated advanced renal cell carcinoma. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 8th August 2019. A response from the company via NICE was received by the ERG on September 2nd 2019 and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section B.13 of the CS provides an overview of the key aspects of the aetiology and subtypes of RCC, its epidemiology and the clinical pathway of treatments including the proposed position of pembrolizumab plus axitinib. The ERG considers that the CS generally provides an accurate overview of RCC and its management. We summarise the key facts of relevance together with supplemental information where deemed appropriate below. The CS does not describe the impact of RCC on health-related quality of life (HRQoL) and we have provided a brief summary to highlight the potential impact RCC and its treatment has on an individual.

As stated in the CS, around 80% of all kidney cancer cases are RCC.[1] RCC typically originates in the lining of the tubules of the kidney; the tubules are responsible for filtering the blood and making urine. There are a number of subtypes of RCC according to the type of cells affected. The most common RCC subtypes are clear cell (75%), papillary or chromophilic (10-15%) and chromophobe (5%).[2]

RCC occurs more commonly in males than females and typically affects adults over 60 years.[3] The aetiology of RCC is unknown but risk factors include obesity, smoking and hypertension.[4] According to Cancer Research UK, statistics there are approximately 12,600 incidence cases of kidney cancer (no data specifically for RCC) each year (based on data from 2014-2016).[5] The CS states that incidence rates have increased rapidly (by 85%) since the early 1990s.[5]

RCC can be asymptomatic in the early stages and as such diagnosis can be made later in the disease process. In kidney cancer some 40% are diagnosed at a late stage.[5] The CS also states that in RCC around 44% presented at stage III or IV and that 25% to 31% had metastases;[5] the ERG note that these data are for kidney cancer generally rather than RCC. Initial symptoms that may be experienced by a person with RCC are haematuria (blood in the urine) and / or persistent lower back pain or pain between the ribs and hipbone.[3, 33]

RCC is typically staged from stage I to IV according to how far the cancer may have spread; stage III indicates that the cancer has advanced locally (within regional lymph nodes) and stage IV indicates that metastases beyond the regional lymph nodes are present (see Section 2.4 discussing this in the context of the NICE scope and CS decision problem).

Survival in RCC is linked to the stage of the cancer at diagnosis. In all kidney cancer cases the 1-year survival rate is 95% for those diagnosed at stage I compared with 37% for those diagnosed at stage IV.[5] Overall around 50% of people with kidney cancer live for at least 10 years.[5]

2.2 Symptoms and health-related quality of life

The CS does not describe the effect RCC can have in terms of symptoms or HRQoL. In a 2007 literature review of 12 studies, used as context for the development of a RCC symptom measure, the most commonly reported symptoms included fatigue, weakness, pain, anorexia, nausea and dyspnoea.[6] In a small (n=31) cross-sectional study that followed the literature review the five most reported symptoms in advanced RCC were fatigue, weakness, worry, shortness of breath and irritability.[6] In advanced RCC HRQoL is impaired by disease burden. The poor prognosis together with the symptoms associated with the disease can affect all domains of HRQoL including physical function, psychological factors such as depression and irritability, emotional status, sleep and social functioning[6, #38, #39] HRQoL improvements in advanced (metastatic) RCC have, however, been associated with tumour response, delayed progression and lower rates of adverse events from targeted treatments compared with previous treatments.[7, 39, 40]

2.3 Critique of company's overview of current service provision

The CS provides a limited overview of how advanced RCC is managed in UK clinical practice, summarising the NICE pathway for first-line treatment options (see CS Figure 2) and the European Association of Urologists (EUA) guideline for metastatic clear-cell RCC.[8] The EUA guidelines recommends first line pembrolizumab and axitinib as standard of care for people with International Metastatic RCC Database Consortium (IMDC) favourable risk disease (discussed in decision problem section below) except in those who cannot receive or are intolerant to immune checkpoint inhibitors (the class of drug that pembrolizumab belongs to). Pembrolizumab and axitinib is also recommended as a treatment option for people with IMDC intermediate or poor risk.[8]

2.4 Critique of company's definition of decision problem

The company's decision problem is as follows:

- Population: Adults with untreated advanced RCC.
- Intervention: Pembrolizumab in combination with axitinib
- Comparators: Tivozanib; pazopanib; sunitinib; cabozantinib (for disease that is intermediate- or poor-risk as defined in the IMDC criteria)
- Outcomes: overall survival (OS); progression-free survival (PFS); objective response rate (ORR); adverse events (AE); HRQoL.

The company's decision problem is largely consistent with the NICE scope. The population in the NICE scope is 'adults with untreated locally advanced or metastatic RCC'. The decision problem is 'untreated advanced RCC', and the ERG's clinical experts confirm that this can be taken to mean the same thing as on a practical level they both require systematic treatment. The CS decision problem also introduces a subgroup that was not noted in the NICE scope (there were no subgroups in the NICE scope). This was people with intermediate / poor risk category as defined by IMDC. The rationale for this addition is not made explicitly clear in the CS. The company's network meta-analysis states that the effect modification by RCC risk group is a justification for subgroup analyses (we discuss this further in section 3.1.7 of this report). The comparator treatment cabozantinib in the NICE scope is applicable only for this subgroup.

The CS summarises the IMDC risk evaluation in CS Table 4 as this was part of the stratification at randomisation for the participants in the pivotal phase III RCT KEYNOTE-426 (discussed in Section 3.1.3 of this report). Patients are assessed on six risk factors:

- Karnofsky performance status (PS) <80%
- Time from diagnosis to treatment of <1 year
- Haemoglobin < lower limit of normal
- Platelets > upper limit of normal
- Corrected calcium > upper limit of normal
- Neutrophils > upper limit of normal

Participants are then placed in to one of three risk categories by totalling the number of risk factors: Favourable (0 factors); Intermediate (1 or 2 factors); Poor (3 or more factors).[9,10] Expert clinical advice to the ERG is that there is biological hypothesis for differential effect by prognostic risk and that the greater the risk the more likely patients will respond to an immune-oncology combination, than to tyrosine kinase inhibitor (TKI) monotherapy. Expert clinical advice also suggested that favourable risk patients have pre angiogenic characteristics with less tumour mutations, whereas intermediate/poor patients are less driven by angiogenesis, have more mutations, and higher PD-L1 expression. Thus, immunotherapy may be more effective in these patients than in favourable risk patients.

The company provides a summary description of pembrolizumab (but not axitinib) and its mechanism of action in CS Table 2. The ERG confirms this is consistent with the draft summary of product characteristics (SmPC, CS Appendix C). In addition to the differences between the NICE scope and the CS decision problem, the ERG notes that the evidence presented from the KEYNOTE-426 trial was not completely aligned with the decision problem. The trial population had locally advanced or metastatic RCC with clear cell component +/- sarcomatoid features (the latter refers to a highly aggressive form of RCC). The population may therefore not be generalisable to the wider RCC population (i.e. the estimated 25% without clear cell RCC). The ERG notes that the pivotal trials of the comparator treatments also comprised mostly or exclusively clear cell RCC patients. Previous NICE appraisals of these drugs did not restrict the patient population to those with clear cell RCC. Therefore, the current trial evidence is not out of line with that included in previous NICE appraisals. Additionally, there were some participants who had recurrent disease which may have been treated at the advanced stage.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The literature search for clinical effectiveness studies is detailed in CS Appendix D. The search was designed to inform evidence submissions in a number of countries and thus had a broader scope than that of the current submission to NICE. Consequently, the strategy contains terms for treatments that are not used in the UK. The systematic review inclusion criteria were restricted to just those treatments included in the NICE scope. The search informs the company's network meta-analysis (NMA).

An appropriate range of databases was searched: Medline (including In-Process and other non-indexed citations); Embase and the Cochrane Central Register of Controlled Trials.
The search terms contain appropriate subject headings together with relevant free-text terms. A published search filter was used to identify RCTs. The sets are correctly combined and the number of hits (records retrieved) per line is documented for transparency. A combination of MeSH and free text terms were used. The description of the search process is transparent.

Supplementary searching was undertaken to identify ongoing trials on the National Institute of Health's (NIH) clinical trial registry (www.clinicaltrials.gov), the European Union (EU) Clinical Trials Register (www.clinicaltrialsregister.eu). Manual (by hand) searches of relevant conferences for the last two years was performed, including the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (EMSO). It is not stated whether reference lists of relevant studies were searched to identify further additional relevant studies.

The original database search was conducted in November 2018, and updated in February 2019. The ERG agrees that the company would be aware of all relevant RCTs for pembrolizumab plus axitinib (as stated on CS page 17). However, the ERG has run targeted searches for more recent evidence for the comparator trials included in the NMA. We used a citation pearl growing approach in Google Scholar on 16/08/19. We identified the pivotal trials of each of the comparators (cabozantinib[11], pazopanib[12] and tivozanib[13]) and used the characteristics of these articles to search for other relevant and authoritative materials. We cross-checked all studies

citing the three key publications for the trials in this indication against the studies identified by the CS. We also checked the clinicaltrials.gov database records for additional publications and ran a simple search on PubMed limiting studies to those published since February 2019. This search identified two unique references:

- An article in press which reports post hoc subgroup analyses of the COMPARZ trial of pazopanib versus sunitinib.[14] This article reports characteristics of pazopanib responders, patient subgroups who achieved better outcomes, and the effect of dose modification on efficacy and safety.
- An article in press which reports subgroup analyses of the CABOSUN trial of cabozantinib versus sunitinib (published ahead of print on August 9, 2019[15]

These articles do not appear to contain data relevant to the company's NMA and therefore we do not consider them any further in this report.

ERG conclusion:

The search strategies are comprehensive, well documented and are fit for purpose. It is unlikely that any potentially relevant studies of pembrolizumab plus axitinib and comparator treatments that were not identified and included.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

A broad systematic literature review was conducted to meet the needs of multiple countries. The eligibility criteria for the broad review are not reported; a subset of the broader criteria is presented in CS Appendix D1.1 Table 1, which the company states reflect the target population for the UK NMA, and is discussed below. The aim was to identify studies to inform direct and indirect comparisons between the intervention and comparators of interest.

Population: the inclusion criteria specify adults diagnosed with histologically confirmed RCC with clear cell component with or without sarcomatoid features with the following staging:

- locally advanced (T3a–T4 per American Joint Committee on Cancer [AJCC])
- metastatic (Stage IV per AJCC), or chemo-naïve or chemo-experienced relapsed/recurrent disease of earlier AJCC stage.

These criteria reflect the eligibility criteria for the KEYNOTE-426 trial, but are narrower than the population specified by the NICE scope (RCC not limited to clear cell type).

Interventions and comparators: first line therapy with any of the following as monotherapy or combination therapy compared with each other or with placebo were eligible:

- Pembrolizumab plus axitinib
- Sunitinib
- Pazopanib
- Cabozantinib
- Tivozanib

These interventions are in line with the NICE scope (other than placebo, which is an appropriate comparator for inclusion in an NMA). In order to connect tivozanib to the network, the company included two interventions not relevant to UK practice. This meant inclusion of two trials that do not meet the eligibility criteria reported in CS Appendix D1.1 Table 1 (CS 2.9.3.1); see section 3.1.7 below.

Outcomes: eligible outcomes included those specified in the NICE scope (OS, PFS, response rates, adverse effects, HRQoL).

Study design: parallel group and cross-over RCTs, post-hoc subgroup analyses and open-label extension studies, and pooled analyses of RCTs (phase II and phase III) were eligible. Non-RCTs were excluded.

Other: Only studies published in English were eligible.

A flow diagram of study selection is presented in CS Appendix D1.1.2 Figure 1. The reasons for exclusion in the earlier stages reflect the criteria for the broader systematic review, with limits to first line treatment of clear cell RCC and interventions of interest to the UK scope occurring in the final stages. In response to clarification question C1, the company provided an updated flow diagram including numbers and reasons for exclusion of citations during the final stages (company clarification document Figure C1), although the ERG notes that this contains an error in the number of unique trials included/excluded. A total of 125 citations were excluded during the final stages: 67 were not relevant to first-line clear cell, and 58 had an intervention not of interest to the UK scope. A list of 728 studies excluded after full-text review of the broader review and reasons for exclusion is presented in CS Appendix D1.1.3 Table 9. This contains 70

references excluded for the reason 'Intervention not relevant to UK perspective'; it is not clear why this is greater than the 58 stated in the flow chart.

ERG conclusion

The company has not been explicit about any potential bias in the selection of studies. Study selection was undertaken by two independent reviewers. Two trials of interventions not included in the decision problem were included, and it was not clear how these were identified, necessitating an ERG clarification question. It was explained that these were included to facilitate a connected network analysis.

3.1.3 Identified studies

One RCT, funded by Merck Sharpe & Dohme, compared pembrolizumab plus axitinib with one of the scoped comparators, sunitinib (KEYNOTE-426).[16] Two additional RCTs of the relevant comparators were also included for the NMA (see section 3.1.7 of this report).

Summary details of KEYNOTE-426 are presented in CS section B.2.2, including trial design, eligibility criteria, setting and locations, interventions, outcomes and statistical analysis (such as sample size and power, description of intention-to-treat (ITT) analysis). Details of participant flow are presented in Appendix D1.3 Figure 38. The trial journal publication,[16] protocol and clinical study report (CSR) were provided by the company.

KEYNOTE-426 included patients with previously untreated locally advanced/metastatic clear cell RCC, specified as newly diagnosed Stage IV RCC per American Joint Committee on Cancer or those with recurrent disease (CS page 21). The company clarified that Stage IV includes patients with T4, any N and M0, and any T, any N and M1 [ERG note: where T is size of tumour, N is lymph node involvement and M is distant metastases]. Those with T4, any N and M0 are considered as locally advanced as there is no metastatic disease. For those with recurrent disease, if disease recurred only within the renal fossa or with unresected kidney, this is also considered as locally advanced (clarification response A1).

As noted in CS section 1.3.1, clear cell RCC accounts for 75% of RCCs. Expert clinical opinion to the ERG is that type of RCC is not prognostic but describes a distinct clinical and biological entity. Almost all RCC treatment trials are conducted with patients with clear cell RCC and

require at least part of the tumour to have this histology. Other subtypes (e.g. papillary, chromophone) are different types of cancer but due to their rarity there are few trials in these disease subtypes. They are sometimes grouped together as 'non-clear cell RCC'.

The ERG noted that the baseline characteristics suggest some of the cases of recurrent disease may have been previously treated for stage III and IV disease, as 305 of the pembrolizumab plus axitinib arm and 328 of the sunitinib arm had stage III or IV at initial diagnosis and yet 238 and 231 were reported as having recurrent disease (CS Table 7). The company clarified that among participants with recurrent disease, 11 received adjuvant therapy and none received neo-adjuvant therapy. In the pembrolizumab plus axitinib arm, 4 participants had stage III RCC at initial diagnosis and received adjuvant therapy. None with recurrent disease and initial diagnosis of stage IV RCC received prior therapy (clarification response A2).

A total of 861 participants were randomised to receive:

- Pembrolizumab 200mg every 3 weeks by IV infusion for up to 35 doses (about 24 months) and
- Axitinib 5 mg twice daily orally (n=432)

or

- Sunitinib 50mg daily orally, 4 weeks on, 2 weeks off (n=429)

Treatments were continued until progressive disease was confirmed by blinded independent central review (BICR) or further confirmation by the investigator (details of this were provided by the company in response to clarification question A5 and are considered appropriate by the ERG), unacceptable adverse events, intercurrent illness preventing further administration of treatment, death or withdrawal of consent. If a participant was progression-free after 35 doses of pembrolizumab, treatment with axitinib was continued as monotherapy until progressive disease was confirmed. If either pembrolizumab or axitinib were discontinued because of toxicity or intolerance, treatment with the other drug was continued as monotherapy until progressive disease was confirmed. For both arms, if a complete response was observed and confirmed, treatment could be discontinued at the discretion of the investigator after a minimum of eight cycles of treatment (about 24 weeks) in the pembrolizumab plus axitinib arm or four cycles of treatment (about 24 weeks) in the sunitinib arm had been received. Retreatment (termed 'second course phase' in the CS) with pembrolizumab plus axitinib was permitted for up to 17

additional infusions of pembrolizumab therapy for participants who progressed after stopping treatment. The criteria for this were:

- Initial treatment with pembrolizumab stopped after a confirmed complete response and received at least 8 doses of pembrolizumab.

or

- Completed 35 doses (approximately 2 years) of pembrolizumab treatment without progressive disease.

and

- Investigator-confirmed radiographic disease progression after stopping initial treatment with pembrolizumab.
- No anti-cancer treatment since the last dose of pembrolizumab.
- Karnofsky Performance Status (KPS) of ≥ 70%.
- Adequate organ function.
- No history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with participation for the full duration of the trial or is not in the best interest of the subject to participate.

The trial was undertaken in 16 counties. CS p.23 states 475 participants were enrolled in European sites (which equates to 55% of the 861 randomised) and this is confirmed on CS p.43 'Consideration of UK clinical practice', which states 55% of patients were recruited in Europe. However, CS Table 7 presents a lower proportion of 36.8% (317/861) of European participants. In response to clarification A6, the company states that the different proportions relate to the proportion enrolled (n=475, 55%) and the proportion after randomisation (n=317, 36.8%) and that some of the patients enrolled were not randomised. The ERG notes that based on these figures, the total sample size of the number enrolled is 861, the same as the total randomised (CS Appendix D1.3 Figure 38). The discrepancy is therefore not explained and the ERG considers that the higher proportion is misleading. CS p.23 states that 48 participants were enrolled in the UK, but the number randomised was not reported.

Baseline characteristics are presented in CS Table 7. These were balanced between groups and are summarised in Table 4. The median age of the trial population was 62 years (range 26 to 90 years) and 73% were men. About 80% had a KPS score of 90/100, and common metastatic sites were lung (72%), lymph node (46%) and bone (24%).

Table 4 Summary of baseline characteristics – KEYNOTE-426

	Pembrolizumab + axitinib (n=432)	**Sunitinib (n=429)**
Mean age (SD)	61.2 (10.0)	60.8 (10.2)
Median (range)	62.0 (30 to 89)	61.0 (26 to 90)
Male, %	71.3	74.6
White, %	79.4	9.5
Karnofsky Performance Scale, %		
90/100	80.3	79.5
70/80	19.4	20.5
Missing	0.2	0.0
IMDC Risk Category, %		
Favourable	31.9	30.5
Intermediate	55.1	57.3
Poor	13.0	12.1
PD-L1 Status, %		
CPS ≥ 1	56.3	59.2
CPS < 1	38.7	36.8
Not Available	0.9	0.5
Missing	4.2	3.5
Sites of Metastatic Disease, %		
Lung	72.2	72.0
Lymph Node	46.1	45.9
Bone	23.8	24.0
Adrenal Gland	15.5	17.7
Liver	15.3	16.6
Sarcomatoid Feature, %	11.8	12.6
Unknown, %	33.8	31.5
Missing, %	0.2	0.2
RCC Tumour Fuhrman Grade, %		
Grade 1, %	5.3	5.6
Grade 2, %	31.9	29.6
Grade 3, %	27.8	32.2
Grade 4, %	24.1	21.7
Missing, %	10.9	11.0
Disease Status at Baseline, %		
Recurrent	55.1	53.8
Newly Diagnosed	44.9	46.2
RCC Stage at Initial Diagnosis		
I	15.7	14.5
II	12.7	8.9
III	22.2	23.5
IV	48.4	52.9
Missing	0.9	0.2

IMDC, International metastatic RCC Database Consortium; PD-L1, program death-ligand 1; KPS, Karnofsky performance status; CPS, combined positive score; RCC, renal cell carcinoma.

Although typical of a phase III trial population, expert clinical advice to the ERG is that these patients are younger and fitter than the general population with untreated locally advanced/metastatic RCC.

Overall survival follow-up of the trial is ongoing, with an estimated completion date of January 2020.

ERG conclusion

The evidence for the clinical effectiveness of pembrolizumab plus axitinib versus one of the NICE scoped comparators, sunitinib, comes from one phase III RCT. The participants in the trial had previously untreated locally advanced/metastatic clear cell RCC. Other (non-clear cell) types of RCC, accounting for 25% of patients with RCC, were not included, but this is line with other trials of RCC. The majority (63%) of participants were from outside of Europe, and the number of participants randomised in the UK unclear.

3.1.4 Description and critique of the approach to validity assessment

The company provided a quality assessment of KEYNOTE-426 using the Cochrane Risk of Bias criteria (version 1). A comparison of the company and ERG assessments is presented in Table 5. The ERG has also completed additional questions from the NICE recommended quality criteria. The ERG generally agrees with the company's judgements, and where there are disagreements the ERG's judgements are in a more positive direction. The ERG considers that the risk of selection bias due to inadequate concealment of allocations prior to assignment was low due to the use of a central interactive voice response system /integrated web response system. Also, while the open-label design of the trial meant that there was a high risk of performance bias due to knowledge of the allocated interventions by participants and personnel, the risk of detection bias was low due to the use of blinded central review of progression and response. The groups were similar at baseline in terms of prognostic factors, and appropriate intention to teat analysis and methods to account for missing data were used.

Table 5 Company and ERG assessment of trial quality for KEYNOTE-426

	CS response	ERG response
Cochrane risk of bias domain		
Sequence generation	Low risk	Low risk
Allocation concealment	Unclear risk	Low risk (central randomisation using an interactive voice response system /integrated web response system
Blinding of participants, personnel and outcome assessors	High risk	High risk for participants and personnel Low risk for outcome assessors
Incomplete outcome data	Low risk	Low risk
Selective outcome reporting	Low risk	Low risk
Other sources of bias	Low risk	Low risk
Additional NICE quality assessment criteria		
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Not reported	Yes – low risk
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not reported	Yes – low risk

[a] Low = low risk of bias, high = high risk of bias, unclear = uncertain risk of bias.

ERG conclusion

There is a risk of performance bias in the trial, but the ERG considers the trial to have a low risk of bias for the other domains.

3.1.5 Description and critique of company's outcome selection

All outcomes specified by the NICE scope [overall survival, progression-free survival (PFS), response rates, adverse effects of treatment and health-related quality of life (HRQoL)] were measured in KEYNOTE-426 and are presented in the CS. Other relevant outcomes assessed in KEYNOTE-426 included time to deterioration, duration of response (DOR) and disease control rate (DCR); these are presented in CS Appendix L.

Overall survival and PFS were dual primary endpoints in the trial. Overall survival was defined as the time from randomisation to death due to any cause, with censoring at the date of the last-follow-up for participants without documented death at the time of final analysis (see section

3.1.6). PFS was defined as the time from randomisation to the first documented disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria assessed by blinded independent central review (BICR) or death due to any cause. PFS based on investigator assessment (RECIST 1.1) is presented in CS Appendix L Table 3 (the ERG notes the heading of this table states BICR, however we have checked against the CSR that these are indeed investigator assessment). The investigator assessments produced similar results that were also statistically significant, although the HR was slightly larger (less favourable towards pembrolizumab plus axitinib), see section 3.3 of this report. The ERG considers the BICR assessment to be have a lower risk of bias than the investigator assessment.

The following outcomes were secondary endpoints. Objective response rate (ORR) was defined as the proportion of participants with a complete response (CR) or partial response (PR). For those with CR or PR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause. DCR was defined as the proportion who achieved CR, PR or stable disease (SD) for ≥ 6 months. Assessments were by BICR according RECIST 1.1 criteria. ORR, CR and PR based on investigator assessment (RECIST 1.1) are not presented in the CS but are available in the CSR; the ERG notes that these were similar to BICR results, see Results section 3.3.2. DOR and DCS based on investigator assessment are presented in CS Appendix L Tables 7 and 10, see Results section 3.3.2.

HRQoL was assessed by longitudinal score changes from baseline in the global health status/quality of life scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30), a validated PRO measure. The ERG is aware that minimal clinically important differences have been identified for a population with advanced cancer (including renal cancer); these vary for each of the scales and symptoms.[17] The trial protocol also states that the proportions of people with deterioration/stable/improvement at 42 weeks (based on expected median PFS of 11 months in the control group) into the study will be described, however this is not presented in the CS (proportions at 30 weeks are available in the CSR). Supportive analyses of five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting and pain) and six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact) were also undertaken, however only selected scales are presented in CS Appendix L and the CSR (physical functioning, role functioning,

nausea/vomiting, diarrhoea) (the ERG requested results for all scales, clarification question A7, and these were subsequently provided by the company).

Utility was measured using the EQ-5D-3L as an exploratory endpoint; this is a standardised and validated generic instrument and is NICE's preferred measure of HRQoL in adults. EQ-5D-3L utility data at baseline and end of trial for each arm of the trial are not presented in the CS or related appendices; only the EQ-5D visual analogue score (VAS) is presented. This is a qualitative measure of health reflecting the patient's own judgement, on a scale from 'best imaginable health state' to 'worst imaginable health state'. On request from the ERG the company provided the EQ-5D-3L index data at baseline and week 30 for each treatment (clarification question A8).

The PROs were completed prior to all other study procedures and were assessed on Day 1 of each cycle in the pembrolizumab plus axitinib group, and on Days 1 and 29 of each cycle up to Cycle 4, then on Day 1 of each subsequent cycle following the two-week-off treatment period in the sunitinib group. 'Compliance and completion rates' (as one outcome) for the FKSI-DRS, EORTC-QLQ-30 and EQ-5D-3L at baseline and at week 30 are reported in CS Appendix L Table 14. Compliance rates appeared to be slightly lower in the pembrolizumab plus axitinib arm at both baseline and week 30. In both treatments arms, rates decreased between baseline (pembrolizumab plus axitinib: approx. 92%, sunitinib approx. 97%) and week 30 (pembrolizumab plus axitinib: approx. 86%, sunitinib approx. 89%).

Adverse events and serious adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Drug-related adverse events were determined by the investigator to be related to the drug.

Overall survival, PFS, utilities from EQ-5D-3L, and Grade ≥3 all-cause adverse events occurring occurred in at least 5% of patients are used in the economic model.

ERG conclusion

The ERG considers that the outcomes included in the CS are appropriate and relevant to the NICE scope.

3.1.6 Description and critique of the company's approach to trial statistics

3.1.6.1 Sample size calculation and hypotheses

The trial was designed to test the superiority of pembrolizumab plus axitinib vs sunitinib with respect to PFS and OS, the co-primary outcomes.

The sample size calculation was conducted for the two primary outcomes of the study, PFS and OS. The power calculation was based on the final number of randomised patients (n=861, an increase on the original power calculation based on 840 patients).

- Expected median PFS in the sunitinib arm was 13 months. Based on 487 required PFS events the trial had approximately 99% power to detect a HR of 0.60 for PFS (pembrolizumab plus axitinib vs sunitinib) at alpha=0.2% (1-sided).
- Expected median OS in the sunitinib arm was 33 months. Based on 404 required death events, the study had 80% power to detect a HR of 0.75 for OS at alpha=2.3% (1-sided).

The CS states that the assumptions for PFS and OS were based on emerging data from the sunitinib arm of the CheckMate 214 trial of nivolumab plus ipilimumab.[18]

3.1.6.2 Data analysis timepoints

Three analysis timepoints were planned, two interim and one final.

Interim analysis 1 (IA1) – the first interim analysis for PFS and OS, after completion of enrolment and a minimum 7-month follow-up. The minimum expected PFS events was n=305; the required OS events was n=195, or 48% of expected number. Data cutoff was the 24th August 2018. Median duration of follow-up at this time was 13.2 months (pembrolizumab plus axitinib) and 12.1 months (sunitinib). The study showed statistically significant improvement in both co-primary endpoints and key secondary endpoint. Efficacy testing was therefore stopped at IA1.

Interim analysis 2 (IA2) – the final analysis for PFS (n=487 events expected) and the second interim analysis for OS (n=299 events expected, 74%). However, this analysis was not conducted. Instead, a second (unplanned) data cut was taken in January 2019 for US Food and

Drug Administration (FDA) regulatory purposes (Safety Update Report). The statistical significance of all pre-specified tests was already achieved at IA1, so this analysis provides no further formal hypothesis testing results. Results are presented in CS Appendices F, N and O. These are not used in the assessment of cost-effectiveness in the CS.

Final analysis – the final planned analysis for OS (if not already declared successful), to take place when 404 events have occurred.

The CS does not mention any implications of the early stopping of the trial analysis at interim analysis 1 on the estimation of the size of the treatment effect. The ERG notes that there have been debates in the literature about the impact of early stopping of trials on the effect estimates.[19] Early stopping can sometimes result in over-estimation of treatment effect. A simulation study showed that in trials with a well-designed interim-monitoring plan, stopping the trial when 50% or greater of the information has been collected has a negligible impact on estimation.[20] A total of 395 PFS events had been recorded at this time, which is 81% of the total events required overall (n=395/487). Thus, this outcome is unlikely to have been over-estimated. However, for OS only 156 events had been recorded, which is 39% of the overall total required (n=156/404). Thus, the available OS results at the interim analysis are potentially over-estimated and should be interpreted with caution due to immaturity.

3.1.6.3 Analysis populations

Two statistical analysis populations are included in the trial:

- Intention to treat (ITT) population (n=861/861 randomised, 100%), defined as all randomised patients included in the trial. Patients were analysed in the treatment group to which they were randomised. This ERG regards this as an appropriate way of conducting ITT analysis. The ITT population was used for the analysis of efficacy outcomes.
- All Subjects as Treated (ASaT) population (n=854/861 randomised, 99%). This consisted of all randomised patients who received at least one dose of study treatment. Patients were analysed in the treatment group corresponding to the study treatment they received. This population was used for the analysis of safety outcomes.

The ERG considers the definitions of these two analysis populations appropriate.

3.1.6.4 Disease progression assessment

CS Table 10 summarises the primary censoring rule used, and variations of the rules explored in sensitivity analysis (results of these given in the CS Appendix L).

The primary censoring rule for death or disease progression was estimated by the date of the first assessment at which progressed disease was objectively documented (per RECIST criteria 1.1) by blinded independent central review (BICR). Patients who did not experience a PFS event were censored at the last disease assessment. Any patients who commence new anti-cancer therapy were censored at the last disease assessment prior to the initiation of new anti-cancer therapy.

Three further potential censoring scenarios are proposed, based on different possibilities on the number and timing of missed disease assessments are proposed (CS Table 10). The primary censoring rules and sensitivity analyses associated with these scenarios are stated. The range of scenarios explored and assumptions about when progression occurred appears to be comprehensive.

Sensitivity analyses were performed for the comparison of PFS based on investigator's assessment and PFS with progressive disease as determined per RECIST by immune-related BICR. Results of the sensitivity analyses are reported in CS Appendix L.

The CS reports that the proportional hazards assumption for PFS could be examined using both graphical and analytical methods. No information is reported regarding proportionality for OS. See section 3.1.7.5 of this report for further discussion of the proportional hazards in relation to the NMA and section 4.3.5 in relation to the survival curves used in the economic modelling.

3.1.6.5 Subgroup analyses

Pre-specified subgroup analyses were performed to determine whether the treatment effect was consistent across the following subgroups:

- IMDC risk category (favourable versus intermediate versus poor; favourable versus intermediate plus poor)
- Geographic region (North America versus Western Europe versus Rest of the World)
- PD-L1 status (combined positive score [CPS] <1 versus CPS ≥ 1)

- Age (< 65 versus ≥ 65)
- Sex (male versus female)
- Race (white versus non-white)

Results are presented in the CS Appendix E for PFS and OS and additionally for ORR in the clinical study report. The ERG notes that results for two additional subgroups are presented for these outcomes, Karnofsky performance scale score at baseline (90/100; 70/80) and number of metastatic organs (1; ≥2). These are not mentioned as being pre-specified subgroups in the CS, or trial protocol, so the ERG assumes that these were included post-hoc.

The ERG considers that these chosen subgroups are appropriate to this disease and we are not aware of any other key subgroups that have been omitted. The interpretation of the results of the subgroup analyses should be made with caution as the number of patients in some subgroups is relatively small. Further caution is required for subgroup analyses by OS, as data for this outcome is currently immature.

The ERG asked the company to specify whether any statistical interaction tests were conducted during the subgroup analyses (clarification question A4). The company responded that there were no pre-specified interaction tests performed for subgroup analyses in the trial because at the study design stage, an interaction effect between subgroups was not expected. Statistical interaction tests can confirm statistically significant differences in effect between subgroups of interest, if detected.

3.1.6.6 Statistical tests used

The non-parametric Kaplan Meier (KM) method was used to estimate the PFS and OS curves in each treatment group.

The statistical tests used for PFS and OS were the stratified Logrank test estimation. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (HR) between the treatment groups. The stratification factors were those used in the randomisation process (i.e. IMDC risk status, and geographic region). The ORR was assessed by the stratified Miettinen and Nurminen method.

3.1.6.7 Multiplicity in statistical testing

Running multiple statistical tests increases the probability of finding statistically significant results by chance even if there is no underlying effect. A pre-specified multiplicity strategy was applied to the two primary outcomes, PFS and OS, and the secondary outcome ORR. The strategy was based on the approach of Maurer and Bretz (CS Figure 4). In summary, the Type I error (α) allocated to a hypothesis that was successfully tested is re-distributed for testing of the other two hypotheses.

Initially, α=2.3% (23/25 of the overall total α = 2.5% for testing the OS, PFS and ORR) is allocated to the OS hypothesis and α =0.2% (2/25 of the overall total α =2.5%) is allocated to the PFS hypothesis. A series of steps was then followed whereby if the OS null hypothesis was rejected, half of its α was reallocated to PFS testing, and if the null hypothesis for OS and ORR were both rejected all α's were reallocated to the PFS hypothesis test. Similar steps were followed for the testing of the OS hypothesis. The ORR hypothesis was initially allocated a Type I error α =0% and thus could be tested unless one or both PFS or OS null hypotheses were rejected. Full details of the multiplicity strategy can be found in CS section 2.4.1.

The ERG considers the procedures followed in the trial to prevent statistically significant effects being detected by chance to be appropriate.

3.1.6.8 Analysis of safety

The CS reports that the safety analyses used a tiered approach. The tiers differed with respect to the analyses that was performed. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages are provided using the Miettinen and Nurminen method. There were no Tier 1 events in this trial. The CS does not define which events would be classified according to which tier. However, this information can be found in the trial protocol.

ERG conclusion

The statistical analyses in the KEYNOTE-426 trial are appropriate for the evaluation of a cancer therapy, and appear to have been implemented correctly. The trial was adequately statistically powered for the primary efficacy outcomes; procedures were

used to address potential multiplicity in statistical hypothesis tests; an appropriate ITT analysis was conducted; appropriate censoring rules for assessing PFS were used (with sensitivity analyses to examine robustness of the censoring approach); and appropriate pre-specified subgroup analyses were conducted.

3.1.7 Description and critique of the company's approach to the evidence synthesis

As only one trial of pembrolizumab plus axitinib in this indication was included in the submission (KEYNOTE-426), a meta-analysis of pembrolizumab trials was not possible. The CS provides a narrative review of the trial, with data presented in tables and text. As the only head-to-head comparison available was between pembrolizumab plus axitinib versus sunitinib it was necessary to conduct indirect comparisons to the other treatments in the decision problem. The company uses network meta-analyses (NMA) for this purpose.

3.1.7.1 Overview of network meta-analysis (NMA) approaches used

The CS reports two types of Bayesian approaches for indirect comparison of pembrolizumab plus axitinib with other treatments:

- Network meta-analysis (NMA) assuming constant hazards
- NMA assuming time-varying hazards based on fractional polynomials.

Both of these NMAs assess OS and PFS outcomes, but not the other outcomes relevant to the decision problem (response rate, HRQoL, adverse events).

The NMA assuming constant hazards appears to be the 'primary' indirect comparison method reported in the CS. The results of this analysis are reported in CS section 2.9.3. Details of the NMA using fractional polynomials are largely reported in appendices (CS appendix D and M).

It should be noted that these NMAs do not inform all estimates of cost effectiveness in the economic model. For the base case economic analysis the economic model uses patient-level data on OS, PFS and safety from the KEYNOTE-426 trial, with pazopanib and tivozanib assumed to be clinically equivalent to sunitinib. In section 4.3.5 of this report we give further detail on the clinical effectiveness estimates used in the economic model, and we note that the sunitinib PFS estimates from KEYNOTE-426 are in line with previous pivotal trials of sunitinib.

The NMA results do inform the economic model for the comparison of pembrolizumab plus axitinib and cabozantinib. As will be explained below, this analysis was restricted to patients at intermediate/poor RCC risk and is analysed separately as a sub-group analysis.

It should also be noted that in previous NICE appraisals of first line treatments for advanced RCC the appraisal committees have agreed, based on expert clinical opinion, that sunitinib, pazopanib and tivozanib are broadly similar to each other in efficacy and safety, and therefore have not considered indirect comparisons as a key factor in their decision making (see Appendix 9.1). However, the current appraisal includes cabozantinib as a comparator, and this has not been directly compared against pembrolizumab plus axitinib.

Notwithstanding potential judgements about the necessity of an NMA in the current appraisal, we have conducted a critique of the NMA, detailed in in the following sub-sections. A summary of the NMA results are presented in section 3.3.5 of this report.

3.1.7.2 Evidence networks

CS section B.2.9.1 provides an overview of the evidence networks constructed for the NMA. The company's systematic review of clinical effectiveness identified four RCTs evaluating five treatments relevant to the decision problem and inclusion in the NMA (CABOSUN,[11], COMPARZ,[12] KEYNOTE-426,[16] and TIVO-1[21]). A further two trials of treatments not included in the decision problem are included in the NMA to allow tivozanib to be connected to the network (see below for a discussion of these trials).[22, 23]

The networks are presented as a base case analysis, which included all patients irrespective of baseline RCC risk status, and subgroup analyses for patients at intermediate/poor RCC risk, and patients at favourable RCC risk.

Base case analysis

A visual representation of the base case network for all included RCTs and for all outcome measures is provided in CS Figure 10, reproduced below in Figure 1 (CS Figure 10), and tabulated in Table 6. This applies to the constant hazards NMA and the time-varying fractional polynomials NMA.

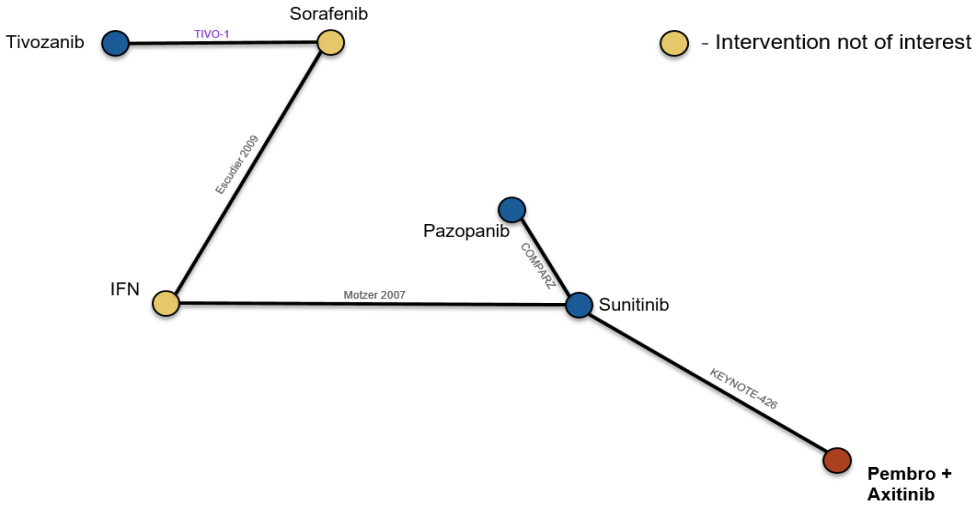

Figure 1 Network of RCTs in the base case NMA (all outcome measures)

Reproduced from CS Figure 10
NB. The CABOSUN trial (cabozantinib vs. sunitinib) is not included in this network diagram as this trial included IMDC intermediate/poor risk category patients only

Table 6 Summary of RCTs included in the NMA

Trial identifier	Intervention A	Intervention B
CABOSUN[11]	Cabozantinib	Sunitinib
COMPARZ[12]	Pazopanib	Sunitinib
KEYNOTE-426[16]	Pembrolizumab + axitinib	Sunitinib
TIVO-1[13]	Tivozanib	Sorafenib
Escudier et al[a]	Sorafenib[a]	Interferon alpha[a]
Motzer et al[a]	Sunitinib	Interferon alpha[a]

[a] Intervention not relevant to the decision problem. Included in network to connect relevant treatments together

The base case includes six RCTs evaluating four of the five treatments relevant to the decision problem (pembrolizumab and axitinib, sunitinib, pazopanib, tivozanib). The fifth treatment, cabozantinib, is only included in the intermediate/poor risk subgroup (see below). Two treatments not included in the decision problem (interferon alpha and sorafenib, from two RCTs[22, 23]) were only included to allow tivozanib to be connected to the network. The CS does not report how these two trials were identified, whether from the company's systematic review of clinical effectiveness, or another source. The ERG asked the company to clarify how these studies were identified and selected, and whether there were any other relevant studies which

could have been used (clarification question A9). The company responded that the two studies were identified from a broader systematic literature review they conducted for health technology assessments in multiple countries (NB, the systematic review of clinical effectiveness for the current appraisal was a subset of this broader systematic review, and included UK relevant treatments only). The company states that based on their latest literature search (conducted in February 2019), no other studies were identified that could be used to facilitate a connection of tivozanib to the evidence network. The ERG has checked the list of studies excluded from the systematic review of clinical effectiveness (CS appendix D1.1.3) and previous NICE appraisals of first line treatment for advanced RCC, and is not aware of any other relevant trials that could have been included in the NMA to connect tivozanib to the network.

Outcome-specific networks are depicted in CS Figure 11 (PFS) and Figure 12 (OS). The OS network contains fewer trials and relevant treatments than depicted in Figure 1 (CS Figure 10) due to the lack of available HR and Kaplan-Meier data needed for the constant HR and the time-varying hazard analyses, respectively. Notably, tivozanib is not included in the OS network since the connecting study Escudier 2009 did not report OS. Table 7 provides an overview of which treatments were included in the NMA base case and subgroup analyses (constant hazard and time-varying hazard fractional polynomial), by outcome measure.

Table 7 Treatments included in the NMA base case and subgroup analyses (constant hazard and time-varying hazard fractional polynomial), by outcome measure

Treatment	Base case		Intermediate/poor risk subgroup		Favourable risk subgroup[a]	
	PFS	OS	PFS	OS	PFS	OS
Pembrolizumab + axitinib	✓	✓	✓	✓	✓	✓
Sunitinib	✓	✓	✓	✓	✓	✓
Pazopanib	✓	✓	N/A	N/A	✓	✓
Tivozanib	✓	×	N/A	N/A	×	×
Cabozantinib	N/A	N/A	✓	✓	N/A	N/A

✓ = analysis conducted, × = analysis not possible
N/A = analysis not applicable
[a] constant hazard NMA only

Note that the TIVO-1 trial enrolled patients to receive first-line or second-line treatment. Therefore, subgroup data, rather than the data from all randomised patients, from this trial were used in the NMA. NMA results for TIVO-1 should be interpreted with caution as randomisation has been broken for this trial.

The CS reports that patient crossover occurred in one trial, TIVO-1 (in which 62% of patients in the sorafenib arm of the trial switched to tivozanib on disease progression) but noted that "outcomes included in the analyses described herein do not include patients who crossed over" (CS Appendix D.1.2). However, this is at odds with the company's response to clarification question A19 which states "The data used in the NMA does not account for cross-over, therefore, OS results where TIVO-1 is included is confounded by cross-over. Crossover was allowed only for patients who progressed on sorafenib to receive tivozanib, which may confound OS" (clarification question A19 response). The previous NICE appraisal committee for TA512 (tivozanib) were critical of the NMA for not adjusting for crossover in the included trials. The committee concluded that not adjusting for crossover meant that the results of the NMA were likely to be confounded with the direction of bias unknown. However, we do not believe this to be an issue in this current appraisal as OS from tivozanib is not included in the NMA. A crossover-adjusted HR for OS (using inverse probability of censoring weights method) was available in the tivozanib technology appraisal guidance (tivozanib vs sorafenib HR 1.02, 95% CI 0.67, 1.55) but could not have been used in the analysis as the "connecting" trials did not report OS. Similarly, the Escudier 2009 study also permitted crossover but only pre-crossover results are included in the NMA. Despite the apparent contradictory statements in the CS and clarification response, since no further connecting studies could be found the ERG considers no further analyses or adjustment necessary.

Subgroups

The NICE scope for this appraisal did not specify any subgroups of relevance. However, the company conducted separate NMAs for RCC risk subgroups: intermediate/poor and favourable. As a justification for these analyses the CS states that RCC risk score is an effect modifier in the treatment of RCC. The ERG notes that the subgroup analysis of the KEYNOTE-426 trial did not report statistically significant subgroup interactions by RCC risk group. As mentioned earlier in this report, the company stated in response to an ERG clarification question that there were no pre-specified interaction tests performed for subgroup analyses in the trial because at the study design stage, an interaction effect between subgroups was not expected.

Expert clinical advice to the ERG is that RCC risk status is an important prognostic factor. The experts also commented that there is empirical evidence that it is an effect modifier, as demonstrated in a recent phase III RCT of ipilimumab plus nivolumab, the Checkmate 214 RCT,[18] which was designed to show treatment effect differences according to risk groups. The

ERG asked the company to provide evidence to back up the assertion of effect modification for these risk subgroups (clarification question A20). In response, the company stated that risk status is a recognised prognostic factor in RCC and thus was therefore considered a potential treatment effect modifier. They cite the COMPARZ and CABOSUN trials as empirical evidence of this.

The ERG agrees with the company's decision to conduct a separate NMA for the intermediate/poor RCC risk group, as inclusion in the CABOSUN trial was restricted to patients in these risk groups, and cabozantinib is recommended by NICE only for patients at intermediate/poor risk (as defined by the IMDC criteria) (NICE TA542[24]).

As can be seen from Table 7 (and Figures 7 to 10 in CS Appendix D), the IMDC intermediate/poor risk network includes three treatments from two RCTs: pembrolizumab plus axitinib versus sunitinib (KEYNOTE-426), and cabozantinib versus sunitinib (CABOSUN). Pazopanib and tivozanib are missing from the network since no relevant subgroup data were reported. The intermediate/poor risk patients comprise the whole randomised population in the CABOSUN trial, but they are a subgroup of the KEYNOTE-426 trial (n=592/861;69%).

The favourable risk RCC NMA subgroup comprised three treatments (from two RCTs – KEYNOTE-426 and COMPARZ) Table 7 (and Figures 11 to 14 in CS Appendix D): pembrolizumab and axitinib; sunitinib and pazopanib. It was not possible for the company to conduct a time-varying fractional polynomial NMA in this subgroup as only one trial reported the necessary Kaplan Meier data necessary (KEYNOTE-426). This is the only network where both a constant hazard and a fractional polynomial model could not be conducted. The CS does not report separate cost-effectiveness estimates for patients with favourable RCC risk.

The ERG notes that the CABOSUN trial showed differences in PFS between intermediate and poor risk groups: in both groups the HR favoured cabozantinib over sunitinib, however in the poor risk group the confidence interval was wide and crossed one (likely due to small subgroup sample size). The ERG asked the company to run separate NMA scenario analyses for (i) intermediate risk patients, and (ii) poor risk patients (clarification question A21). We summarise these results in section 3.3.5 of this report, and our overall conclusion is that it cannot necessarily be concluded that there are differences in effect (for PFS) between poor and intermediate risk subgroups.

Overall, caution is required in the interpretation of the subgroup NMA analyses. They are based on a subset of randomised patients from the KEYNOTE-426 trial, and this can increase uncertainty about the precision of treatment effects.

3.1.7.3 Clinical heterogeneity assessment

CS Appendix D1.2 details the characteristics of the included trials (Table 10, Table 12, Tables 14 to 17; Figures 15 to 37). Details of the two trials of treatments not included in the decision problem[22,23] (interferon alpha and sorafenib) included to connect tivozanib to the network are provided in the company's response to ERG clarification question A9.

All trials were phase III RCTs, except CABOSUN and the trial by Escudier et al which were both phase II trials. They ranged in sample size from 157 patients (CABOSUN) to 1110 (COMPARZ). The trials were similar in terms of: inclusion criteria; sunitinib dosing schedule (where applicable); patient demographic characteristics (age, gender, race/ethnicity – where reported) and prior radiotherapy treatment.

The trials were generally similar in terms of the proportion of patients with lung, bone, liver and lymph node metastases. However, the CABOSUN trial and the trial by Escudier et al had a slightly higher proportion of patients with bone metastases (around 35% compared to 15% to 24% amongst the other trials). The ERG report for the cabozantinib NICE appraisal (NICE TA542) notes that the cabozantinib CS states that patients with bone metastases have a poor prognosis and experience poorer health outcomes with currently available treatments compared with patients without bone metastases. The current CS does not mention this. Expert clinical advice to the ERG states that bone metastases has a worse prognosis and can pose management problems. One expert commented that it may not be essential to consider evidence in patients with bone metastases separately from evidence in patients without.

In terms of baseline cancer performance score, four trials reported the distribution of Eastern Cooperative Oncology Group (ECOG) scores of the patients (CABOSUN, Escudier et al, Motzer et al; TIVO-1), and two reported Karnofsky scores (COMPARZ and KEYNOTE-426). Expert clinical advice to the ERG is that the Karnofsky scale (from which the ECOG is derived) is less commonly used but its scores can be mapped to ECOG scores to assess comparability. The majority of patients across the trials were classed as either ECOG 0 or 1 (meaning the patient is

able to function day to day without serious restriction), or Karnofsy score 90 to 100 (able to carry on normal activity and work; no special care needed). Only the CABOSUN trial included ECOG 2 patients (defined as ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours around (13% of patients). This is likely because this trial included only patients at intermediate or poor RCC risk, and ECOG performance status is one of the constituent variables in the IMDC risk status assessment. With this exception, overall the ERG concludes that the trials can be considered similar in terms of patient cancer performance status.

RCC risk status was measured by IMDC criteria in two trials (CABOSUN; KEYNOTE-426) and by MSKCC in four trials (COMPARZ and TIVO-1). The COMPARZ trial also assessed risk according to prognostic criteria by Heng et al[9], which was the basis of the later IMDC risk criteria [10]. As already discussed, expert clinical advice to the ERG is that the IMDC and MSKCC risk criteria can be considered similar. Thus, differences between the trials in the risk status patients were classified as would be unlikely. With the exception of CABOSUN trial and the trial by Escudier et al, the trials were similar in the distribution of patients across risk categories: 27-35% favourable risk; 55-64% intermediate risk, 5-13% poor risk. As already noted above, CABOSUN only included patients at intermediate or poor risk, with the proportion of randomised patients in these categories at 81% and 19% respectively. Escudier et al included a greater proportion of patients at favourable risk (52%) and intermediate risk (47%), with only 1% (a single patient) at poor risk.

There was some variation between the trials in the proportion of patients receiving prior nephrectomy. In one trial prior nephrectomy was an inclusion criterion (TIVO-1). With the exception of CABOSUN, in the other trials the proportion ranged from 94% (Escudier et al) to 83% (COMPARZ and KEYNOTE-426). The proportion was lowest in CABOSUN (75%). Expert clinical advice to the ERG suggests this may be explained by the fact that patients with more favourable RCC risk are more likely to receive nephrectomy, hence why nephrectomy was lower amongst intermediate/poor risk patients in CABOSUN. Expert clinical advice also notes that prior nephrectomy may be associated with a better treatment outcome, thus raising the potential risk of bias in the NMA results. However, expert advice suggested that evidence for this is contradictory and it is an issue undergoing debate at scientific conferences.

The ERG is not aware of any key prognostic factors or effect-modifying characteristics that differ between the included trials. Expert clinical advice to the ERG agrees.

ERG conclusion

The trials included in the NMA can be considered similar to each other in terms of patient demographic and prognostic characteristics and in sunitinib treatment regimens. An exception to this is the CABOSUN trial which differed from the other trials on a number of characteristics, as outlined above (e.g. phase II trial, smaller sample size; only included patients at intermediate or poor RCC risk; higher proportion of patients with bone metastases; lower proportion of patients receiving prior nephrectomy; inclusion of patients with ECOG 2 performance status). These differences are likely to be an artefact of the intermediate/poor risk status of the patients in this trial. The impact of these differences on the results of the NMA are mitigated by exclusion of CABOSUN in the base case NMA. Instead, it is included in a subgroup analysis of patients with intermediate/poor risk.

3.1.7.4 Critical appraisal of trials included in the NMA

CS Appendix D.1.2.5 provides a risk of bias assessment of the four trials included in the NMA, using Cochrane risk of bias criteria (version 1). The CS considers that, overall, the trials were considered to have low risk of bias, aside from bias associated with open-label trials. The ERG conducted an independent risk of bias assessment of the trials (Appendix 9.2) and mostly agreed with the appraisal judgements of the company, with some exceptions. These exceptions tended to be where the ERG considered the risk of bias to be unclear, rather than low or high. The ERG concurs with the company's overall conclusions that the trials were at low risk of bias, except for bias arising from lack of blinding.

3.1.7.5 Proportional hazards assumptions

Indirect comparisons of time-to-event data are generally made using the assumption of proportional hazards. Where the proportional hazards assumption is not supported alternative approaches can be used, based on the assumption of time-varying hazards. The *a priori* rationale for using both constant hazards and time-varying hazards NMA assumptions in the CS is not explicitly stated. The CS provides cumulative hazard plots and log cumulative hazard plots for KEYNOTE-426 (CS section B.3.3). The log-cumulative hazard plots for OS in the trial

cross suggesting the proportional hazard assumption does not hold. Additional tests of proportional hazards, such as Schoenfeld residual, were not presented in the CS. For other trials in the NMA, only Kaplan Meier plots were available to the company to inform assessments of proportional hazards.

In CS Section B 2.9.4 the company discuss assumptions of proportional hazards based on a comparison of the results of the constant hazards and the time-varying hazards fractional polynomial NMAs. The company concluded proportional hazards did not hold for PFS (base case) and OS (intermediate/poor subgroup) (Table 8) However, in response to ERG clarification question A16 the company maintained that despite the violation of proportional hazards assumption, the fractional polynomial models are "more sensitive and detect chance fluctuations in the observed hazards in the tail ends of follow-up" hence use of a constant hazards may still be appropriate when length of follow-up is short (as in the Escudier 2009 study in the base case) and when sample size is small (in the Intermediate/poor subgroup). Hence, even when there was evidence the proportional hazards assumption was violated, the company preferred the constant hazards model over the time-varying fractional polynomials NMA.

The ERG assessed the data and agrees with the company's conclusions (Table 8). There was no strong evidence to doubt the proportional hazard assumption for OS (base case) and PFS (intermediate/poor subgroup).

3.1.7.6 Statistical NMA approaches used – constant hazards

The constant hazards NMA was performed using a regression model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial (or comparison) in the network (cited according to 'Dias et al' with no reference provided. The ERG believe this refers to NICE Decision Support Unit Technical Support Document (TSD) 2).[25]

Normal non-informative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000.

As there were no closed loops in the networks (i.e. there were no direct and indirect comparisons of the same treatments), an evaluation of network internal consistency was not required.

Table 8 The company and ERG interpretation of proportional hazards assumptions

	Base case	**Intermediate/poor risk**
Outcome	**Studies included in NMA**	
OS	KEYNOTE, COMPARZ	KEYNOTE, CABOSUN
PFS	KEYNOTE-426, TIVO-1, COMPARZ, Motzer 2007, Escudier 2009	KEYNOTE-426, CABOSUN
The company's interpretation		
OS	PH assumption not violated. Pembrolizumab+axitinib vs sunitinib and pazopanib vs sunitinib did not vary significantly over time (CS B.2.9.4)	PH assumption violated (KEYNOTE-426). However, given low numbers of events constant HR is preferred as it is more stable (CS B.2.9.4)
PFS	PH assumption violated (CS B.2.9.4)	PH assumption not violated. HRs did not vary over time significantly (KEYNOTE-426, CABOSUN) (CS B.2.9.4)
The ERG's interpretation		
OS	KM plots unclear whether PH assumption violated for KEYNOTE-426. Log cumulative hazard plots in CS Figure 20 suggests PH assumption does not hold for KEYNOTE. However, it is unclear if these figures refer to the base case or intermediate/poor subgroup. Unclear whether PH assumption violated in TIVO-1 and COMPARZ	PH assumption violated in CABOSUN, unclear in KEYNOTE-426
PFS	KM plots unclear whether PH assumption violated for KEYNOTE-426. Log cumulative hazard plots in CS Figure 27 suggests PH assumption does not hold for KEYNOTE. However, it is unclear if these figures refer to the base case or intermediate/poor subgroup. PH assumption violated in TIVO-1, COMPARZ, Escudier 2009. Unclear whether PH assumption violated in Motzer 2007.	PH not violated in CABOSUN (NICE TA542 presents Schoenfeld residuals and log cumulative hazard plots). Unclear whether PH assumption violated in KEYNOTE-426.

PH = Proportional hazard; KM = Kaplan Meier

The ERG replicated the company's constant hazard NMA to check consistency in results using the TSD 2 code from for contrast data.[25] When using the company's data reported in CS Tables 22,24,26 & 28 results were comparable. However, when the ERG examined the underlying data from the published RCTs a number of discrepancies were found in the company's data and calculations. These are shown in Appendix 9.33 of this report. The results showed differences in PFS for tivozanib (base case) and cabozantinib (intermediate/poor risk subgroup). However, as the ERG's analyses led to slightly higher hazard ratios for these treatments the CS scenario can be viewed as conservative.

3.1.7.7 Statistical NMA approaches used – fractional polynomials

The CS cites fractional polynomial methodology introduced by Jansen[26] (CS Appendix D.1.2.3). Jansen describes this method as an alternative to NMA of survival data in which the treatment effect is represented by a constant HR. A multi-dimensional treatment effect approach is used in which hazard functions of interventions compared in an RCT are modelled, and the difference between the parameters of these fractional polynomials within a trial are synthesized (and indirectly compared) across studies. The fractional polynomial analysis generates results which reflect the time course of the log-hazard function and as such can be expressed as log-hazard function curves and their parameters (intercept and slope). Credible interval curves can be plotted alongside the log-hazard function curves.

Two orders of fractional polynomial model were considered for inclusion: first-order, and second order. The power level for each order can be chosen from the following set -2. -1, -0.5, 0, 0.5, 1, 2, 3. A first order model with a p1=0 would be equivalent to a Weibull model, and a first order model with p1=1 would correspond to a Gompertz model. Survival distributions were considered using the multivariate NMA framework: Weibull, Gompertz, and second order fractional polynomials including p_1=0 or 1 and p_2= -1, 0.5, 0, 0.5, or 1. The ERG asked the company to clarify the rationale for testing fractional polynomials with a relatively narrow range of powers (i.e. p_1 in the range 0,1, and p_2 in the range -1 to +1) (clarification question A11). The company responded that in their experience fractional polynomial models with p2=-2 or 2 were too sensitive to outliers and therefore did not reflect underlying hazard rates.

Model fitting

The deviance information criterion (DIC) was used to compare the goodness-of-fit of the competing fractional polynomial survival models. The model with the lowest DIC was chosen for analysis.

The ERG asked the company to clarify whether the choice of model was influenced by other considerations, such as the clinical plausibility of the model chosen with respect to PFS and OS curves as observed in the trials (clarification question A13). The company responded that clinical plausibility was examined by cross-referencing time-varying HRs against constant HRs from published studies and checking if results were stable across fractional polynomial models. However, the company do not elaborate further on this process and whether/how it informed their choice of model.

The DIC model fit estimates for the NMA are provided in CS Appendix M. However, only the p1=0,1 and p2=0,1 model fit results are presented. In clarification question A12, the ERG asked the company to present the model fit statistics for all the fractional polynomial models considered, to permit independent assessment of all the DIC values. The company provided a detailed appendix to the clarification responses including time-varying hazard plots and parameterisations of all fitted 1st and 2nd order fractional polynomials.

The best fitting fractional polynomial models were:

- Base case PFS – 2nd order FP model with p1=0, p2=0.
- Base case OS – 2nd order FP model with p1=0, p2=0.
- Intermediate/poor risk subgroup PFS - 2nd order FP model with p1=0, p2=0.
- Intermediate/poor risk subgroup OS – 2nd order FP model with p1=1, p2=0.

NMA results are presented for the best fitting fractional polynomials in CS Appendix M (August 2018 KEYNOTE-426 data cut) and Appendix N (January 2019 KEYNOTE-426 data cut). Results are presented as time-varying hazard ratio plots; tabulated time-varying hazard ratios (at three month intervals up to 18 months); and basic parameter estimates (d0/ d1 estimate and variance; correlation). The ERG asked the company to provide the results for each of the fractional polynomial models fitted (i.e. first order and second order p_1=0 or 1 and p_2= -1, 0.5, 0, 0.5, or 1), to enable comparison of the variation in hazard ratios between different order models

(clarification questions A12 and A14). The company provided these in the appendix to the clarification response document.

Given that the appraisal committee in NICE TA512[27] raised concerns that choice of fractional polynomial model had a substantive impact on cost-effectiveness and thereby uncertainty, we examined the impact of alternative fractional polynomial models with similar fit (Table 9) (see ERG scenario analyses in section 4.4 of this report for the cost effectiveness results). For PFS in the base case, the ERG selected the next best fitting based on DIC values (2nd order FP p1=1, p2=0). For OS in the intermediate/poor risk subgroup, since the next best fitting model (2nd order FP p1=1 p2=1) had a very similar fit to the company's best fitting model ([redacted]) for our scenario we chose the model with the third lowest DIC (2nd order FP p1=0, p2=1). We considered that the results of this fractional polynomial model ([redacted]).
[redacted] were more aligned to the respective Kaplan Meier OS curves from the KEYNOTE-426 and CABOSUN trials, and thus in our view, are more clinically plausible. (NB. all three fractional polynomial models showed no appreciable difference in fit, commonly interpreted as a difference in DIC of 2-3 or less).

The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS software package. A first series of iterations from the OpenBUGS sampler were discarded as 'burn-in', and the inferences were based on additional iterations using two chains. All analyses were performed using R version 3.0.3 (http://www.r-project.org/) and OpenBUGS version 3.2.3 (OpenBUGS Project Management Group). In response to ERG clarification question A17, the company provided R code and OpenBUGS code for the models. However, the R code provided is incomplete and doesn't state which packages are used or defined the functions used. Furthermore, the data provided in the numerous spreadsheets referring to each study is not the exact data used in the NMA. Instead, it is presented as probabilities of death, the interval is unclear, as is how/whether they use the numbers at risk. The format of the data needed for the code is also unclear and initial values are not provided. Nevertheless, the ERG was able to validate the OpenBUGS code provided against that provided in published papers and is satisfied it has been conducted correctly.

Table 9 Company selected fractional polynomial model and ERG scenarios

	OS	PFS
Base case		
Company FP choice	PH assumption not violated – constant hazards used	2nd order FP p1=0, p2=0. [redacted] (best fitting model)
ERG scenario	PH assumption not violated – constant hazards used	2nd order FP p1=1, p2=0. Clarification responses appendix Tables 43, 44 [redacted] (second best fitting model)
Intermediate/poor risk subgroup		
Company FP choice	2nd order FP p1=1, p2=0 [redacted] (best fitting model)	PH assumption not violated – constant hazards used
ERG scenario	2nd order FP p1=0, p2=1 Clarification responses appendix Tables 129, 130. [redacted] (third best fitting model)	PH assumption not violated – constant hazards used

FP= Fractional polynomial; DIC = Deviance information criterion

ERG conclusion

Based on the information provided the ERG considers that the methods used to implement the two NMA methods are appropriate and correspond to the methods specified in the original methodological texts.

3.1.7.8 Choice between random effects and fixed effect models

Fixed effects models were chosen for all the NMAs presented. Random effects models are preferred in networks such as this which include small numbers of trials and where there is the potential for clinical heterogeneity[28]. However, the CS states that insufficient trials were available to achieve stable estimates of between-study heterogeneity. The ERG asked the company if an informative prior could have been used for random effects as specified by Turner et al[29] and if so to re-run the NMAs using a random effects model (clarification question A10). The company responded that collection and validation of meta-epidemiologic data as proposed by Zondervan-Zwijnenburg (2017)[30] would not have been possible within the time frame. The company therefore did not run random effects models using published informative priors. Whilst the mean effect sizes would have been the same the use of an informative prior would have

widened the credible intervals. On balance, however, we consider the trials to be generally similar in patient and other characteristics (see 3.1.7.3 above) so a fixed effect analysis is acceptable.

3.1.7.9 Summary of ERG critique of the NMA

The CS reports two types of Bayesian approaches for indirect comparison of pembrolizumab plus axitinib with other treatments:

- NMA assuming constant hazards
- NMA assuming time-varying hazards based on fractional polynomials.

These NMAs were reported for OS and PFS outcomes. The NMA assuming constant hazards appears to be the 'primary' indirect comparison method reported in the CS.

The networks are presented as a base case analysis, which included all patients irrespective of baseline RCC risk status, and subgroup analyses for patients at intermediate/poor RCC risk and patients at favourable RCC risk. The base case includes six RCTs evaluating four of the five treatments relevant to the decision problem (pembrolizumab plus axitinib, sunitinib, pazopanib, and tivozanib). The fifth treatment, cabozantinib, is only included in the intermediate/poor risk subgroup (see below).

The ERG agrees with the decision to conduct a separate NMA for the intermediate/poor RCC risk group, as inclusion in the CABOSUN trial was restricted to patients in these risk groups, and cabozantinib is recommended by NICE only for patients at intermediate/poor risk (as defined by the IMDC criteria). Expert clinical opinion is that risk status is a key prognostic variable in RCC, and there is some evidence to suggest it is an effect modifier. Caution is required in the interpretation of the subgroup NMA analyses as they are based on a subset of the KEYNOTE-426 randomised trial population, which can increase uncertainty about the precision of treatment effects.

The NMA does not inform the economic model for the base case analysis (all patients irrespective of baseline RCC risk status). However, the NMA informs the economic model for the intermediate/poor risk subgroup analysis comparing pembrolizumab plus axitinib versus cabozantinib.

In terms of clinical heterogeneity, the trials included in the NMA can be considered similar to each other in terms of patient demographic and prognostic characteristics and in sunitinib treatment regimens. An exception to this is the CABOSUN trial which differed from the other trials on a number of characteristics (e.g. smaller sample size; only included patients at intermediate or poor RCC risk). These differences are likely to be related to the intermediate/poor risk status of the patients in this trial. The impact of these differences on the results of the NMA are mitigated by exclusion of CABOSUN in the base case NMA, and its inclusion in the intermediate/poor RCC risk subgroup. Overall, the trials were considered to have low risk of bias, aside from bias associated with open-label trials.

The *a priori* rationale for using both constant hazards and time-varying hazards NMA assumptions in the CS is not explicitly stated. The company discusses these assumptions based on a comparison of the results of the constant hazards and the time-varying hazards fractional polynomial NMAs. The company concluded proportional hazards did not hold for PFS (base case) and OS (intermediate/poor subgroup). However, the company maintained that despite the violation of the proportional hazards assumption, the use of constant hazards is more appropriate than time-varying fractional polynomials when length of follow-up is short, or sample size is small. The ERG assessed the data and agrees with the company's conclusions.

The constant hazards NMA was conducted according to standard methods as recommended by the NICE DSU.[25] The fractional polynomials model was conducted according to methods proposed in a journal paper by author Jansen.[26] The DIC was used to compare the goodness-of-fit of the competing fractional polynomial survival models. The model with the lowest DIC was chosen for analysis.

Given that the appraisal committee in NICE TA512 (tivozanib)[27] raised concerns that the choice of fractional polynomial model had a substantive impact on cost-effectiveness and thereby uncertainty, we examined the impact of alternative fractional polynomial models with similar fit in an ERG scenario analysis (see section 4.4 of this report).

Fixed effect models were chosen by the company for all the NMAs presented. Random effects models are preferred in networks such as this which include small numbers of trials and where there is potential for heterogeneity. The CS states that insufficient trials were available to achieve stable estimates of between-study heterogeneity, and it was not possible to use an

informative prior for a random effects analysis. The ERG concurs that fixed effect model is acceptable given the general low clinical heterogeneity (see above).

Overall, the ERG considers the methods and assumptions used to conduct the NMAs to have been appropriately exercised, though with some uncertainties due to relatively small data sets.

3.2 Summary statement of company's approach to evidence synthesis

The ERG's appraisal of the CS systematic review of clinical effectiveness is summarised in Table 10.

Table 10 ERG critical appraisal of company's systematic review of clinical effectiveness

Item	ERG response
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Although the eligibility criteria used for population includes a narrower population of RCC with clear cell component.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes. There was a sufficient effort to search for relevant research. Although the search was around five months out-of-date the ERG has run targeted searches for recent evidence and no studies of relevance appear to have been missed.
3. Is the validity of included studies adequately assessed?	Yes. Although the ERG differed with some of the company's judgements (more favourably).
4. Is sufficient detail of the individual studies presented?	Yes. Sufficient details were reported.
5. Are the primary studies summarised appropriately?	Yes. The CS summaries of the key characteristics of the relevant trials and their results appeared accurate and appropriate.

The ERG considers the systematic review processes undertaken by the company were reasonable (two reviewers undertook all stages) with the exception of post hoc inclusion of two trials in the NMA. The evidence presented reflects the decision problem with the exception of the population having a more precise definition for clear cell (+/- sarcomatoid features) and

some participants may have been treated at an advanced stage previously. There is a low chance of systematic error in the results of the systematic review.

3.3 Summary of submitted evidence

The ERG has summarised results from the August 2018 data-cut and noted similarities or differences from the January 2019 data-cut. We consider BICR assessments of response to be the least biased, however investigator assessments are also noted for comparison.

3.3.1 Survival

At the August 2018 data-cut and a median follow-up of 13.2 months (range 0.1 to 21.5 months) in the pembrolizumab plus axitinib arm and 12.1 months (range 0.4 to 22.0 months) in the sunitinib arm, median OS was not reached in either group. Overall survival rates at 6, 12 and 18 months favoured pembrolizumab plus axitinib (Table 11). The HR for OS was 0.53 (95% CI 0.38, 0.74), p=0.00005. Results from the January 2019 data cut [redacted], CS Appendix O Table 6.

Median PFS based on BICR was 15.1 months with pembrolizumab plus axitinib and 11.1 months with sunitinib, HR 0.69 (95% CI 0.57 to 0.84, p=0.00014) at the August 2018 data-cut. PFS rates at 6, 12 and 18 months favoured pembrolizumab plus axitinib (Table 11), although 95% confidence intervals overlapped at 6 and 18 months. Results from the January 2019 data cut [redacted] (CS Appendix O Table 7). PFS at the August 2018 data-cut based on investigator assessment was less favourable but remained statistically significant (HR 0.82, 95% CI 0.67 to 1.00, p=0.022) (CS Appendix L Table 3).

Although both OS and PFS inform the economic model, hazard rates of PFS were only based on the observed Kaplan-Meier curve up to week 13, with parametric models fitted to data after this time point (see section 4.3.5).

3.3.2 Response rates

At the August 2018 data-cut, the ORR was 59.3% in the pembrolizumab plus axitinib arm and 35.7% in the sunitinib arm based on BICR according to RECIST 1.1, a difference of 23.6% (95% CI 17.2 to 29.9, p<0.0001).

Table 11 Survival outcomes at August 2018 data-cut

	Pembrolizumab + axitinib (n=432)	Sunitinib (n=429)	Treatment effect (95% CI), p value
Overall survival			
Median OS, months	Not reached	Not reached	HR 0.53 (0.38, 0.74), p=0.00005
6 month OS rate, % (95% CI)	94.9 (92.3, 96.6)	89.0 (85.6, 91.6)	NR
12 month OS rate, % (95% CI)	89.9 (86.4, 92.4)	78.3 (73.8, 82.1)	NR
18 month OS rate, % (95% CI)	82.3 (77.2, 86.3)	72.1 (66.3, 77.0)	NR
PFS			
Median PFS, months	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)	HR 0.69 (0.57, 0.84), 0.00014
6 month PFS rate, % (95% CI)	74.0 (69.5, 77.9)	66.0 (61.1, 70.4)	NR
12 month PFS rate, % (95% CI)	59.6 (54.3, 64.5)	46.2 (40.6, 51.6)	NR
18 month PFS rate, % (95% CI)	41.1 (33.5, 48.5)	32.9 (25.4, 40.5)	NR

NR, not reported.

A complete response was experienced by 5.8% of the pembrolizumab plus axitinib arm and 1.9% of the sunitinib arm (Table 12).

[redacted].

The difference in DCR based on BICR was 11% (95% CI 4.8 to 17.0) in favour of pembrolizumab plus axitinib, with [redacted] at the January 2019 data-cut (CS Appendix O Table 9). The difference based on investigator assessments was lower at 6.6% (95% CI 4.8 to 17.0) at August 2018 (CS Appendix L Table 10).

Median DOR based on BICR in people with a CR or PR was not reached at the August 2018 data-cut in the pembrolizumab plus axitinib arm and was 15.2 months in the sunitinib arm (Table 12). Median DOR based on investigator assessment was 18.0 months (range 1.3+ to 18.2+) and 15.2 months (range 1.2+ to 15.4+), respectively (CS Appendix L Table 7). At the January 2019 data-cut these outcomes were [redacted](CS Appendix O Table 2).

Table 12 Response rates and DOR based on BICR at August 2018 data-cut

	Pembrolizumab + axitinib (n=432)		Sunitinib (n=429)		Difference (95% CI), p value
	n (%)	95% CI	n (%)	95% CI	
Objective response rate (CR+PR)	256 (59.3)	54.5, 63.9	153 (35.7)	31.1, 40.4	23.6 (17.2, 29.9), p<0.0001
Disease control rate (CR+PR+SD ≥ 6 months)	309 (71.5)	67.0, 75.7	260 (60.6)	55.8, 65.3	11.0 (4.8, 17.0) p=NR
CR	25 (5.8)	3.8, 8.4	8 (1.9)	0.8, 3.6	NR
PR	231 (53.5)	48.6, 58.3	145 (33.8)	29.3, 38.5	NR
SD	106 (24.5)	20.5, 28.9	169 (39.4)	34.7, 44.2	NR
PD	47 (10.9)	8.1, 14.2	73 (17.0)	13.6, 20.9	NR
Non-evaluable[a]	8 (1.9)	0.8, 3.6	6 (1.4)	0.5, 3.0	NR
No assessment[b]	15 (3.5)	2.0, 5.7	28 (6.5)	4.4, 9.3	NR
Median DOR (in CR or PR), months (range)	Not reached (1.4+ to 8.2+)		15.2 (1.1+ to 15.4+)		NR

[a] post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) with insufficient data for assessment of response per RECIST 1.1. or CR/PR/SD < 6 weeks from randomisation). [b] no post-baseline assessment available for response evaluation. For best overall response of CR and PR, only confirmed responses are included. CR, complete response; DOR: duration of response; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease. '+' indicates there was no progressive disease by the time of last disease assessment.

3.3.3 Health related quality of life

Utilities at baseline and end of study measured with the EQ-5D-3L were not presented in the CS. These were provided by the company in response to clarification request A8, and changes from baseline are summarised in Table 13. There was no statistically significant difference between treatments.

The CS states there were no clinically meaningful differences in EQ-5D VAS between baseline and week 30 in either group, and changes from baseline at week 30 were similar between groups (Table 13). The CS does not define what a clinically meaningful difference is, however the ERG notes that a minimal important difference of 7 has been applied in kidney cancer previously.[31] [redacted] were found at the January 2019 data-cut (CS Appendix O Table 10). Similarly, no differences between groups were found in EORTC QLQ-C30 global health status/QoL score (Table 13). Results from the January 2019 data-cut were not reported.

Selected functional and symptom scales of the EORTC-QLQ-30 were presented in CS Appendix L Figure 6. The results for all EORTC-QLQ-30 scales were provided by the company in response to clarification request A7 in Figures A7.1 and A7.2. A greater worsening of the

diarrhoea symptom scale was observed in the pembrolizumab + axitinib group. Reporting of diarrhoea as an adverse event is discussed in section 3.3.6. The other scales (Global health status/QoL, functional scales, symptom scales and items) were similar between treatments.

Table 13 Patient reported outcomes at August 2018 data-cut

	Pembrolizumab + axitinib (n=432)	Sunitinib (n=429)	Difference in LS mean (95% CI), p value
EQ-5D-3L index			
Change from baseline, LS mean (95% CI)	n=427 -0.005 (-0.026, 0.016)	n=421 -0.013 (-0.035, 0.010)	0.007 (-0.022, 0.037) p=0.619
EQ-5D VAS			
Change from baseline, LS mean (95% CI)	n=427 -3.31 (-5.18, -1.43)	n=421 -1.92 (-3.90, 0.05)	-1.38 (-3.89, 1.12), p=0.277
EORTC QLQ-C30 global health status/QoL score			
Change from baseline, LS mean (95% CI)	n=427 -4.05 (-6.03, -2.07)	n=423 -2.35 (-4.44, -0.26)	-1.70 (-4.34, 0.94), p=0.207

Source: CS Table 19; CS Appendix L Table 13; clarification response Table A8.

3.3.4 Sub-group analyses for overall survival and PFS

As described earlier in section 3.1.6, a number of patient subgroups were analysed in the KEYNOTE-426 trial. At the August 2018 data cut, OS results for the subgroups were consistent with the overall effect (subgroup HRs ranging from 0.2 to 0.69 with wider confidence intervals for some; overall HR 0.53), (CS Appendix E Figure 1).

[redacted]

PFS was consistent across all subgroups, with HRs ranging from 0.54 to 0.87 (overall HR 0.69), (CS Appendix E Figure 2).

[redacted].

No statistical tests of interaction were presented and the CS states these subgroups lack statistical power, therefore these results should be viewed with caution.

ERG conclusion

OS and PFS results were in favour of pembrolizumab plus axitinib over sunitinib, although median OS was not reached in either group. Objective response rate and disease control rate were also in favour of pembrolizumab plus axitinib. There were no differences between treatments for the EQ-5D-3L index, EQ-5D VAS or EORTC QLQ-C30 global health status/QoL score and most other scales of the EORTC QLQ-C30, apart from a greater worsening on the diarrhoea scale with pembrolizumab plus axitinib. Subgroup analyses of OS and PFS were consistent with the overall effect [redacted].

3.3.5 Network meta-analysis results

For brevity summarise the results of the constant hazards NMA, with brief reference to the results of the time-varying fractional polynomial NMA. Please refer to section 3.1.7 for a description of the evidence networks for the base case and subgroup analyses, and the statistical procedures used to conduct the NMAs.

3.3.5.1 Progression free survival

Table 14 reports the NMA inputs to the constant HRs for the outcome of PFS in the base case.

Table 14 Constant HRs NMA (fixed effects) for PFS, NMA base case

Trial	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
COMPARZ	Sunitinib	Pazopanib	[redacted]	[redacted]
Escudier 2009	IFN-α	Sorafenib	[redacted]	[redacted]
KEYNOTE-426 (IA1 Aug 2018 data cut)	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]
Motzer 2007	Sunitinib	IFN-α	[redacted]	[redacted]
TIVO-1*	Sorafenib	Tivozanib	[redacted]	[redacted]

Note: * denotes trials in grey used subgroup first-line data
Grey rows represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.
Reproduced from CS Table 22.

The CS reports that treatment with pembrolizumab plus axitinib resulted in a [redacted] in the duration of PFS compared to all relevant competing interventions including [redacted] (Table 15).

Table 15 HRs estimated from fixed-effects constant hazard NMA of PFS; base case

Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**IFN-a**	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Sorafenib**	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Pazopanib**	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Tivozanib**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Pembrolizumab +axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
Grey cells represent treatments that were not of interest but facilitated indirect treatment comparisons for treatments of interest.
All bolded values are statistically meaningful at the 0.05 significance level.
Reproduced from CS Table 23.

Results using the January 2019 KEYNOTE-426 data-cut show [redacted] results.

The results of the time-varying fractional polynomial NMA showed that pembrolizumab plus axitinib [redacted] (relative to sunitinib) than tivozanib and pazopanib, and achieved [redacted] compared to the other comparators over time.

Table 16 reports the NMA inputs to the constant HRs for the outcome of PFS in the intermediate/poor risk subgroup.

Table 16 Error! Reference source not found.**Constant HRs for PFS; intermediate/poor risk s ubgroup**

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN	Sunitinib	Cabozantinib	[redacted]	[redacted]
KEYNOTE-426 (IA1 - Aug 2018 data-cut)	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Reproduced from CS Table 26

The CS reports that both cabozantinib and pembrolizumab plus axitinib were associated with lower HRs compared to sunitinib, indicating longer PFS (Table 17).

Table 17 HRs estimated from fixed-effects constant hazard NMA of PFS; intermediate/poor risk subgroup

Sunitinib	[redacted]	[redacted]
[redacted]	**Cabozantinib**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
Reproduced from CS Table 27
[redacted] were obtained when using the January 2019 data cut.

The results of the time-varying fractional polynomial NMA showed that pembrolizumab plus axitinib had a [redacted] compared to sunitinib up to six months and cabozantinib had a [redacted] compared to sunitinib [redacted]. There was [redacted] between pembrolizumab plus axitinib and cabozantinib [redacted]

3.3.5.2 Overall survival

Table 18 reports NMA inputs to the constant HRs for the outcome of OS in the base case.

Table 18 Constant HRs for OS; NMA base case

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
COMPARZ	Sunitinib	Pazopanib	[redacted]	[redacted]
KEYNOTE-426 (IA1 - Aug 2018 data-cut)	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Reproduced from CS Table 24

As can be seen, tivozanib is omitted from this network. The CS reports that treatment with pembrolizumab plus axitinib resulted in a [redacted] in the duration of OS compared to pazopanib ([redacted]) and sunitinib ([redacted]) (Table 19).

Table 19 HRs estimated from fixed-effects constant hazard NMA of OS; base case

Sunitinib	[redacted]	[redacted]
[redacted]	**Pazopanib**	**1.73 (1.21, 2.49)**
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level.

Reproduced from CS Table 25

[redacted] were obtained when using the January 2019 data cut.

The results of the time-varying fractional polynomial NMA showed that pembrolizumab plus axitinib versus sunitinib was associated with [redacted] HRs over time compared to pazopanib versus sunitinib. There [redacted] between treatments [redacted]

Table 20 reports the NMA inputs to the constant HRs for the outcome of OS, based on the intermediate/poor risk subgroup.

Table 20 Constant HRs for OS; intermediate/poor risk subgroup

Study	Reference	Intervention	HR Int. vs. Ref	Log HR (SE) Int. vs. Ref
CABOSUN	Sunitinib	Cabozantinib	[redacted]	[redacted]
KEYNOTE-426 (IA1 - Aug 2018 data-cut)	Sunitinib	Pembrolizumab + axitinib	[redacted]	[redacted]

Reproduced from CS Table 28

The CS reports that pembrolizumab plus axitinib resulted in a [redacted] in OS compared to sunitinib ([redacted]) (Table 21).

Table 21 HRs estimated from fixed-effects constant hazard NMA of OS; intermediate/poor risk subgroup

Sunitinib	[redacted]	[redacted]
[redacted]	**Cabozantinib**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level.
Reproduced from CS Table 29

[redacted] were obtained when using the January 2019 data cut from KEYNOTE-426.

The results of the time-varying fractional polynomial NMA showed that pembrolizumab plus axitinib was associated with [redacted] compared to cabozantinib versus sunitinib. However, differences between pembrolizumab plus axitinib and cabozantinib [redacted] due to [redacted]

As stated in section 3.1.7, the ERG asked the company to run separate NMA scenario analyses for (i) intermediate risk patients, and (ii) poor risk patients (clarification question A21). The results of the scenario analyses (constant hazards NMA only) showed that HRs were [redacted]. Due to the relatively small sample sizes in the poor risk subgroups it cannot necessarily be concluded that there are significant differences in effect (PFS) between intermediate and poor risk subgroups.

3.3.6 Summary of adverse events

Safety data for the KEYNOTE-426 trial are reported in CS section B.2.10 (August 2018 data cut) and also in CS Appendices F (additional data from August 2018) and O (January 2019 data cut). A summary overview of all AEs is presented in CS Table 33 and reproduced in Table 22. Data on discontinuations and deaths due to AEs were presented in CS Appendix O p211-212. Where possible the ERG has cross-checked these data with the KEYNOTE-426 journal publication or the CSR. As reported in the CS, the overall incidence of AEs was generally similar in the pembrolizumab plus axitinib and sunitinib trial arms. The majority of patients in both treatment arms reported at least one any Grade AE (pembrolizumab plus axitinib 98.4%;

sunitinib 99.5%). In the pembrolizumab plus axitinib arm drug-related AEs were experienced by 96.3% of patients; 75.8% any Grade 3-5 AE and 7.7% patients discontinued both drugs simultaneously owing to an AE. In the sunitinib arm 97.6% of patients experienced a drug-related AE; 70.6% any Grade 3-5 AE and 13.9% discontinued sunitinib owing to an AE. Rates of discontinuations of either pembrolizumab or axitinib or both are reported in CS Table 33.

The rate of serious adverse events (SAEs) was higher in the pembrolizumab plus axitinib group; 40.3% of participants reported SAEs in the pembrolizumab plus axitinib arm compared with 31.3% in the sunitinib arm (CS Appendix F Table 2 provides details of specific SAEs the most common in the pembrolizumab plus axitinib arm being diarrhoea, 2.8%). Deaths due to AEs occurred in 2.6% of the pembrolizumab plus axitinib arm (four of these were drug-related AEs: myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis) and 3.5% of the sunitinib arm (7 were drug-related AEs). Adverse event rates were [redacted] at the January 2019 data cut (Table 22) with the exception of [redacted] (although the difference between trial arms was similar to the 2018 data-cut).

As reported in the CS (Table 30) there were differences in treatment exposure between the two arms of the KEYNOTE-426 trial. The mean duration on any therapy was 320.6 days (total exposure 4766.94 person-months) in the pembrolizumab plus axitinib arm and in the sunitinib arm this was 255.6 days (total exposure 3924.64 person-months) (Table 23). The CS presents exposure-adjusted event rates for the key adverse events to account for the different times on therapy. This is presented as the event rate per 100 person-months of exposure, calculated as the event count multiplied by 100 divided by person-months of total exposure of all participants in that group (time between the first dose date plus 1 day and the earlier of the last dose date plus 30 or the database cut-off date). No further details were presented in the CS and the ERG was unable to find details in the CSR or trial protocol. Note that the adjusted rate is based on the count of events, rather than the number of people experiencing the event, therefore includes multiple occurrences of events. Details of any censoring in the arms was not reported. The exposure-adjusted incidence rate is most appropriate when the risk of each event is constant over the duration of follow-up,[32] but the ERG notes some adverse events may be more likely to occur earlier or later with treatment (see below).

When the exposure-adjusted rates are considered, the CS states that there were no clinically meaningful differences in overall rates including SAEs (CS p66), CS Table 34 (reproduced in Table 24).

Table 22 Summary of adverse events in KEYNOTE-426, All Subjects as Treated (ASaT) population

Event, %	Pembrolizumab plus axitinib, n=429, 2018 data cut ([redacted])	Sunitinib, n=425, 2018 data cut ([redacted])
Any AE	98.4 ([redacted])	99.5 ([redacted])
Any drug-related AE	96.3 ([redacted])	97.6 ([redacted])
Grade 3-5 AE	75.8 ([redacted])	70.6 ([redacted])
Grade 3-5 drug-related AE	62.9 ([redacted])	58.1 ([redacted])
SAE	40.3 ([redacted])	31.3 ([redacted])
Treatment discontinuation for AE	7.7[a] ([redacted])	13.9[b] ([redacted])
Drug-related AE leading to discontinuation	6.3[c] ([redacted])	10.1 ([redacted])
Death related to AE	2.6 ([redacted])	3.5 ([redacted])

[a]discontinuation of both drugs simultaneously; [b]CS Appendix F reports 13.4% [c]discontinuation of both drugs

Table 23 Overview of duration on any therapy in KEYNOTE-426, ASaT population

Duration[a], days	Pembrolizumab plus axitinib, n=429	Sunitinib, n=425
Mean (SD)	320.6 (163.2)	255.6 (165.6)
Median (range)	317 (1 to 646)	238 (2 to 623)

[a]days between first dose date and last dose date

Table 24 Exposure adjusted summary of AE in KEYNOTE-426, ASaT population

	Pembrolizumab plus axitinib, n=429	Sunitinib, n=425
Total exposure[a] in person-months	4766.94	3924.64
Rate (event count / 100 person-months)[b]		
Any AE	147.20	179.69
Any drug-related AE	83.74	126.25
Grade 3-5 AE	17.75	20.97
Grade 3-5 drug-related AE	11.56	14.40
SAE	5.96	5.12
AE leading to discontinuation	3.78	1.66
Drug-related AE leading to discontinuation	3.19	1.20
Death related to AE	0.23	0.41

[a] defined as the time between the first dose date plus 1 day and the earlier of the last dose date plus 30 or the database cut-off date. [b] event rate per 100 person-months of exposure = event count *100/person-months of exposure.

3.3.6.1 Commonly reported AEs

The most common types of AEs (any grade) and drug-related AEs (any grade) can be seen in Table 25. Participants receiving pembrolizumab plus axitinib had a greater likelihood of

dysphonia, arthralgia, diarrhoea and pruritis amongst others. Participants receiving sunitinib were more likely to have anaemia, thrombocytopenia, dysgeusia, and neutropenia. CS Figure 15 displays between treatment comparisons of the most common AEs sorted by risk difference. The frequency of drug-related AEs showed similar patterns (Table 25) and the drug-related AEs reported by the later data cut (January 2019) were very similar (CS Appendix O, Table 14).

Table 25 Commonly reported AEs and drug-related AEs in the KEYNOTE-426 trial, ASaT population, August 2018 data-cut

%	**Any AE (≥15% in at least one arm)**		**Drug-related AE**	
	Pembrolizumab plus axitinib n=429	**Sunitinib n=425**	**Pembrolizumab plus axitinib n=429**	**Sunitinib n=425**
Diarrhoea	54.3	44.9	49.0	41.2
Hypertension	44.5	45.4	41.7	43.3
Fatigue	38.5	37.9	30.3	33.4
Hypothyroidism	35.4	31.5	31.5	28.0
Decreased appetite	29.6	29.4	21.9	24.9
Palmar-plantar erythrodysaesthesia syndrome	28.0	40.0	27.7	39.5
Nausea	27.7	31.5	21.2	26.1
ALT increased	26.8	15.1	23.8	12.7
AST increased	26.1	16.2	22.6	13.9
Dysphonia	25.4	3.3	22.8	2.8
Cough	21.2	13.6	7.5	2.8
Constipation	20.7	14.6	7.2	6.8
Arthralgia	18.2	6.1	12.1	3.5
Weight decreased	17.7	11.1	9.6	8.5
Proteinuria	17.5	11.1	15.4	9.2
Dyspnoea	16.1	10.8	6.5	3.8
Headache	15.9	16.2	8.2	7.8
Stomatitis	15.6	20.9	14.2	20.2
Asthenia	15.2	14.8	11.7	12.7
Pruritus	15.2	5.9	12.4	4.2
Vomiting	15.2	18.6	7.9	13.2
Mucosal inflammation	13.3	21.9	12.8	21.2
Dysgeusia	11.0	30.8	9.3	30.4
Anaemia	7.9	23.5	2.8	16.2
Platelet count decreased	3.7	18.1	3.3	17.9
Thrombocytopenia	2.6	23.3	1.9	22.1
Neutropenia	1.9	19.3	1.4	18.6

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

While not directly comparable, the exposure-adjusted values for these AEs according to observation period (overall rates [CS Table 36], not presented for drug-related events) appear to mirror the same trends. The company notes that the exposure-adjusted total AE rate was lower

for pembrolizumab plus axitinib compared with sunitinib during months 0 to 3, similar during months 3 to 6 and higher from 6 months onwards.

The adverse events in Table 25 are summarised for any grade. Of these, the most common grade 3 to 5 AEs and grade 3 to 5 drug-related AEs (occurring in ≥5% of any arm) are shown in Table 26 (reproduced from CS Table 37 and 38). Apart from fatigue, most of these grade 3 to 5 events were drug-related. CS Appendix F Figure 2 presents between treatment comparisons for grade 3 to 5 AEs sorted by risk difference. Pembrolizumab plus axitinib had a higher risk of increased alanine aminotransferase, increased aspartate aminotransferase and diarrhoea. Sunitinib had a higher risk of fatigue, thrombocytopenia and neutropenia among others. The exposure-adjusted values for the individual AEs were not reported in the CS (only the overall event rates as discussed above, Table 24). The grade 3 to 5 AE rates were [redacted] with longer follow-up (data cut January 2019), CS Appendix O Tables 13 and 15.

Table 26 Commonly reported Grade 3 – 5 AEs and drug-related Grade 3 – 5 AEs in KEYNOTE-426, August 2018 data-cut

%	Grade 3-5 AE (≥5% in either group)		Grade 3-5 drug-related AE (≥5% in either group)	
	Pembrolizumab plus axitinib n=429	Sunitinib n=425	Pembrolizumab plus axitinib n=429	Sunitinib n=425
Hypertension	22.1	19.3	21.2	18.4
ALT increased	13.3	3.1	12.1	2.6
Diarrhoea	9.1	4.7	7.2	4.5
AST increased	7.0	2.4	6.8	1.6
Palmar-plantar erythrodysaesthesia syndrome	5.1	3.8	5.1	3.5
Fatigue	2.8	6.6	[redacted]	[redacted]
Neutropenia	0.2	6.6	0.2	6.6
Thrombocytopenia	0.0	5.9	0.0	5.2
Neutrophil count decreased	0.2	6.8	0.2	6.8
Platelet count decreased	0.2	7.3	0.2	7.3

[a]data for completeness although incidence <5%. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase
Reproduced from CS Table 37 and 38

3.3.6.2 Adverse events of special interest

CS Appendix F reports that adverse events of special interest (AEOSI) are a selection of immune-related adverse events developed by the company considered during the pembrolizumab monotherapy research programme considered to be causally related to pembrolizumab. These are classified according to a medical concept which is comprised of

subcategories or preferred terms, an example given is 'immune-related hypothyroidism' which has preferred terms of hypothyroidism, hypothyroidic goitre, myxoedema, myxoedema coma and primary hypothyroidism. When pembrolizumab is combined with other treatments there may be overlapping adverse events and in these cases the CS says these events may then not always be immune-related. The example of hypothyroidism is given (however the CS considers hypothyroidism as an AEOSI). Similarly, the CS says that if an active control has an adverse event profile that overlaps with the preferred terms it may not be considered immune-related unless the control drug itself is an immunomodulatory agent. Clinical advice to the ERG confirms that some toxicities can be both immune-mediated or caused in other ways by other agents. Examples are diarrhoea and hypothyroidism; these can be immune-mediated but they are also side effects of TKIs via a different mechanism.

It is unclear whether these AEOSIs were specified apriori as neither the trial protocol or the CSR discuss this.

The CS reports (page 82) that the overall incidence of AEOSI was higher for pembrolizumab plus axitinib compared with sunitinib across all categories, in accordance with expectations. Additionally, there were higher rates of AEOSI in the pembrolizumab plus axitinib group than would be expected for pembrolizumab monotherapy. The higher incidence of AEOSI was mostly from thyroid-related events (hypothyroidism, hyperthyroidism, and thyroiditis). The CS also states that the majority of events were grade 1 or 2 (i.e. mild to moderate). The overall incidence of AEOSI at grades 3-5 can be seen in Table 27.

The ERG requested results of AEOSI by grade in a clarification question to the company (question A3) and the information supplied confirms that the majority of events within the preferred terms were grade 1 or 2. As none of these have incidences of >5% at grade 3 or above the ERG has not summarised these here. Reflecting the overall pattern of AEOSIs, the grade 3 AEOSIs had higher incidence in the pembrolizumab plus axitinib arm compared with the sunitinib arm.

Table 27 Grades 3-5 AEOSI by treatment group in KEYNOTE-426, August 2018 data-cut

AEOSI, %	Pembrolizumab plus axitinib, n=429	Sunitinib, n=425
Grade 3	8.4	1.6
Grade 4	1.6	0.0
Grade 5	0.7	0.2

In the CS Appendix F (page 217) it reports that there were higher incidences of hepatic AEs in the pembrolizumab plus axitinib arm (overall with one or more hepatic adverse event 40.6% pembrolizumab + axitinib; 26.6% sunitinib). Of these, hepatitis was considered an AEOSI and the incidence of hepatitis was reported to be pembrolizumab plus axitinib (2.8%) compared with sunitinib (0.5%) in CS Appendix F (page 214). In the company's response to clarification question 3 (Table A3) it can be seen that in the pembrolizumab plus axitinib arm grade 3 autoimmune hepatitis occurred in 0.5% patients; grade 4 drug-induced liver injury occurred in 0.2%; grade 3 or 4 hepatitis occurred in 1.4% and grade 3 immune-mediated hepatitis in 0.2%. These events did not occur in the sunitinib arm where there was one case of grade 5 hepatitis fulminant and one case of grade 1 hepatitis.

In summary a greater number of AEOSI were reported by the company for pembrolizumab plus axitinib, but not all of these events are necessarily immune-related (the company does not classify which) and in most cases they were not grade 3 or 4 events.

3.3.6.3 Additional sources of AE data

The ERG considered whether the adverse events reported in the pembrolizumab plus axitinib phase Ib study (KEYNOTE-035[33]}) would be informative. The phase Ib study was a dose finding study and as the dose of pembrolizumab was not directly comparable with the dose of pembrolizumab in the KEYNOTE-426 trial (2mg/kg versus 200mg respectively) we have not summarised the key AEs from the phase Ib study.

3.3.6.4 Safety overview

Overall, the CS considers that the safety profile of pembrolizumab plus axitinib is acceptable. The overall rate of AEs was similar across both arms of the trial, particularly when adjusted for exposure of the drugs. The most commonly reported AEs at grade 3 or more were hypertension, diarrhoea, alanine aminotransferase and aspartate aminotransferase increases and Palmar-plantar erythrodysaesthesia syndrome. The CS also states that the safety profile of pembrolizumab plus axitinib is generally consistent with the established safety profile of pembrolizumab monotherapy in solid tumours and the observed safety profile for axitinib monotherapy. No evidence of AEs from axitinib monotherapy was provided except for reference to published data. The ERG has checked the two references cited in the CS (CS references 31 and 47, p84) and although the AEs presented in these publications were not wholly comparable with the rates reported for the key events shown in Table 26, they appear to

show consistent effects with the KEYNOTE-426 trial. No studies of pembrolizumab as monotherapy in RCC were identified.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The company's submission to NICE includes:

i) a review of published economic evaluations of comparator therapies to pembrolizumab in treating patients with advanced RCC.
ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of pembrolizumab plus axitinib is compared with sunitinib, tivozanib, pazopanib and cabozantinib for adults with untreated advanced RCC.

4.2 Company's review of published economic evaluations

A systematic search of the literature was conducted by the company to identify economic evaluations of pembrolizumab plus axitinib and comparator therapies in a patient population with unresectable advanced RCC, in addition to resource use and costs associated with treating advanced renal cell carcinoma. The following databases were searched alongside a thorough review of the grey literature: EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials (CCTR), the Cochrane Database of Systematic Reviews (CDSR), EconLit, the NHS EED and the Tufts Cost-Effectiveness Analysis Registry. An initial search was conducted between March and April 2018, followed by an updated search of all the previously searched databases. This updated search was conducted in February 2019.

The inclusion and exclusion criteria for the systematic review are listed in Table 1 of the CS Appendix G, page 221. The inclusion criteria state that primary research studies (including observational studies, RCTs and economic evaluations) and HTA documents of pembrolizumab monotherapy or in combination with another agent indicated for first-line metastatic RCC versus any comparator of interest (including placebo and best supportive care) in adults 18 years and above with unresectable metastatic RCC would be included. The exclusion criteria excluded studies of patients with early stage RCC and comparators such as surgery, radiotherapy and treatments used in adjuvant therapy.

The company's systematic literature review identified 1,351 studies and after abstract screening, 218 were deemed eligible for full-text screening. Of these, 212 studies were excluded because they did not meet the study design inclusion criteria and/or contained outcomes that were not of interest. The company identified an additional three studies through the grey literature and from the final appraisal determination of nivolumab with ipilimumab for untreated advanced renal cell carcinoma in May 2019. These studies were added to the initial six studies, bringing the total number of studies included for full review and data extraction to 10.[24 , 34-41] None of these 10 studies contained a cost-effectiveness analysis for pembrolizumab in combination with axitinib. A full list of these studies is reported in Table 2 of CS Appendix G and they are all studies of comparator technologies. In the company's final inclusion, one of these 10 studies (Mickisch et al[42]) was excluded because it did not inform an HTA submission or contain a comparator relevant to this appraisal. Of the remaining nine studies, seven considered a UK NHS perspective while the remaining two were based on the perspective of the Scottish healthcare system. The results of the cost-utility analyses of these studies are reproduced below in Table 28.

Table 28 Results of cost-utility analyses for studies included in the company's search

Authors	Year	Intervention	Comparator	Incremental costs	Incremental QALYs	ICER (QALYs)
Amdahl et al	2017	Pazopanib	Sunitinib	-£912.00	0.0594	Dominant
Hoyle et al	2010	Temsirolimus	Interferon-alpha	£22,331	0.24	£94,632
Kilonzo et al	2013	Sunitinib	Pazopanib	Not reported	Not reported	£1,790
		Interferon-alpha	Pazopanib	Not reported	Not reported	£38,925
		Best supportive care	Pazopanib	Not reported	Not reported	£32,898
NICE	2009	Sunitinib	Interferon-alpha	Not reported	Not reported	£49,304
SMC	2011	Pazopanib	Sunitinib	£4,263	0.068	£62,414
		Pazopanib	Interferon-alpha	£32,062	0.717	£44,697
		Pazopanib	Best supportive care	£36,356	0.979	£37,126
SMC	2007	Sunitinib	Interferon-alpha	Not reported	Not reported	£33,371
Thompson Coon	2010	Sunitinib	Bevacizumab plus interferon-alpha	Not reported	Not reported	£171,301

		Sunitinib	Interferon-alpha	Not reported	Not reported	£71,462
NICE	2019	Nivolumab + ipilimumab	Sunitinib	Not reported	1.75	£28,068.31
			Pazopanib	Not reported	1.75	£28,021,92

Adapted from CS Appendix G, Table 3.

The ERG conducted ad hoc searches and these yielded a study of interest not captured in the company's searches.[43] This is likely to be because the study was published online in June 2019, after the company had conducted its last search. The study is a cost-effectiveness analysis of pembrolizumab plus axitinib versus sunitinib in first-line advanced RCC in China. It concludes that pembrolizumab plus axitinib was not likely to be cost-effective at a threshold of US$29,306 per QALYs gained. Although the study is not based on a UK perspective, it estimates mortality risk based on the OS curve of the KEYNOTE-426 trial also used to inform the company's model in the current appraisal.

In the CS, the company has narrowed down its focus to five previous NICE technology appraisals that are considered the most relevant comparators. These are TA169,[37] TA215,[44] TA 512,[27] TA542[24] and TA581[41] for sunitinib, pazopanib, tivozanib, cabozantinib and nivolumab plus ipilimumab respectively. The features of the models informing these TAs are summarised in comparison with the company's model in CS Table 41. Nivolumab plus ipilimumab is not listed as a comparator in the CS but nivolumab is featured as a second line treatment.

ERG conclusion

The ERG considers the company's search strategies and study selection criteria are robust and relevant to the decision problem.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

Table 29 shows that the company's economic evaluation adheres to the NICE reference case requirements.

Table 29 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	CS Table 1, page 10.
Comparator: As listed in the scope developed by NICE	Yes	Discussed in section 4.3.4.
Perspective on costs: NHS and PSS	Yes	Not explicitly stated in CS
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	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	Outcomes as per NICE scope (CS Table 1)
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	Cost utility analysis
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Systematic literature review conducted to identify RCT relevant to submission. (CS section B.2.2).
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	Time horizon of 40 years.
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes	EQ-5D data collected in company's trial.
Source of data for measurement of health related quality of life: Reported directly by patients and/or carers.	Yes	
Source of preference data: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	

4.3.2 Model structure

The model structure, described in CS B.3.2 and illustrated in Figure 16, is reproduced in Figure 2 below. It is a partitioned survival model, containing three mutually exclusive health states: progression free (PF); progressed disease (PD) and death. Patients start in the PF state, following initiation of one of the included first-line treatments. At disease progression, patients

transition to the PD state, which is irreversible, so patients cannot return from PD to PFS. Patients in PF and PD states may die from cancer or other causes.

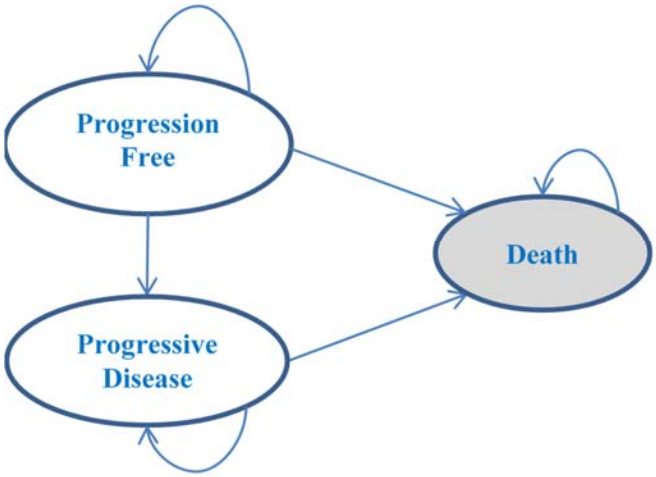

Figure 2 Structure of economic model

Reproduced from CS B.3.2 Figure 16

As mentioned above, all patients start in the PF state. At the end of each model cycle, patients may transition into a different state as estimated using a partitioned survival approach which is underpinned by the PFS and OS curves. The PFS curve estimates the proportion of patients who are progression free and is constrained by the OS curve i.e. the PFS cannot exceed the OS curve at any time point. The OS curve estimates the proportion of patients alive at each time point, while patients in the PD state are calculated as the remaining patients who are not dead and have progressed.

The submitted model includes analyses for two patient populations:

- The overall population of KEYNOTE-426;
- Subgroup population of patients with intermediate / poor RCC risk status in the KEYNOTE-426 population.

The PFS, OS and TTD curves for pembrolizumab plus axitinib, and sunitinib were based upon survival data from the KEYNOTE-426 trial. Sunitinib is assumed clinically equivalent to tivozanib and pazopanib. For the subgroup population of intermediate / poor RCC risk, pembrolizumab plus axitinib is compared to to sunitinib, pazopanib and tivozanib using survival data from the KEYNOTE-426 trial and is compared to cabozantinib using effect estimates from the company's

NMA, as no head-to-head comparison was available (NB. Cabozantinib is recommended only in patients at intermediate / poor RCC risk)

Subsequent treatment is incorporated in the model for some patients at the time of disease progression (described in more detail in section 4.3.7). Costs and utilities are applied to each of the health states (described in more detail in section 4.3.6 and 4.3.7).

The company's model also includes the following features and assumptions:

- **Cycle length**: 1 week with half cycle correction implemented.
- **Perspective**: NHS and PSS
- **Time horizon**: 40 years in the base case
- **Discounting**: 3.5% per year for costs and QALYs
- **Duration of treatment effects**: based on extrapolation of PFS and OS curves fitted to trial data and clinical expert judgement. A persistence of treatment effect throughout the model time horizon was assumed in the company's base case. Treatment waning after 10 years was tested in a scenario.
- **Adverse events**: includes grade 3 and above all-cause adverse events which occur in at least 5% of patients for all first-line treatments. Adverse events related to subsequent treatments are not explicitly modelled.
- **Utility and QALY calculations**: HRQoL estimates evaluated from the KEYNOTE-426 trial are used in the model. The company base case uses the estimation of utilities based on time-to-death. Two other approaches were used to estimate quality of life: estimation of utilities based on progression-free and progressed disease states (with or without differentiation by treatment). These approaches are discussed in detail in ERG Section 4.3.6. An age-based utility decrement is also applied.
- **Health resource use and costs**: The model estimates costs associated with: acquisition and administration of first-line and subsequent treatments, with adjustment for dose intensity; monitoring and disease management in PF and PD states; treatment of included TEAEs for first-line treatments; and terminal care costs in the last cycle before death.
- **Uncertainty**: the model incorporates macros to conduct: deterministic sensitivity analysis (DSA) with results presented in a tornado diagram; scenario analyses varying selected model assumptions; and probabilistic sensitivity analysis (PSA), producing a cost-effectiveness scatterplot and cost-effectiveness acceptability curve.

ERG conclusion

The three-state partitioned survival model is a standard modelling approach and has been applied in previous NICE appraisals for untreated advanced RCC. We consider that the model structure and partitioned survival approach is appropriate. The use of a 40 years model time horizon estimates lifetime costs and benefits, given the starting population age in the model. The company's model also includes an adjustment for age-related increase in mortality in the general population, by capping the projected OS curves to general population mortality rates.

4.3.3 Population

The model uses a cohort in the economic evaluation based upon the overall patient population of the KEYNOTE-426 trial. The key characteristics of patients included in the model are shown in Table 30 (CS Table 40). Expert clinical advice to the ERG is that patients starting first-line treatment for advanced RCC are slightly older than patients in the trial. (See section 3.1.3 of this report for more detail on the patient characteristics in the trial).

Table 30 Patient population characteristics in the model

Baseline characteristics	Model values
Age (years)	61.5
Male	71.3%
Patient weight (Kg)	81.5
Favourable RCC risk	Not explicit
Intermediate RCC risk	
Poor risk RCC	

The model also estimates cost-effectiveness for a subgroup of patients with intermediate or poor risk by IMDC classification. This subgroup was not specified in the NICE scope for this appraisal, but as explained earlier in this report, we consider this a clinically meaningful subgroup for assessment of cost-effectiveness.

4.3.4 Interventions and comparators

The economic model compares the cost effectiveness of pembrolizumab plus axitinib versus sunitinib, pazopanib, and tivozanib for the overall patient population, and compares against sunitinib, pazopanib, tivozanib and cabozantinib for the intermediate / poor RCC risk group. The ERG notes that the NICE technology appraisal of avelumab with axitinib for this indication is ongoing at the time of writing, and guidance is expected in early 2020. It is therefore not included as a comparator in the NICE scope or the company's decision problem.

In the base case analysis, tivozanib and pazopanib have been considered clinically equivalent to sunitinib. The company notes that this was accepted by the NICE appraisal committee in previous NICE appraisals for pazopanib, tivozanib, cabozantinib and nivolumab plus ipilimumab.

4.3.5 Treatment effectiveness and extrapolation

The company notes the follow-up period in KEYNOTE–426 was much shorter than the time horizon of the economic model and therefore extrapolation was necessary for OS, PFS and time on treatment (ToT) for the area-under-the-curve (AUC) partitioned survival approach. These extrapolations are discussed in more detail in this section for OS and PFS and ToT is discussed in section 4.3.7.

The company fitted parametric models to the KEYNOTE-426 KM data as recommended by the NICE DSU technical support document (number 14) on extrapolating survival data from clinical trials.[45] Firstly they estimated the goodness-of-fit statistics (i.e. Akaike information criterion [AIC] and Bayesian Information Criterion [BIC] and visual inspection of the agreement between the predicted and observed PFS, OS and ToT curves). Secondly, they examined the clinical plausibility of long-term extrapolations beyond the trial period.

4.3.5.1 Overall survival

The company assessed whether the proportional hazards assumption is reasonable by examining cumulative and log-cumulative hazard plots (CS Figure 19 and 20) for OS for pembrolizumab plus axitinib and for sunitinib from the KEYNOTE–426 trial. The company noted that the log–cumulative hazard plots of OS crossed and are not parallel and concluded that the proportional hazards assumption does not hold. Further, they concluded that the use of fully parametric modelling was most appropriate for extrapolation, as there were no abrupt changes in the log-cumulative hazard plots. The ERG agrees with the company's conclusions regarding

the proportional hazards assumption and notes that the methods used are consistent with the NICE DSU guidelines.[45] We provide our assessment of proportional hazards for PFS and OS in relation to the NMA earlier in this report (Table 8).

AIC and BIC statistics are shown for OS in CS Table 43. According to the AIC/BIC statistics, the best-fitting curve for pembrolizumab plus axitinib is the exponential, followed by the Gompertz. For sunitinib the best-fitting curve is the lognormal, following by the exponential. The company's clinical experts suggested that treatment with first-line sunitinib would be associated with 5 and 10 year survival between 20-25% and 10-15% respectively. The company's clinical experts suggested a five-year OS of approximately 50% when treated with pembrolizumab plus axitinib. One of the ERG's clinical experts suggested that the five-year survival of 50% for those treated with pembrolizumab plus axitinib may be optimistic.

The long-term OS predictions of pembrolizumab plus axitinib and sunitinib are shown in Table 31 and Table 32 (CS Appendix P Tables 3 and 4). On the basis of these predictions, the company concludes that the Gompertz, generalized gamma and lognormal distributions lead to clinical implausible outcomes.

Table 31 Long term OS predictions of pembrolizumab in combination with axitinib

Year	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Generalized Gamma
1	88.3%	88.6%	88.5%	88.3%	88.9%	88.7%
2	78.0%	76.2%	76.8%	79.2%	74.4%	75.6%
5	53.5%	44.9%	51.9%	62.4%	20.3%	38.5%
10	28.7%	16.5%	31.6%	47.6%	0.0%	6.2%
20	8.2%	1.7%	16.5%	31.0%	0.0%	0.0%

Reproduced from CS Appendix P Table 3

Table 32 Long term OS predictions for sunitinib

Year	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Generalized Gamma
1	79.9%	80.1%	79.7%	79.5%	79.7%	79.3%
2	63.9%	62.6%	63.6%	65.5%	65.5%	66.8%
5	32.5%	28.2%	37.3%	43.6%	42.0%	48.4%
10	10.6%	6.9%	20.9%	27.9%	27.6%	35.4%
20	1.1%	0.3%	10.5%	15.5%	17.9%	22.8%

Reproduced from CS Appendix P Table 4

The company compared the long-term OS predictions (exponential) of sunitinib against published study estimates, for external validation (CS Figure 23). The ERG compares the long-term OS predictions of sunitinib using the exponential, Weibull and Log-logistic with the trial with the longest follow-up, i.e. the COMPARZ trial (Figure 3).

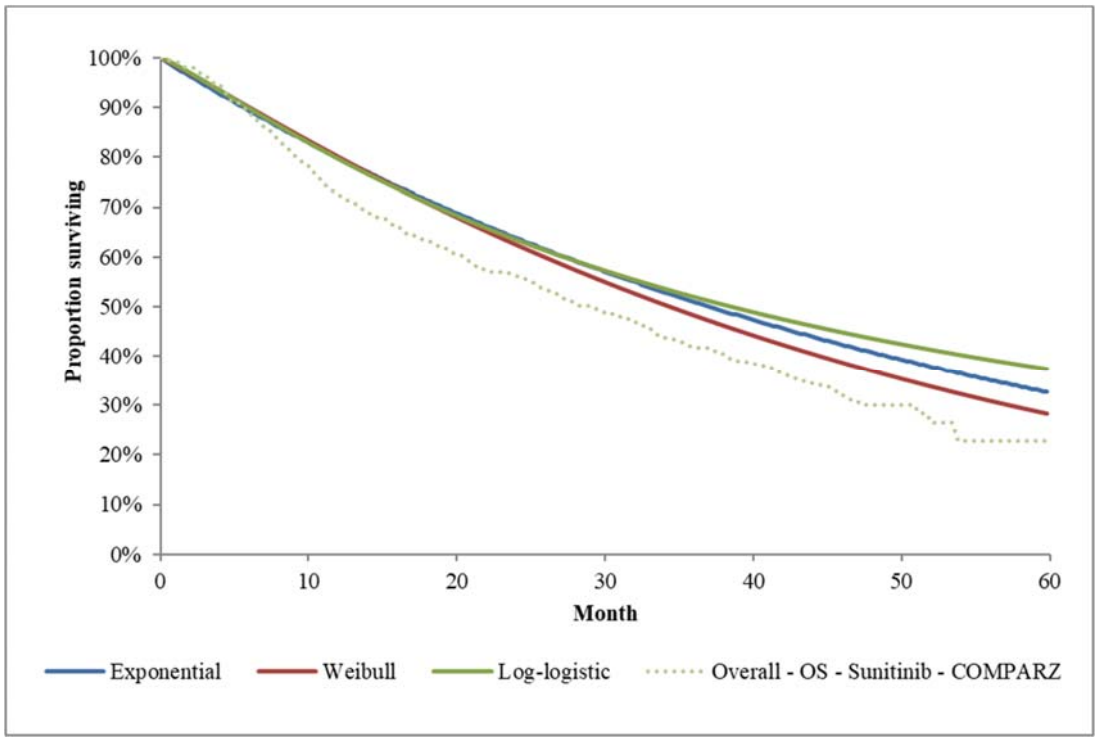

Figure 3 Modeled OS vs. selected OS external validation source for sunitinib

The company chose the exponential as the most appropriate distribution to extrapolate OS for the sunitinib arm. They justify this by stating that the log-cumulative hazard plots show a constant hazard over time suggesting the exponential is appropriate, the AIC and BIC showed close statistical fit to the observed data, the exponential distribution provides long-term OS estimates expected to be seen with sunitinib according to external data and in line with estimates from clinical experts.

The company chose the log-logistic as the most appropriate distribution to extrapolate OS for the pembrolizumab plus axitinib arm. They justify this choice on the basis the AIC/BIC showed a good statistical fit to the observed data and the tail of the log-logistic curve was considered by clinical experts to be more credible based on the expectation that a percentage of patients would derive a long-term survival benefit from the combination of an immunotherapy with a

tyrosine kinase inhibitor. This immunotherapeutic effect would imply a declining, rather than a constant hazard over the long term.

The company notes that NICE technical support document 14 states that "While fitting separate parametric models to individual treatment arms may be justified, it is important to note that fitting different types of parametric model (for example a Weibull for one treatment arm and a log normal for the other) to different treatment arms would require substantial justification".[45] The company's justification is that the mode of action of combination of immunotherapy with a TKI is not comparable to the mode of action associated with TKI monotherapy. The company also states that none of the parametric distributions gave clinically plausible long-term OS estimates for both arms simultaneously.

The ERG disagrees with the company's justification to use a different distribution for treatment arms due to a different mode of action of combination immunotherapy plus TKI to TKI monotherapy. The ERG notes that the OS survival data is immature and for pembrolizumab plus axitinib the data does not demonstrate an underlying hazard that is similar to the log-logistic. Furthermore, the underlying hazard is similar to sunitinib. Finally, the ERG notes that the NICE appraisal committee did not consider that the modelling of the immunotherapeutic effect was substantiated by evidence in TA581[41] for nivolumab plus ipilimumab and that it could not generalise the size of this effect from one cancer to another. It concluded "that there was no robust evidence on the size of the association between a clinically meaningful definition of response and long-term survival for nivolumab and ipilimumab"' The ERG considers the committee's decision is relevant to this current appraisal.

The ERG considers that both the exponential and Weibull distributions are plausible for OS for pembrolizumab plus axitinib and sunitinib and that the Weibull distribution provides a better fit for the long-term OS of sunitinib (Figure 4). Therefore, we have chosen this as the most appropriate distribution, although we caution that due to the immature OS data this choice may be somewhat speculative. The ERG base case analyses use the Weibull distribution for OS and are shown in section 4.4. We consider scenarios with exponential and log-logistic extrapolations for OS in section 4.4. We have also run scenarios using time varying hazard ratios in section 4.4.

The company has not included the assumption of treatment effect waning (reducing) in their base case. They justify this by the fact that waning of effect has not been included in previous NICE appraisals for RCC, and that patients continue to be treated with axitinib after the 2-year stopping rule for pembrolizumab. In addition, the company states that they believe a proportion of patients would derive a long-term survival benefit from the combination of an immunotherapy with a TKI. The ERG notes that a proportion of patients would receive second-line treatment after disease progression and this second-line treatment would influence their survival. Further, many patients who receive sunitinib as first line treatment would receive nivolumab as second-line therapy and so it may be the case that OS for patients receiving second-line treatment may be similar between treatment arms. However, as the OS data from KEYNOTE-426 is immature, we have only included treatment waning in a scenario analyses.

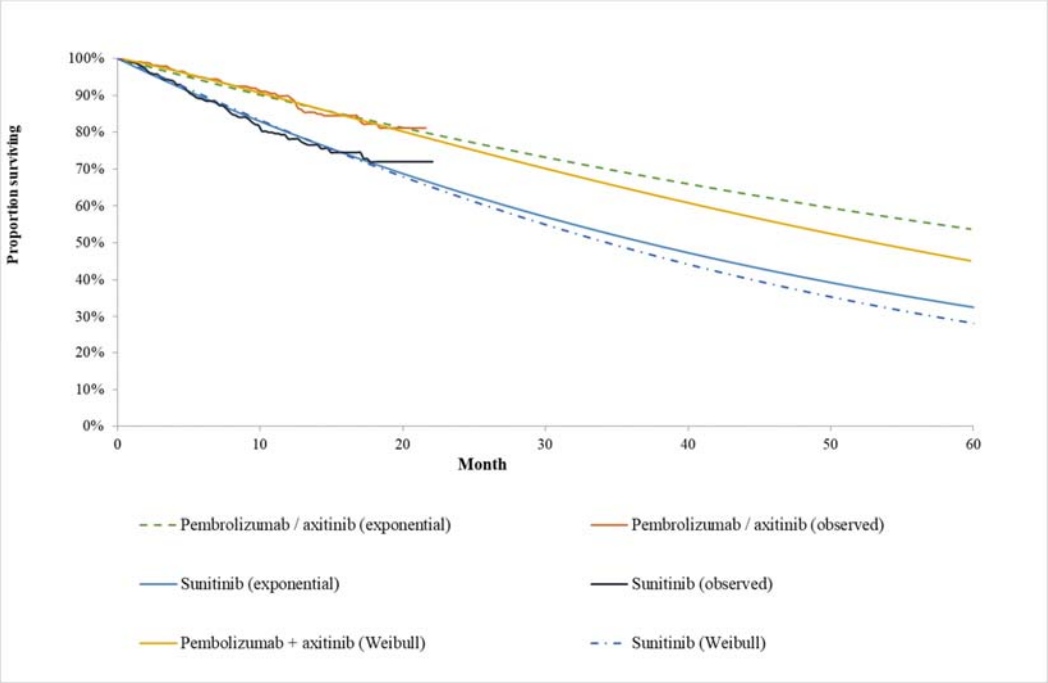

Figure 4 OS from KEYNOTE–426 compared to fitted curves for the exponential and Weibull distributions

4.3.5.2 Progression-free survival

The best AIC and BIC statistical fit for PFS for the pembrolizumab plus axitinib was the log-normal distribution, followed by the generalized gamma distribution. The best AIC/BIC statistical fit for the sunitinib arm was the exponential distribution, followed by the Weibull distribution. Based upon the AIC/BIC and visual fit, the company chose the exponential distribution for both treatment arms. The modelled PFS is compared against the observed data in CS Figure 31 (Figure 5).

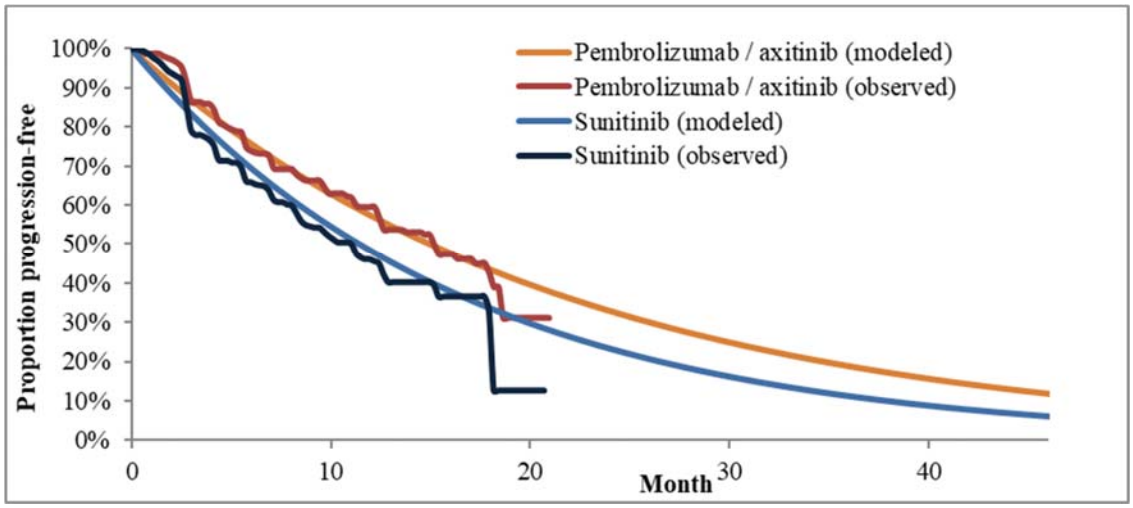

Figure 5 PFS KM curves vs fitted 2-phase piecewise model with cut off at 13 weeks and exponential distribution thereafter

The company noted that there was a steep increase in patients' disease progressing at 13 weeks due to the imaging being performed at 12 weeks. They have therefore used piecewise modelling whereby the KM data is used for the first 13 weeks and an exponential distribution is used thereafter. The ERG considers this approach to be appropriate as the exponential provides a good fit to the COMPARZ trial data[12] for PFS and a good statistical and visual fit. However, we note that if the KM data is to be used, it could be used for a longer time-period than for 13 weeks, such as for 54 weeks. We requested a scenario analysis from the company using the KM data for a longer time-period of 54 weeks (clarification question B15). The results were only marginally different. We conduct scenario analyses with Weibull and log-logistic extrapolations for PFS in section 4.4.

4.3.5.3 Intermediate / poor RCC risk subgroup analysis

The company compares pembrolizumab plus axitinib versus sunitinib pazopanib, tivozanib and cabozantinib for patients with intermediate or poor risk status. For this subgroup, the company fits curves for OS, PFS and ToT for pembrolizumab plus axitinib and sunitinib. The same distributions were used as described above for the base case analysis. The company provides more detail on the fitting process in response to a clarification question (B9). As for the overall RCC population, the ERG agrees with the company's choice for PFS for the intermediate or poor risk score population, but disagrees with the company's choice of the log-logistic for OS for pembrolizumab and axitinib. The ERG prefers to use the Weibull for both treatment arms for OS.

For cabozantinib, the model uses a time-constant HR for OS and PFS. The hazard ratio is taken from the company's NMA (PFS HR = [redacted] and OS HR = [redacted] vs. pembrolizumab plus axitinib (see section 3.1.7 of this report). For tivozanib and pazopanib, PFS and OS was assumed equivalent to that estimated by the sunitinib arm. For this to be clinically meaningful the survival estimates from the sunitinib arm of KEYNOTE-426 should be representative of estimates from pivotal phase III trials of sunitinib. In the phase III registration trial for sunitinib[23] the median PFS was 11 months, which is similar to the 11.1 months estimate from KEYNOTE-426. Expert clinical advice to the ERG is that the sunitinib PFS estimates from KEYNOTE-426 accord with what those seen in the earlier pivotal trial.

ERG conclusion

The methods used to extrapolate OS and PFS for the economic model are reasonable and consistent with NICE recommended methodology, although the ERG disagrees with the choice of curves chosen for OS. Parametric survival curves were fitted to both the pembrolizumab plus axitinib and sunitinib treatment arms for the KEYNOTE-426 trial. The trial data for OS are immature which makes the choice of a parametric curve extrapolating beyond the trial duration more uncertain. Further, the model results were very sensitive to changes in the parametric curve used for OS extrapolation. The company uses a log-logistic distribution for pembrolizumab plus axitinib and an exponential distribution of OS extrapolation. The ERG prefers the Weibull distribution for the OS extrapolation for pembrolizumab plus axitinib and for sunitinib as the Weibull distribution provides a better fit for the long-term OS of sunitinib, and in principle the same distribution should be used for both treatment arms. The company used the exponential distribution for the PFS extrapolation, and we agree with this choice.

4.3.5.4 Adverse events

Adverse events are included in the economic model for Grade 3+ all-cause AEs which occurred in at least 5% of patients (for any grade AE). Adverse event data for pembrolizumab plus axitinib and sunitinib are from the KEYNOTE-426 trial (CS Table 46 for Grade 3+). In response to clarification question B4, the company noted that some of the values in this table were incorrect. The correct values are shown in Table B4.1 of the clarification response document. The safety profile for tivozanib and pazopanib is assumed to be equal to the safety profile of sunitinib. The incidence AEs for cabozantinib was taken from the published data from that NICE TA542 (cabozantinib).[24]

In the base case, the impact of AEs was incorporated by estimating weighted average disutilities and costs per patient, as described in section 4.3.6 and 4.3.7.

4.3.6 Health related quality of life

The company conducted a systematic literature review to identify HRQoL (in terms of utilities) associated with metastatic RCC. The company search strategy is described in CS Appendix H. The company conducted an initial search on March 14, 2018, with an update search completed on 20th February 2019. The company searched EMBASE, MEDLINE, the Cochrane Central Register of Controlled trials and the Cochrane Database of Systematic Reviews. In addition, a targeted search was conducted in various relevant Oncological and Pharmacoeconomic conference proceedings. Further the company searched the grey literature including reports from NICE, Scottish Medical Consortium (SMC) and the Institute for Quality and Efficiency in Healthcare (IQWIG).

The eligibility criteria for the HRQoL studies included generic, disease-specific and preference-based outcome measures (Table 1 in CS Appendix H). The original search identified 25 full-text articles after abstract and full-text screening. The update search found a further seven studies. Of the studies identified, six studies reported utility values (EQ-5D) and these are shown in Table 3 in CS Appendix H. The ERG notes that none of these studies have been used in the economic model for scenario analyses.

EQ-5D-3L data were collected in the KEYNOTE–426 trial (see section 3.3.3 of this report) and these data were used in the economic model. The company states that the estimated utilities

used in the model were derived directly from patients and evaluated using UK-preference scores and this is consistent with the NICE reference case.[46] The ERG agrees that the utility values meet the NICE reference case and are suitable for inclusion in the model.

In KEYNOTE-426, for pembrolizumab plus axitinib, the EQ-5D questionnaire was administered on day one of every cycle from cycle one to nine; on day one of every other cycle from cycle 9 - 19; and on day one of every 4th cycle from cycle 19 until treatment discontinuation and the 30-day post-treatment discontinuation follow-up visit. Each cycle length was equal to 21 days. For sunitinib, the EQ-5D questionnaire was administered on days one and 29 of every cycle from cycle one to cycle four; on day one of every cycle from cycle 5 - 10; and on day one of every other cycle from cycle 10 until treatment discontinuation, and the 30-day post-treatment discontinuation follow-up visit. Each cycle length was equal to 42 days.[47]

A regression analysis consisted of EQ-5D data from 850 individuals. CS Table 47 shows the level of compliance at difference time points, i.e. those who completed the EQ-5D questionnaire. The company analyses the data according to treatment, disease progression, time to death and adverse events. For the company's base case analysis, they used time-to-death utility data, where utility data is estimated for the time-period until death (Table 33). They stated that this approach had been used in NICE appraisals for patients with advanced non-small cell lung cancer who had previously received platinum-based chemotherapy or palliative radiotherapy[48] and in advanced melanoma patients.[49] The utility values based on time-to-death are shown in Table 33 (CS Table 50).

Table 33 EQ-5D health utility scores by time-to-death

	Pooled (N=532), number of observations: 2,704		
	Estimate	**SE**	**95% confidence interval**
≥360 days	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]
90 to 180 days	[redacted]	[redacted]	[redacted]
30 to 90 days	[redacted]	[redacted]	[redacted]
0 to 30 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

Reproduced from CS Table 50

Whilst it has been more common in previous technology appraisals to use health state specific utility values, rather than time to death, Hatswell et al[50] noted that disease progression may not fully capture all predictive factors of patient utility and time-to-death provide a good fit to patient data. The company conducted scenario analyses using treatment-specific health-state based utilities and the pooled health state-based utilities from KEYNOTE–426 (CS Table 67). These scenarios only produced a small change in the cost-effectiveness results. The ERG therefore considers either approach to be reasonable.

In response to ERG clarification question B12, the company provided treatment-specific time to death-based utilities (shown in Table B12.1 of the clarification response document). The ERG notes that the utility values for patients on each treatment are not statistically different from each other and so agrees that is appropriate to assume the same utility values for patients who start on pembrolizumab plus axitinib or sunitinib. The ERG notes that the utility values for patients with ≥360 days until death is higher than the UK population norm for this group. According to Kind et al,[51] the weighted average utility of men and women at this age group is 0.775. We conducted a scenario analysis where the utility value for patients with ≥360 days until death is set to 0.775 (see section 4.4).

The ERG agrees with company's approach to evaluating health utilities. We conducted scenario analyses using the utility values from previous NICE TAs for tivozanib and pazopanib (section 4.4).

4.3.6.1 Adverse event disutilities

Adverse event disutilities were estimated according to the EQ-5D values collected in the KEYNOTE-426 trial for pembrolizumab plus axitinib and sunitinib. These estimates differed according to the method used for calculating the utility values: for the progression status model, this disutility was calculated as [redacted], for the treatment-specific progression status model this disutility was calculated as [redacted] and for the time-to-death utility model, this was calculated as [redacted].

The mean duration of the AE was estimated from KEYNOTE–426, according to the specific AE. This mean duration was applied together with the disutility associated with AEs and the overall incidence rates of AEs to estimate a one-off QALY loss per patient for each treatment ([redacted] for

pembrolizumab plus axitinib and [redacted] for sunitinib). The QALY losses were applied to the first cycle of the model for each treatment arm only.

4.3.6.2 Age-related disutility

The company includes age-related disutility using the formula provided by Ara and Brazier, [52] reweighted using the starting age in the model of 62.5 years. The ERG notes that including age-adjusted utility is recommended by NICE DSU Technical Support Document 12.[53] In response to clarification question B11, the company analyses the effect of age on utility values. The company found that utility values were not associated with age. The ERG suggests that age-related disutility should not be included in the model. The ERG base case analysis therefore does not include an age-related disutility (section 4.4).

ERG conclusion

The company's approach to estimating utility values is reasonable and consistent with the NICE reference case. The use of KEYNOTE-426 utility data is preferable to other sources.

4.3.7 Resource use and costs

The costs included in the economic model consist of drug acquisition and administration for first and subsequent treatments, health state management cost, costs for managing AEs and terminal care costs incurred at the end of life.

The company conducted a comprehensive literature search to identify costs and resource used in the treatment and management of advanced renal cell carcinoma patients. The original search was completed on 14th March 2018, with an update search on 20th February 2019. The search was limited to those studies published after 1st January 2007. Details of the search strategy and eligibility criteria are shown in CS Appendix G. Studies were only included if they reported UK costs and resource use of metastatic renal cell carcinoma from a UK perspective.

After abstract and full-text screening, nine studies were identified and this was increased to 10 studies when the NICE appraisal of nivolumab and ipilimumab for untreated advanced renal cell carcinoma was published. The ten included studies are shown in CS Appendix I. The ERG considers that the company's literature review is likely to reflect the available evidence.

4.3.7.1 First-line drug acquisition costs

The cost per pack for all drugs are taken from the British National Formulary.[54] Dosages are taken from each treatment's Summary of Product Characteristics. Intended dosages were adjusted by the dose intensity observed in the treatments' trials. None of the treatments for first-line or subsequent treatment lines are eligible for vial sharing.

Pembrolizumab is administered as a 30-minute IV infusion of 200mg every three weeks. The list price of a 100mg vial is £2,630. Patients treated with pembrolizumab are treated until disease progression or unacceptable toxicity. There is a stopping rule for pembrolizumab such that patients do not receive treatment with pembrolizumab beyond 24 months. Axitinib is administered twice daily as an oral treatment with a fixed dose of 5mg. The list price of a packet of 56 tablets of axitinib is £3,517. A course of treatment has a four week cycle length. Patients may continue treatment with axitinib beyond 24 months. Pembrolizumab and axitinib are supplied to the NHS with a commercial access agreement and a confidential patient access scheme (PAS) respectively.

The dosing, frequency and unit costs of the first-line drugs are shown in Table 34 (CS Table 52). Several treatments are available with confidential patient access schemes (PAS). The company has reported all analyses using the list price of the treatments. The ERG has replicated the company's analyses using the treatment PAS prices in a separate confidential appendix to this report.

Table 34 Dosing, frequency and unit costs per administration for intervention and comparator

Drug	Dosing Schedule	Frequency of admin-istration	Total dose required per admin (mg)	Cost per administration (assuming no wastage)	Dose intensity	Cost per admin-istration (list price)
Pembrolizumab	200 mg IV Q3W	Q3W	200	£5260.00	[redacted]	£4,986.48
Axitinib	5 mg BID orally	Q4W	280	£3,517.00	[redacted]	£2,975.38
Sunitinib	50 mg QD orally for 4 weeks, then 2 weeks off treatment	Q6W	1,400	£3,138.80	[redacted]	£2,344.68
Pazopanib	800 mg QD orally	Q4W	22,400	£2,092.53	86.0%	£1,799.58

Tivozanib	1.34 mg QD orally for 3 weeks followed by 1 week without treatment	Q4W	28	£2,052.00	94.0%	£1,928.88
Cabozantinib	20/40/60 mg QD orally	Q4W	1,680	£4,800.13	94.3%	£4,526.53

Reproduced from CS Table 52

4.3.7.2 Time on treatment

Parametric curves were fitted to the patient level treatment duration data from KEYNOTE-426. AIC/BIC statistical tests indicated that the best fit was the Weibull for pembrolizumab, log-normal for axitinib and log-normal for sunitinib (CS Table 54). However, the company's clinical expert estimated that about 5-10% of patients would still be receiving sunitinib after 5 years, whilst the log-normal estimated 12% would be receiving treatment. Hence the log-normal was considered implausible. The company chose the exponential distribution for consistency with PFS for axitinib and sunitinib. For pembrolizumab, the Weibull curve was chosen as it had the best statistical and visual fit.

For the subgroup analysis, for the intermediate/poor risk group, the log-logistic distribution was used for pembrolizumab based on visual inspection and AIC/BIC. Exponential ToT curves were used for axitinib and sunitinib. For cabozantinib, the proportion of patients remaining on treatment was based on the modelled PFS curve for this treatment arm.

For first-line treatment, the company's base case does not cap the ToT curves with the PFS curves, meaning that patients could potentially continue to receive treatment even after they have progressed. The ERG observed that PFS and ToT curves are similar and therefore the company's choice to not cap ToT is not likely to drive model results.

There is no waiting period between stopping first-line treatment and starting second-line treatment in the company's model. Patients who progress are assumed to immediately commence second-line treatment. This was considered reasonable by the ERG's clinical experts.

ERG conclusion

The ERG agrees that the log-normal would be an implausible distribution for ToT for axitinib and sunitinib. As described in section 4.3.5 for OS, the ERG considered that the company should use the same distribution for both treatment arms. This is also the case for ToT. Therefore, the ERG considers that the Weibull distribution provides the best visual fit for ToT for sunitinib and pembrolizumab, and it is also a good fit to the company's clinical expert estimate of patients remaining on treatment with sunitinib after 5 years (5 - 10%).

For the intermediate / poor risk subgroup analysis, the ERG prefers to use the same distributions for pembrolizumab plus axitinib and sunitinib. The Weibull appears to provide the best visual fit to the observed data.

4.3.7.3 Second-line treatment use and costs

The company includes second-line treatment costs according to two methods: real-world based and trial based. In the base case the company assumes that upon disease progression patients incur the costs of subsequent therapies in line with the NHS England submission in TA581 for nivolumab and ipilimumab in untreated RCC.[41] In this option, 50% of patients who had progressed were assumed to receive second-line treatment. The distribution of subsequent therapies is shown in Table 35 (CS Table 58).

Table 35 Type and distribution of second line subsequent treatments used in the base case

		First-line treatment				
		Pembrolizumab + axitinib	**Sunitinib**	**Pazopanib**	**Tivozanib**	**Cabozantinib**
Distribution of subsequent therapy	No active treatment	50.00%	50.00%	50.00%	50.00%	50.00%
	Pazopanib	30.00%	0.00%	0.00%	0.00%	0.00%
	Sunitinib	20.00%	0.00%	0.00%	0.00%	0.00%
	Nivolumab	0.00%	30.00%	30.00%	30.00%	30.00%
	Cabozantinib	0.00%	12.50%	12.50%	12.50%	0.00%
	Axitinib	0.00%	7.50%	7.50%	7.50%	7.50%
	Lenvatinib/ everolimus	0.00%	0.00%	0.00%	0.00%	12.50%*

	Source	NHS England Submission in TA581 *Assumption that the proportion of patients treated with cabozantinib in first-line that are expected to receive second-line treatment with cabozantinib were redistributed to lenvatinib/everolimus

Reproduced from CS Table 58

In the model, the proportion of patients estimated to progress in each treatment cycle is distributed between the six active second-line treatments and no treatment. The mean treatment durations from the trials of each treatment are then applied to each of the second-line treatments.[41, 55-65]

In a scenario analysis, the company assumes the same proportion of patients receiving subsequent therapy after disease progression as observed after progression in the KEYNOTE-426 trial. However, the company notes that some of the treatments are not recommended in UK clinical practice. The distribution of subsequent therapies in KEYNOTE–426 are shown in Table 36 (CS Table 59).

Table 36 Type and distribution of second line subsequent chemotherapies used in the base case

		First-line treatment				
		Pembrolizumab + axitinib	**Sunitinib**	**Pazopanib**	**Tivozanib**	**Cabozantinib**
Distribution of subsequent therapy	No active treatment	[redacted]	[redacted]	74.74%	74.74%	39.24%
	Axitinib	[redacted]	[redacted]	11.45%	11.45%	23.08%
	Cabozantinib	[redacted]	[redacted]	0.00%	0.00%	1.28%
	Everolimus	[redacted]	[redacted]	10.18%	10.18%	8.98%
	Lenvatinib / everolimus	[redacted]	[redacted]	0.00%	0.00%	1.28%
	Nivolumab	[redacted]	[redacted]	0.00%	0.00%	10.77%
	Pembrolizumab	[redacted]	[redacted]	0.00%	0.00%	7.18%
	Sunitinib	[redacted]	[redacted]	0.00%	0.00%	14.11%
	Temsirolimus	[redacted]	[redacted]	0.00%	0.00%	8.98%
	Pazopanib	[redacted]	[redacted]	0.00%	0.00%	17.95%
	Cytokines (interferon)	[redacted]	[redacted]	8.90%	8.90%	3.85%
	Source	KEYNOTE-426 trial	KEYNOTE-426 trial	Assume equal to Tivozanib	TIVO-1 trial	CABOSUN trial

Reproduced from CS Table 59

The costs of each subsequent treatment are detailed in Table 37 (CS Table 60). In all cases drug costs have been sourced from the BNF,[54] and applied to dosing regimens as per each therapy's SmPC. Median treatment duration was taken from the relevant trials for each of the treatment and then converted to mean treatment duration by assuming constant hazards.

Table 37 Subsequent therapy- drug formulation, dose, administration, mean treatment duration and total drug acquisition cost

Subsequent treatment	Dosing schedule	Drug acquisition cost per admin (2018 GBP)	Mean treatment duration (months)	Total drug acquisition cost (2018 GBP)[a]
Nivolumab	480 mg IV Q4W or 240 mg IV Q2W	4,846.56	7.9*	41,804.38
Pembrolizumab	200 mg IV Q3W	4,986.48	7.9	57,348.36
Axitinib	5 mg orally BID	3,587.34	11.8*	46,133.02
Cabozantinib	60 mg orally QD	4,800.13	12.1*	63,235.08
Lenvatinib / everolimus	18 mg orally QD	1,810.62	11.0*	42,856.12
	5 mg orally QD	1,785.00	11.0*	n/a
Pazopanib	800 mg orally QD	1,574.63	10.7*	20,884.69
Sunitinib	50 mg orally QD for 4 weeks, then 2 weeks off treatment	2,344.68	10.7*	18,140.54
Everolimus	10 mg orally QD	2,290.23	6.3*	15,803.62
Temsirolimus	25 mg IV QW	103.58	6.3*	13,177.12
Cytokines (Interferon a2B Roferon-A)	10 MU SC three days per week	1,345.20	4.0*	2,458.35

** Mean ToT was calculated as a function of median ToT, based on an assumption of constant hazards.*
Key: BID, twice daily; IV, intravenous; BNF, British National Formulary; Q2W, once every 2 weeks; MG, milligrams; MU, million units; SC, subcutaneously
[a] Values corrected in company's clarification response (B1). Values correct in model so no changes to company's base case results.

Adapted from CS Table 60

The ERG received advice from its clinical experts that the proportion of patients receiving subsequent therapy was between 55% - 70% of those who had progressed after first line treatment. However, NHS England were clear in their submission for NICE TA581[41] that a second line treatment rate of 50% is appropriate in 2018. Further, clinical experts to the ERG advised that more patients would receive cabozantinib after first line treatment with pembrolizumab plus axitinib than the estimates shown in Table 35. The ERG has therefore made changes to the proportion of patients receiving cabozantinib as a second-line treatment for the ERG base case. An alternative scenario is also run where a high proportion of patients receive second-line treatment (section 4.4).

4.3.7.4 Treatment administration costs

The company includes treatment administration costs. Pembrolizumab is administered as a IV infusion (30 minute administration). The administration cost of £174.40 is taken from the National Schedule of Reference Costs (currency code SB12Z).[68] The other first-line treatments are oral chemotherapies and incur an administration cost of (SB11Z). The administration costs of first-line treatments are shown in CS Table 55.

We note that there does not need to be an administration cost for oral chemotherapies in the model. As reported in TA542,[24] the ERG noted that the NHS does incur costs for the delivery of oral chemotherapies. However, the modelled health state costs include a monthly consultant-led medical oncology outpatient visit and blood tests, which was assumed to include the cost of procurement, prescribing and monitoring of oral chemotherapies. The ERG has reduced the administration cost of oral treatment to zero in the ERG base case (section 4.4).

Administration costs for second-line treatment are shown in CS Table 61. The ERG notes that the administration costs for nivolumab were incorrectly reported as £309.20, whereas the value used in the model is £174.40, i.e. the same value as for pembrolizumab.

4.3.7.5 Health state unit costs

The resource use and unit costs of progression-free and progressed disease are shown in Table 38 (CS Table 56). The unit costs were taken from the latest NHS reference costs.[68] The company states that the resources for the health states were based upon those from the NICE TA542.[24]

The health state costs are £51.05 per weekly cycle for the progression-free and progressed health states. An additional cost of £229 was applied in the first cycle of the model for the first attendance outpatient consultation.

The ERG considers that the company's estimates of health state costs are reasonable. They reflect resource use assumptions in previous NICE appraisals for untreated RCC (and experts

consulted by the ERG did not object to the company's assumptions, except that it was noted that in routine NHS care, patients would have some follow-up with a nurse specialist). Unit costs are based on appropriate and up-to-date national sources.[68]

Table 38 Resource use and unit costs of progression-free, progressed and terminal health states within the model

	Resource	Resource use (per cycle)	Reference	Unit cost	Reference[68]
PFS	Outpatient consultation (first attendance)	N/A	NICE TA542	£229.00	NHS reference costs 2017-2018 Currency code WF01B, Service code 370, Medical oncology
	Outpatient consultation (follow-up attendance)	0.25		£166.00	NHS reference costs 2017-2018 Currency code WF01A, Service code 370, Medical oncology
	CT Scan	0.08		£110.00	NHS reference costs 2017-2018 Currency code RD25Z Computerised Tomography Scan of three areas, without contrast
	Blood test	0.25		£3.00	NHS reference costs 2017-2018 Currency Code: DAPS05
	Total cost per week	**Cycle 1: £280.05**		**Subsequent Cycles: £51.05**	
PPS	Outpatient consultation (follow-up attendance)	0.25	NICE TA542	£166.00	NHS reference costs 2017-2018 Currency code WF01A, Service code 370, Medical oncology
	CT Scan	0.08		£110.00	NHS reference costs 2017-2018 Currency code RD25Z Computerised Tomography Scan of three areas, without contrast
	Blood test	0.25		£3.00	NHS reference costs 2017-2018 Currency Code: DAPS05
	Total cost per week		**Every cycle: £51.05**		

Reproduced from CS Table 56

4.3.7.6 Cost of terminal care

The company includes a cost of terminal care of £6,789.76 based upon a previous HTA submission for this disease[24] and inflating to 2017/8 prices. The CS notes that there is limited data for the cost and resource use of RCC patients in terminal care. The cost of terminal care is assumed to be the same for all treatment arms.

The ERG for the cabozantinib TA542[24] considered the cost used was an underestimate of the actual costs of terminal care, due to the omission of costs for local-authority funded social care,

district nursing and GP visits and the company's method of adjusting for inflation. Based on the Nuffield report, they estimate an end of life cost of £7,961 from an NHS and PSS perspective and inflating using the Hospital and Community Health Services price index.[69] However this is for the year 2016-17. We have used a similar methodology to update that cost to £8073 for 2017/8. We include this revised figure in ERG analyses in section 4.4.

4.3.7.7 Adverse event costs

The model includes the costs of managing grade 3+ adverse events. The resources used for the management of adverse events was mainly derived from previous technology appraisals for untreated advanced or metastatic RCC[24, 41] or metastatic urothelial carcinoma.[70] Unit costs were taken from the latest NHS reference costs 2017/8.[68] The unit costs of the management of adverse events and the assumptions used are shown in Table 39 (CS Table 57).

The unit cost of treating diarrhoea is higher than the value used in previous TAs, for example the unit cost of treating diarrhoea in TA581[41] is £788.25. However, changes to the unit cost of treating diarrhoea has minimal effect on the cost effectiveness results.

4.3.8 Model validation

The company states that their modelling approach was validated externally by the University of Sheffield's School of Health and Related Research (SCHARR) with input by two external health economists (CS section B.3.10). It further states that details of this validation include model structure, selection of appropriate datasets, survival analysis undertaken and assumptions surrounding extrapolation of survival, quality of life and healthcare resource use. The CS further states that quality assurance internal validation was carried out by the economists who produced the economic model and no major errors were found.

Below is a list of verification checks undertaken by the ERG. These include checks on input data and technical validation of coding.

Table 39 Unit costs of adverse events

Grade 3+ AE with incidence >5%	Unit Cost	Reference	Rationale
Alanine aminotransferase increased	£0.00	Based on the assumption: Regular blood tests (already considered under health-state management costs)	TA542[24]
Aspartate aminotransferase increased	£0.00	Based on the assumption: Regular blood tests (already considered under health-state management costs)	TA542[24]
Decreased appetite	£615.76	Non-elective short stay	TA581[41]
Diarrhoea	£1248.34	Non-elective short stay	TA581[41]
Fatigue	£657.76	Non-elective short stay, cost of face to face community nurse	TA581[41]
Hyperglycaemia	£156.00	Based on the assumption of 1 visit to endocrinologists, initiation of therapy with anti-diabetic medication: metformin 500mg one daily for one year	TA542[24]
Hypertension	£850.21	Non-elective short stay, consultant medical oncology visit WF01A; *non-admitted face to face attendance, follow-up*, 2 follow up GP visits	TA519[70]
Hyponatremia	£0.00	Based on the assumption: Regular blood tests (already considered under health-state management costs)	TA542[24]
Lipase level increased	£357.13	Regular day and night admission SA04J *Iron deficiency Aneamia with CC score 6-9*	TA581[41]
Lymphocytopenia	£331.90	Assumed that 20% of short stay emergency tariff (weighted average of SA25A-SA35E) and 80% of patients with day case tariff (weighted average of SA35B-SA35E)	TA542[24]
Neutropenia	£80.50	Assumed that 10% of patients require hospital treatment, each requiring two episodes during therapy. Weighted average of mean costs for HRG code WJ11Z *Other disorders of immunity* across non-elective long- and short-stay episodes and day-case admissions	TA519[70]
Neutrophil count decreased	£80.50	Assumed to be equal to neutropenia	TA519[70]
Palmar-plantar erythrodysaesthesia syndrome	£615.76	Non-elective short stay	TA581[41]
Platelet count decreased	£80.50	Assumed to be equal to neutropenia	TA519[70]
Stomatitis	£615.76	Non-elective short stay	TA581[41]
Thrombocytopenia	£357.13	Regular day and night admission SA04J *Iron deficiency Anaemia with CC score 6-9*	TA581[41]

Reproduced from CS Table 57

4.3.8.1 ERG model verification procedures

We conducted a range of manual checks to verify model inputs and calculations ('white box' tests) and to test the face-validity of the model results ('black box' checks):

- Cross-checking of all parameter inputs against values in the CS and cited sources;
- We manually ran scenarios checking all model outputs (for both the IMDC risk subgroup and the overall risk population) against results reported in the CS for the base case, PSA and DSA results.
- We traced input parameters from entry cells in the model ('Raw' inputs sheets), to PSA / DSA sampling (on the "DSA Results" and "PSA Setup" sheets) through to the survival curve and Markov calculation sheets;
- We independently replicated calculations for first and second line drug costs (to check adjustments for dose, intensity and wastage), health state costs and adverse event costs and QALY loss;
- Survival curve calculations were checked ("Effectiveness_survival" sheet, all the treatment effectiveness sheets and "ToT_Parametric Estimation" sheet.
- We estimated cohort sizes in the three states at each cycle using alternate but corresponding formulas.
- We checked QALY and cost calculations on the Markov sheets for all treatments.

ERG conclusion

We spotted a few inconsistencies in parameter values between the CS and the company's model. In response to ERG clarification questions the company states that the values in the model are correct and therefore do not affect the results reported in the CS or the model outputs. The ERG did not spot any errors in the Excel spreadsheet formulas of the company model.

4.3.8.1 Assessment of internal and external validity of model

The company's fitted survival curves are described in detail earlier in this report (section 4.3.5). In the base case, these curves are based on the results of the KEYNOTE-426 trial. In general, the parametric curves chosen by the company provide a good fit to the observed data for PFS, OS and ToT.

The ERG assesses the external validity of the model by comparing mean life years for patients treated with sunitinib with those from previous NICE technology appraisals. The results are shown in Table 40. The mean life years for sunitinib vary between 2.845 – 4.53 years depending on the assumptions used to extrapolate OS. The ERG estimate of mean life years for sunitinib is similar to the ERG estimates in previous NICE appraisals.

Table 40 Mean life years for sunitinib in the current appraisal compared to previous TAs

	Mean life years for sunitinib		
	Current appraisal	TA581[41]	TA512[27]
Company's estimate	3.86	4.53	2.846
ERG's estimate	3.47	3.03	3.31

4.3.9 Cost effectiveness results

Results from the economic model are presented in section B.3.7, page 136 of the CS as incremental costs per QALY gained for pembrolizumab plus axitinib compared against sunitinib, tivozanib and pazopanib. Results are also presented in terms of life years gained. For the overall population, the results are presented pairwise against pembrolizumab plus axitinib for all comparators, with pazopanib and tivozanib assumed to be clinically equivalent in effect to sunitinib. Two sets of pairwise base case results are presented in the CS: Table 64 which presents a comparison with sunitinib and CS Table 65 which presents a pairwise comparisons with tivozanib and pazopanib. These tables are reproduced below in Table 41.

Table 41 Base case cost effectiveness results for the overall patient population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	-	-	-
Sunitinib	[redacted]	3.864	[redacted]	£137,537	2.320	£ 59,292
Pazopanib	[redacted]	3.864	[redacted]	£133,472	2.320	£ 57,540
Tivozanib	[redacted]	3.864	[redacted]	£131,402	2.320	£ 56,648
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Adapted from CS Table 64 and CS Table 65

For the company base case, there is an incremental cost effectiveness ratio (ICER) £59,292 per QALY for pembrolizumab with axitinib compared to sunitinib. ICERs of £57,540 and £56,648 are reported for pembrolizumab plus axitinib compared to pazopanib and tivozanib respectively.

Base case results are also reported for the intermediate/poor risk subgroup. Pairwise cost-effectiveness results are presented for pembrolizumab plus axitinib compared to sunitinib, pazopanib, tivozanib and cabozantinib with the assumption that pazopanib and tivozanib both have equivalent clinical efficacy to sunitinib (CS Tables 68 and CS Table 70). The pairwise results are £59,766, £58,350, £57,611 and £21,452 per QALY gained for pembrolizumab with axitinib compared to sunitinib, pazopanib, tivozanib and cabozantinib respectively.

4.3.10 Assessment of uncertainty

One-way sensitivity analyses were undertaken and reported in the CS for pairwise comparisons of pembrolizumab and axitinib versus sunitinib and these are presented in a tornado plot. Except for annual discount rates, all other model parameters are varied using the 95% confidence intervals to test the sensitivity of the results to individual parameters or groups of parameters. The results are summarised in the tornado graphs in Figure 6 (CS Figure 37).

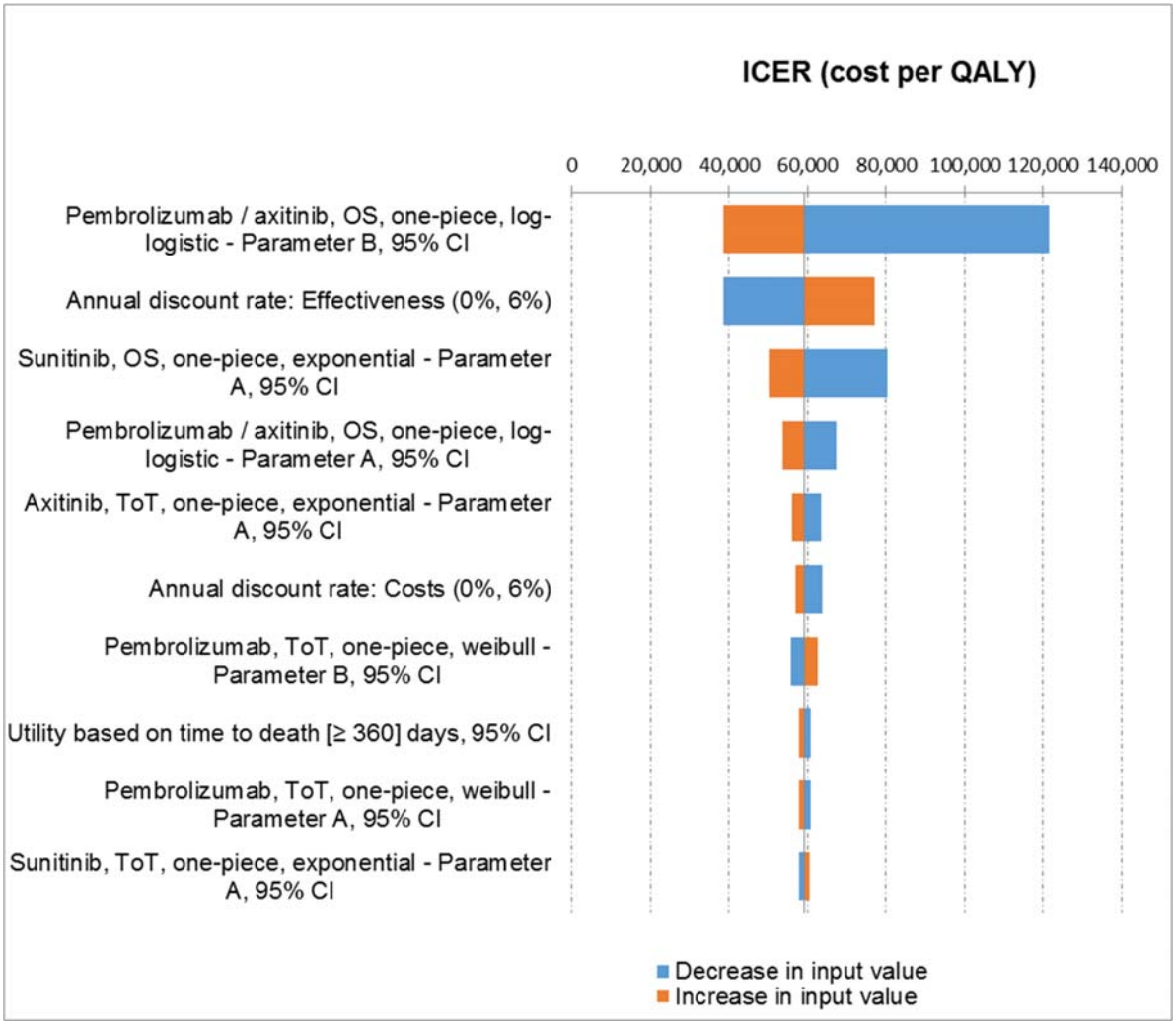

Figure 6 Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most influential variables on cost effectiveness results versus sunitinib

Reproduced from CS Figure 37

The company does not justify its method for selecting the parameters reported in the tornado plot or the ranges used for the one-way sensitivity analysis. However, the ERG considers that the use of the 95% CI ranges is reasonable and a well-established way of testing the sensitivity of individual parameters. The parameters of the OS curve for pembrolizumab plus axitinib have the biggest impact on cost-effectiveness, with the ICER increasing by over £50,000 per QALY gained when a parameter of the log-logistic curve is varied. Other significant drivers of cost-effectiveness include annual discount rate for effectiveness and the sunitinib OS curve.

4.3.10.1 Scenario analysis

The company explores a range of scenarios to test structural and methodological uncertainty. These are reported in CS Table 67. It is not clear if the company's scenario analyses were informed by expert opinion. Generally, the company appears to test scenarios using available data that were not used in the base case. We think the parameters explored by the company are reasonable, although we requested additional analyses which were provided in the company's response to our clarification questions (questions B10 to B16). We felt that these additional analyses by the company are incomplete as some of them do not address the questions raised by the ERG. For instance, the ERG requested a scenario analyses for PFS, OS and time on treatment where the same parametric distributions are used for each treatment arm (clarification question B13). However, the company's response does not answer this question. In our base case and scenario analyses, we provide results for these scenarios.

The company found that the biggest source of uncertainty over cost-effectiveness was the introduction of treatment effect waning after 10 years, with an ICER of £86,712 per QALY gained for pembrolizumab with axitinib compared to sunitinib. The choice of OS curve used in the model and the use of alternative modelling approaches for PFS and ToT also increased the ICER significantly. Introducing a 2-year stopping rule for axitinib reduced the ICER to £50,436 per QALY gained.

The company's scenario analyses are shown in Table 42 (CS Table 67).

4.3.10.2 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis (PSA) results are summarised in scatterplots, cost effectiveness acceptability curves (CEACs) and in a table of incremental cost per QALY gained (CS Figures 35 and 36: CS Tables 66) for pembrolizumab plus axitinib versus sunitinib. The PSA results, which were estimated for 1000 simulations, are stable and similar to the deterministic results. It takes about 1.5 hours to run a thousand iterations on the company's model. The CEAC and cost effectiveness results are reproduced below in Figure 7 and Table 43 (CS Figure 36 and CS Table 66, respectively).

Table 42 Results from the scenario analyses versus trial comparator sunitinib (list price)

Scenario No.	Description	Pembrolizumab + axitinib vs sunitinib		
		Incremental costs (£)	Incremental QALYs	ICER (£)
Base Case	-	£ 137,537	2.320	£59,292
Scenario 1	Landmark Modelling approach[a]	£ 137,249	2.237	£61,341
Scenario 2	Fully parametric exponential OS extrapolation	£ 135,994	1.861	£73,094
Scenario 3	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-constant HR for sunitinib	£ 137,497	2.318	£59,310
Scenario 4	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-varying HR for sunitinib	£ 135,616	1.720	£78,854
Scenario 5	Treatment waning after 10 years	£ 134,833	1.555	£86,712
Scenario 6	Alternative modelling approach of PFS and ToT-PFS pembrolizumab + axitinib lognormal; ToT pembrolizumab Weibull, axitinib lognormal.	£ 182,710	2.320	£78,767
Scenario 7	Health state-based utilities (pooled)	£ 137,537	2.169	£63,400
Scenario 8	Health state-based utilities (treatment specific)	£ 137,537	2.259	£60,876
Scenario 9	Removing age-related disutilities	£ 137,537	2.499	£55,045
Scenario 10	Sunitinib dose intensity = 86% (TA169)[71]	£ 133,690	2.320	£57,634
Scenario 11	Removing AE disutilities	£ 137,537	2.319	£59,300
Scenario 12	Trial-based subsequent therapy distribution	£ 141,482	2.320	£60,993
Scenario 13	Axitinib 2 year stopping rule	£ 116,994	2.320	£50,436
Scenario 14	Remove half-cycle correction	£ 137,537	2.320	£59,289

Adapted from CS Table 67

[a] Details shown in CS appendix P (Scenario 1)

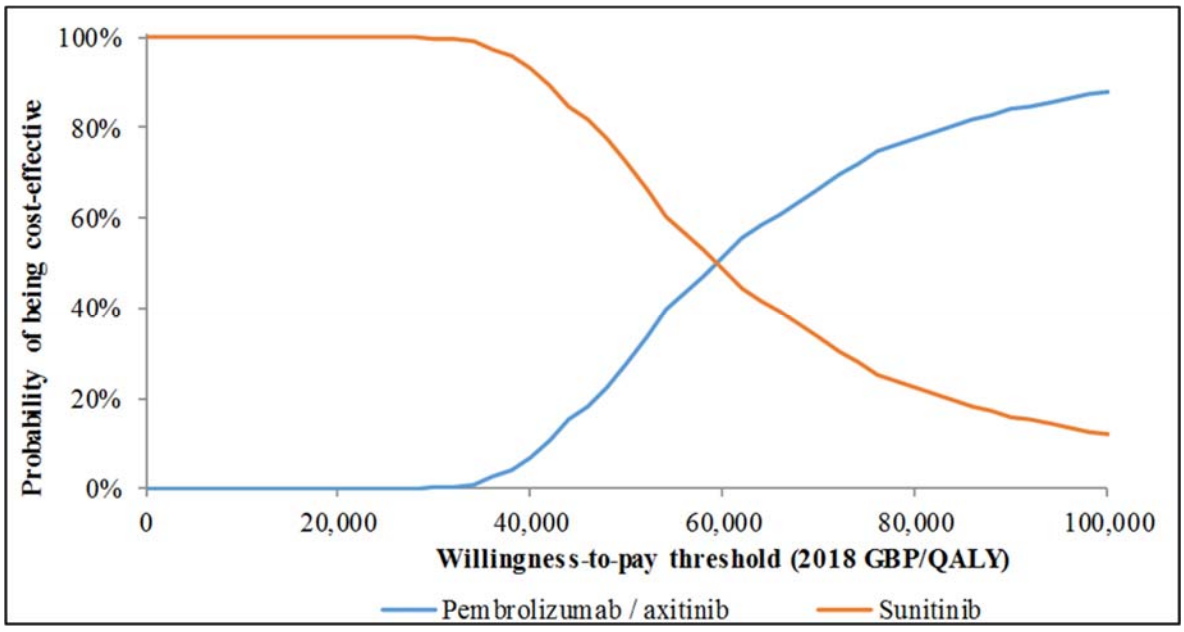

Figure 7 Cost-effectiveness acceptability curve versus sunitinib (list price)

Reproduced from CS Figure 36

Table 43 Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus sunitinib

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Sunitinib	[redacted]	[redacted]	-	-	-
Pembrolizumab + axitinib	[redacted]	[redacted]	£137,352	2.30	£59,726

Reproduced from CS Table 66

The CS reports a 0.3% probability that pembrolizumab plus axitinib is cost-effective at a threshold of £30,000 per QALY gained compared to sunitinib.

All the variables that were included in the PSA are summarised in the CS (Table 62) along with the corresponding distributions. The utility inputs and costs (administrative costs, disease management costs and adverse event management costs) were assigned beta and gamma distributions respectively. We consider these distributions to be appropriate. Drug costs and incidence of AEs for pembrolizumab with axitinib and sunitinib are among parameters not included in the PSA. No justification was provided for the exclusion of these parameters but we consider that drug costs are subject to very little uncertainty, since they are sourced from the BNF.

4.4 Additional work undertaken by the ERG

The ERG did not identify any errors to be corrected in the company model. Table 44 to Table 45 show the assumptions in the company base case and alternatives suggested by the ERG for our base case for the overall patient population. We conduct scenario analyses (Table 46) which use the ERG base case assumptions. We provide justifications for our preferred assumptions. In Table 47, we list the proportion of patients who receive subsequent therapy in our base case and scenario analysis.

Table 44 ERG base case for the extrapolation distributions – overall population

	Overall survival		Progression free survival		Time on treatment		
	Pemb + Ax	Sun	Pemb + Ax	Sun	Pemb	Ax	Sun
Company base case	Log-logistic	Exponential	KM + Exponential	KM + Exponential	Weibull	Exp	Exp

ERG base case	Weibull	Weibull	KM + Exponential	KM + Exponential	Weibull	Weibull	Weibull
Notes	Should use same distribution for both treatments. Weibull provides best fit to sunitinib data.		ERG agrees with company approach.		Should use same distribution for all treatments. Weibull provides best visual fit to data.		

Table 45 ERG base case additional parameters – overall population

Parameter	Company's assumption	ERG preferred assumptions	Reason for ERG preference
Age-adjusted utility	Included age-adjusted utility	Don't include age adjusted utility	See company's response to clarification question B11, no relation found with age and utility.
Subsequent treatment costs	Based on NHS England estimates	ERG base case (see Table 47)	Changes to subsequent treatment: For pembrolizumab + axitinib arm, more patients (20%) would receive cabozantinib See Table 47)
Administration costs	Oral treatments: administration cost of 131.61.	Oral treatments: administration costs £0;	Oral treatments don't normally have costs;
Terminal care cost	£6,789.76	£8,073	Using cost from cabozantinib STA updated to 2017/8.

Table 46 ERG scenarios

Parameter	Company's assumption	ERG preferred assumptions	Scenarios	Reason for ERG preference
Time horizon	40 years	40 years	20 years	20 year horizon used in previous models
Age of cohort	62 years	62 years	57 / 67 years	Exploratory: to assess applicability to the UK RCC population
OS curves	As above	As above	Exponential, Log-logistic for both treatment arms	Other plausible distributions
PFS curves	As above	As above	Weibull, log-logistic	Other plausible distributions
ToT curves	As above	As above	Exponential, log-logistic for both treatment arms	Other plausible distributions
Persistence of OS benefit	No waning effect	No waning effect	Waning effect after 5 / 10 years	Immature OS data. Unclear why there would be a persistence of benefit

				several years after treatment ended.
Time varying HR for PFS and OS	Time varying HR not used	Time varying HR not used	Time varying HR using company's 1st and 2nd / 3rd best fitting FP models	Alternative method to estimate extrapolation of comparator survival curves
Health state utilities	Utilities from company trial for time-to-death	Utilities from company trial for time-to-death	Utilities from previous NICE TAs; tivozanib TA512; pazopanib TA215	
Age-adjusted utility	Included age-adjusted utility	Don't include age adjusted utility	Use age-adjusted utility	See company's response to clarification question B11, no relation found with age and utility.
UK population norms for utility	No adjustment for UK population norms.	No adjustment for UK population norms.	Utility for patients with >360 days to death set to 0.775.	Utility for patients with >360 days to death higher than UK population norms for same age group.
Subsequent treatment costs	Based on NHS England estimates	ERG base case (see Table 47)	ERG scenario analysis (see Table 47)	Based on clinical advice.
	ToT for comparator treatments based on PFS		Apply same assumptions to pembrolizumab / sunitinib	Consistency
Administration costs	Oral treatments: administration cost of 131.61	Oral treatments: administration costs £0;	Oral treatments: administration cost of 131.61;	Oral treatments don't normally have administration costs;

Table 47 ERG base case and scenario analyses on proportion of patients on subsequent-line treatment

	Company base case		**ERG base case**		**ERG scenario analysis**	
Subsequent treatment	**Pembrolizumab + axitinib**	**Sunitinib**	**Pembrolizumab + axitinib**	**Sunitinib**	**Pembrolizumab + axitinib**	**Sunitinib**
Best supportive care	50%	50%	50%	50%	40%	40%
Lenvatinib / everolimus	0%	0%	0%	0%	0%	0%
Axitinib	0%	8%	0%	8%	0%	8%
Cabozantinib	0%	13%	20%	13%	20%	13%
Nivolumab	0%	30%	0%	30%	0%	40%
Pazopanib	30%	0%	20%	0%	25%	0%
Sunitinib	20%	0%	10%	0%	15%	0%

In Table 48, the results for the ERG base-case analysis for the overall population are shown. The pairwise cost-effectiveness results are £120,455, £115,558 and £117,411 per QALY gained for pembrolizumab plus axitinib versus sunitinib, tivozanib and pazopanib respectively. While these results represent our preferred assumptions, they indicate a doubling of the ICERs reported in the CS.

Table 48 ERG base case cost-effectiveness analysis for pembrolizumab + axitinib versus comparators in the overall population (pairwise comparisons)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Pembrolizumab + axitinib	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	£140,895	1.170	£120,455
Tivozanib	[redacted]	[redacted]	£135,168	1.170	£115,558
Pazopanib	[redacted]	[redacted]	£137,335	1.170	£117,411

Table 49 shows the scenario analyses and the effect of these on model results. The results vary between £72,591 - £162,424 per QALY gained for pembrolizumab plus axitinib compared to sunitinib. The scenario analyses are described in more detail in Table 46. Those scenarios which have a large effect on model results are changes to the distributions used for OS, using the log-logistic curve for ToT, including a waning effect and changes to the utility values.

Table 49 ERG scenario analyses for pembrolizumab + axitinib versus sunitinib in the overall population

Scenario	Scenarios	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case		£140,895	1.170	£120,455
Time horizon	20 years	£140,779	1.149	£122,498
Age of cohort	57 years	£140,895	1.170	£120,447
	67 years	£140,894	1.169	£120,510
OS curves	Exponential	£143,209	1.973	£72,591
	Log-logistic	£141,615	1.419	£99,790
PFS curves	Weibull	£140,996	1.170	£120,541
	Log-logistic	£141,019	1.170	£120,561
ToT curves	Exponential	£141,627	1.170	£121,080
	Log-logistic	£166,512	1.170	£142,356
Persistence of OS benefit	Waning effect after 5 years	£137,625	0.847	£162,424
	Waning effect after 10 years	£140,534	1.086	£129,368

Time varying HR for PFS and OS	Company best fitting FP model	£140,784	1.162	£121,183
	Company 2nd best fitting FP model[a]	£140,569	1.074	£130,897
Health state utilities	Utilities from Tivozanib TA512;	£140,895	0.953	£147,873
	Utilities from pazopanib TA215	£140,895	0.883	£159,484
Population norms utility	Utility set at 0.775 for time to death > 360 days	£140,895	1.100	£128,044
Age-adjusted utility	Use age-adjusted utility	£140,895	1.124	£125,389
Subsequent treatment costs	ERG scenario analysis (see Table 47)	£138,591	1.170	£118,485
Administration costs	Oral treatments: administration cost of £131.61;	£140,527	1.170	£120,140

[a] fractional polynomial NMA 2nd best fitting model (company clarification response document appendix Table 43, 44).

Subgroup analysis: intermediate / poor risk group

We also conducted analyses for the intermediate / poor risk group using the ERG's preferred base case assumptions for the overall patient population (Table 44 and Table 45). The results of these are shown in Table 50. The ICER for pembrolizumab plus axitinib compared to cabozantinib is £48,424 per QALY gained.

Table 50 ERG analysis of cost-effectiveness for pembrolizumab + axitinib versus comparators in the intermediate / poor risk subgroup (Pairwise comparisons)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Pembrolizumab + axitinib	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	£141,941	1.010	£140,481
Tivozanib	[redacted]	[redacted]	£137,480	1.010	£136,065
Pazopanib	[redacted]	[redacted]	£139,200	1.010	£137,768
Cabozantinib	[redacted]	[redacted]	£44,012	0.909	£48,424

Table 51 shows the ERG scenario analyses and the effect of these on the model results for the intermediate / poor subgroup. The results vary between £27,892 - £149,347 per QALY gained for pembrolizumab plus axitinib compared to cabozantinib. The scenario analyses are described in more detail in Table 46. Those scenarios which have a large effect on model results are

changes to the distributions used for PFS, using the log-logistic curve for ToT, including a treatment effect waning assumption, using time varying hazards from the fractional polynomial NMA and changes to the utility values.

For the two time varying hazard fractional polynomial models used, the ICER varies between £117,279 and £149,347 per QALY gained. The ERG's critique of the fractional polynomial approach is given in section 3.1.7.5. In this section we note that the company prefers to use the constant HR NMA because the results are more stable than the results of the time varying hazards NMA for the intermediate / poor risk subgroup. The results from our analyses show a large variability in cost-effectiveness compared to the base case which confirms the instability of this approach.

The ERG results shown in Table 48 - Table 51 are calculated using the list price for all treatments. We submitted to NICE a separate confidential appendix which uses the confidential discount prices agreed with the NHS for all treatments for the company and ERG base case analyses.

Table 51 Scenario analyses for pembrolizumab + axitinib versus cabozantinib in the intermediate / poor risk population

Scenario	Scenarios	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case		£44,012	0.909	£48,424
Time horizon	20 years	£43,989	0.904	£48,645
Age of cohort	57 years	£44,012	0.909	£48,424
	67 years	£44,011	0.909	£48,425
OS curves	Exponential	£46,146	1.265	£36,489
	Log-logistic	£46,040	1.651	£27,892
PFS curves	Weibull	£59,261	0.909	£65,201
	Log-logistic			Implausible
ToT curves	Exponential	£40,397	0.909	£44,447
	Log-logistic	£83,907	0.909	£92,318
Persistence of OS benefit	Waning effect after 5 years	£50,525	0.689	£73,290
	Waning effect after 10 years	£44,651	0.872	£51,223
	Best-fitting FP model	£38,473	0.258	£149,347

Time varying HR for PFS and OS	3rd best-fitting FP model[a]	£42,805	0.365	£117,279
Health state utilities	Utilities from tivozanib TA512;	£44,012	0.673	£65,401
	Utilities from pazopanib TA215	£44,012	0.591	£74,530
Population norms utility	Utility set at 0.775 for time to death > 360 days	£44,012	0.855	£51,469
Age-adjusted utility	Use age-adjusted utility	£44,012	0.878	£50,108
Subsequent treatment costs	ERG scenario analysis (see Table 47)	£45,862	0.909	£50,460
Administration costs	Oral treatments: administration cost of 131.61.	£41,639	0.909	£45,813

[b] OS only, company clarification question response appendix Table 129, Table 130. PFS uses constant HR

5 End of life

The CS does not consider pembrolizumab plus axitinib to meet the NICE end of life criteria for the overall RCC patient population (CS Table 39). Estimates of OS for sunitinib in pivotal phase III RCTs are in excess of 24 months (criterion 1 states that the treatment is indicated for patients with a short life expectancy, normally less than 24 months). The ERG agrees with this assertion. However, the CS claims that patients in the IMDC poor risk sub-group would meet the end of life criteria as they have a life expectancy of less than 24 months, and an expected increase in life expectancy of greater than three months with pembrolizumab plus axitinib. The CS appears to use sunitinib as the standard of care for estimating life expectancy and gains in life years in this patient subgroup. However, the ERG notes that cabozantinib is specifically recommended by NICE in poor (and intermediate) risk patients, based on NICE TA542[24] Of note, the CS does not explicitly state the rationale for the choice of the poor risk subgroup when in their assessment of clinical effectiveness and cost effectiveness the subgroup is intermediate / poor risk. Thus, it is not possible for the ERG to generate modelled estimates of OS for poor risk subgroup patients to inform end of life assessment.

In Table 52 we summarise and critique the company's evidence in support of their case for end of life criteria applying to poor risk RCC patients.

Table 52 Summary and critique of the CS case for meeting end of life criteria in poor risk RCC patients

Criterion	Data available	ERG comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The CS cites pivotal phase III trials of first line RCC treatments, including CABOSUN, which included intermediate / poor RCC risk patients. Median OS was 30.3 months for cabozantinib, and 21.8 months for sunitinib. Other trial estimates of OS for sunitinib were in excess of 24 months (though not restricted to intermediate / poor risk patients). The CS cites final results from extended follow-up of a global, expanded-access trial of sunitinib treatment in 4543 patients with metastatic RCC ineligible for registration trials.[72] Median OS stratified by risk group was 56.5 months (favourable risk), 20.0 months (intermediate risk), and 9.1 months (poor risk). The distribution of patients across IMDC risk categories was 22%, 48% and 20%, respectively.	The median OS of 30.3 months for intermediate / poor risk patients in the CABOSUN trial exceeds the end of life criterion of less than 24 months life expectancy. This is a large study reflective of a real world population. However, cabozantinib is not included in this study, which is one of the NICE recommended treatment options for patients at intermediate / poor risk.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The CS provides median OS rates for pembrolizumab plus axitinib versus sunitinib from KEYNOTE-426, at 12 months. The CS also provides OS rates from their economic model at 2 years and 3 years. The ERG notes that these are for the overall RCC population, rather than the poor risk population.	The ERG reports mean undiscounted life years based on the company's model, and the ERG's modelled base case (Table 53), for the intermediate / poor risk subgroup. Pembrolizumab + axitinib extended life by greater than 3 months compared to sunitinib and

	The CS does not attempt to translate these OS rates into life years gained.	cabozantinib, in both the ERG and the company's base case models.

Table 53 ERG and company modelled estimates of overall survival in the intermediate / poor risk subgroup

Treatment	Mean undiscounted life years	
	ERG base case modelled estimate	**Company base case modelled estimate**
Pembrolizumab + axitinib	4.492	7.691
Sunitinib	3.000	3.266
Cabozantinib	3.129	4.664

ERG conclusion

The ERG agrees with the company that pembrolizumab plus axitinib does not meet the first end of life criterion in the overall RCC population (treatment is indicated in patients with a short life expectancy, normally less than 24 months). The ERG disagrees with the company that pembrolizumab plus axitinib meets the first end of life criterion in the poor RCC risk subgroup, based on cabozantinib being specifically recommended by NICE in this subgroup. The ERG is in agreement with the company that pembrolizumab plus axitinib meets the second end of life criterion (treatment offers an extension to life, normally of at least an additional three months, compared with current NHS treatment). We are therefore of the opinion that pembrolizumab plus axitinib does not fully meet the NICE criteria for being considered as a life-extending treatment for people with a short life expectancy.

6 Innovation

The company considers pembrolizumab in itself to be innovative in the first line treatment of RCC, noting that it is available for a wide range of indications. It has a Breakthrough Therapy Designation by the US Food and Drug Administration and a positive scientific opinion from the UK MHRA's Early Access schemes for some of these indications. The company also considers that the innovative immuno-oncology combination regimen of pembrolizumab plus axitinib represents a "step-change" in the management of RCC (CS page 79) as it targets both

angiogenesis and immune-checkpoint pathways. The CS states that other novel anticancer agents have shown improvements over the original immunotherapies, but there remains an unmet need because disease progression occurs in most people within two years. The pembrolizumab plus axitinib combination provides additional clinical benefit over the standard of care. The company states that pembrolizumab should be considered innovative by its potential to make a significant and substantial impact in an area of high unmet need. The ERG clinical advisors agree there does remain an element of unmet need and that the rationale for the combination in RCC is made, however there are other potential treatments that should be considered in relation to pembrolizumab and axitinib (e.g. avelumab plus axitinib – currently the subject of a separate NICE technology appraisal).[73, 74]

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The company's decision problem is largely consistent with the NICE scope, although the population in the CS is restricted to patients with clear cell RCC. The results will not be generalisable to patients with non-small cell RCC types (approximately 25% of patients). The ERG notes that previous NICE appraisals of treatments for RCC also did not restrict the scope to clear cell, despite the pivotal trials comprising mostly or exclusively of clear cell RCC patients. The current CS is therefore in line with evidence accepted in previous NICE appraisals.

The evidence for clinical effectiveness of pembrolizumab plus axitinib is from a large multinational RCT, KEYNOTE-426. The outcomes and statistical analyses of the trial are appropriate, and other than its open-label design, the trial has a low risk of bias. The generalisability of the trial to the UK population is uncertain, as most participants were randomised outside of Europe and less than 6% were from the UK. The participants in the trial are younger and fitter than a typical population with advanced untreated RCC, but similar in these aspects to other pivotal trials of treatments in this indication appraised by NICE.

At the first interim analysis, KEYNOTE-426 demonstrated a significant improvement in PFS with pembrolizumab plus axitinib (15.1 months) compared with sunitinib (11.1 months). Median OS was not reached in either arm. Efficacy testing was stopped early at the first interim analysis,

which can sometimes result in over-estimation of treatment effect. In this case the ERG considers it is unlikely that PFS has been over-estimated, but OS results should be viewed with caution as they are immature.

The company conducted an NMA in order to indirectly compare pembrolizumab plus axitinib with the other treatments in the NICE scope (tivozanib, pazopanib, and cabozantinib for intermediate/poor risk according to IMDC criteria). Previous NICE appraisals of first line treatments for advanced RCC have accepted the assumption that sunitinib, pazopanib and tivozanib are broadly similar to each other in efficacy, and therefore the committees have not considered indirect comparisons as a key factor in their decision making. In the current appraisal the company likewise assumes that pazopanib and tivozanib are similar to sunitinib, and therefore use the direct comparison between pembrolizumab plus axitinib from the KEYNOTE-426 trial to inform clinical effectiveness estimates in the model (i.e. the NMA is not used in the model). However, there is no direct trial comparison between pembrolizumab plus axitinib and cabozantinib, the comparator treatment relevant to patients in the intermediate / poor risk patient subgroup. Therefore, the indirect comparison of these two treatment regimens via NMA is of importance as it informs the economic model cost effectiveness estimates for this subgroup. Overall, the ERG considers the methods and assumptions used to conduct the NMAs to have been appropriately exercised, though the results of the intermediate / poor risk sub-group NMA should be treated with caution as it is based on a sub-set of the randomised population of the KEYNOTE-426 trial, rather than the full trial population.

7.2 Summary of cost effectiveness issues

The company's base case analysis of pembrolizumab plus axitinib versus sunitinib, based on extrapolation curves for OS, PFS and TTD from the overall population of the KEYNOTE–426 trial, gave an ICER of £59,292 per QALY gained. Pazopanib and tivozanib were considered clinically equivalent to sunitinib. In the company's analysis, pazopanib and tivozanib were slightly more expensive than sunitinib and when compared with pembrolizumab plus axitinib, there was an ICER of £57,540 and £56,648 per QALY gained for tivozanib and pazopanib.

The company also provided a comparison against cabozantinib in the intermediate / poor risk RCC population (as defined by the IMDC criteria). The ICER was £21,452 per QALY gained for pembrolizumab plus axitinib compared to cabozantinib.

The ERG identified a number of uncertainties in the company's model and tested an alternative set of assumptions and input parameters relating to the method of fitting the OS and TTD curves, age-adjusted utility, administration costs and terminal care costs.

The ERG-preferred analyses gave higher ICER estimates: £120,455 per QALY for pembrolizumab plus axitinib compared with sunitinib for the overall population and an estimated ICER of £48,424 per QALY for pembrolizumab plus axitinib compared with cabozantinib in the intermediate / poor risk subgroup.

The above analyses have been completed using list price for the treatments. We present results for the above analyses using existing PAS discounts for first and subsequent line treatments in a confidential addendum to this report.

8 REFERENCES

1. Cancer Research UK. Kidney cancer: stages, types and grades. Secondary Kidney cancer: stages, types and grades. https://www.cancerresearchuk.org/about-cancer/kidney-cancer/stages-types-grades/types-grades.
2. Kidney Care UK. What is Kidney Cancer. Secondary What is Kidney Cancer. https://www.kcuk.org.uk/kidneycancer/what-is-kidney-cancer/.
3. NHS. Overview: Kidney Cancer. Secondary Overview: Kidney Cancer. 2016. https://www.nhs.uk/conditions/kidney-cancer/.
4. Kidney Care UK. Kidney Cancer. Secondary Kidney Cancer. https://www.kidneycareuk.org/about-kidney-health/conditions/kidney-cancer/.
5. Cancer Research UK. Kidney cancer statistics. Secondary Kidney cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer#heading-Zero.
6. Harding G, Cella D, Robinson DJ, et al. Symptom burden among patients with Renal Cell Carcinoma (RCC): content for a symptom index. Health and Quality of Life Outcomes 2007;**5**.
7. Cella D. Beyond Traditional Outcomes: Improving Quality of Life in Patients with Renal Cell Carcinoma. The Oncologist 2011;**16**:23-31.
8. Albiges L, Powles T, Staehler M, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma. European Urology 2019;**76**:151-56.
9. Heng D, Xie W, Regan M, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. Journal of Clinical Oncology 2009;**34**:5794-99.
10. Heng D, Xie W, Regan M, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. . Lancet Oncology 2013;**14**:141-48.

11. Choueiri K, Halabi S, Sanford B, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. Journal of Clinical Oncology 2017;**35**.
12. Motzer R, Hutson T, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. . New England Journal of Medicine 2013;**369**:722-31.
13. Motzer R, Nosov D, Eisen T, et al. Tivozanib Versus Sorafenib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma: Results From a Phase III Trial. Journal of Clinical Oncology 2013;**31**:3791-99.
14. Sternberg CN, Motzer RJ, Hutson TE, et al. COMPARZ Post Hoc Analysis: Characterizing Pazopanib Responders with Advanced Renal Cell Carcinoma. Clinical Genitourinary Cancer 2019.
15. George DJ, Hessel C, Halabi S, et al. Cabozantinib Versus Sunitinib for Untreated Patients with Advanced Renal Cell Carcinoma of Intermediate or Poor Risk: Subgroup Analysis of the Alliance A031203 CABOSUN trial. Oncologist 2019.
16. Rini B, Plimack E, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. New England Journal of Medicine 2018;**380**:1116-27.
17. Bedard G, Zeng L, Zhang L, et al. Minimal important differences in the EORTC QLQ-C30 in patients with advanced cancer. Asia-Pacific Journal of Clinical Oncology 2014;**10**(2):109-17.
18. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. New England Journal of Medicine 2018;**378**(14):1277-90.
19. Guyatt G, Briel M, Glasziou P, et al. Problems of stopping trials early. BMJ 2012;**344**:e3863.
20. Freidlin B, Korn E. Stopping clinical trials early for benefit: impact on estimation. Clinical Trials 2009;**6**:119 - 25.
21. Mehta A, Sonpavde G, Escudier B. Tivozanib for the treatment of renal cell carcinoma: results and implications of the TIVO-1 trial. Future oncology 2014;**10**:1819-26.

22. Escudier B, Szczylik C, Hutson T, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. Journal of clinical oncology 2009;**27**:1280-89.
23. Motzer R, Hutson T, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine 2007;**356**:115-24.
24. National Institute for Health and Care Excellence. TA542 Cabozantinib for untreated advanced renal cell carcinoma. 2018.
25. Dias S, Welton N, Sutton A, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials (last updated September 2016). Secondary NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials (last updated September 2016) 2011. http://www.nicedsu.org.uk.
26. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Medical Research Methodology 2011;**11**(1):61.
27. National Institute for Health and Care Excellence. TA512: Tivozanib for treating advanced renal cell carcinoma. 2018.
28. Jansen J, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011;**14**:417-28.
29. Turner RM, Jackson D, Wei Y, et al. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine 2015;**34**(6):984-98.
30. Zondervan-Zwijnenburg M, Peeters M, Depaoli S, et al. Where Do Priors Come From? Applying Guidelines to Construct Informative Priors in Small Sample Research. Research in Human Development 2017;**14**(4):305-20.
31. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health and Quality of Life Outcomes 2007;**5**(70):http://www.hqlo.com/content/5/1/70.

32. Liu G, Wang J, Liu K, et al. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. Statistics in Medicine 2006;**25**:1275–86.
33. Atkins M, Plimack E, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncology 2018;**19**:405-15.
34. Amdahl J, Diaz J, Sharma A, et al. Cost-effectiveness of pazopanib versus sunitinib for metastatic renal cell carcinoma in the United Kingdom. PloS one 2017;**12**(6):e0175920.
35. Hoyle M, Green C, Thompson-Coon J, et al. Cost-Effectiveness of Temsirolimus for First Line Treatment of Advanced Renal Cell Carcinoma. Value in Health 2010;**13**(1):61-68.
36. Kilonzo M, Hislop J, Elders A, et al. Pazopanib for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma. Pharmacoeconomics 2013;**31**(1):15-24.
37. National Institute for Health and Care Excellence. TA169 Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. 2009. https://www.nice.org.uk/guidance/ta169/documents/ta169-renal-cell-carcinoma-sunitinib-review-decision-may-2012.
38. Scottish Medicines Consortium. Sunitinib (Sutent) First line treatment of advanced and/or metastatic renal cell carcinoma (MRCC). 2007.
39. Scottish Medicines Consortium. Pazopanib (Votrient) For the first-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease. 2011.
40. Thompson-Coon J, Hoyle M, Green C, et al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. 2010.
41. National Institute for Health and Care Excellence. TA581 Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. 2019.

42. Porta C. Regarding:'Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-α2a compared with sunitinib'. British journal of cancer 2010;**102**(7):1196.
43. Chen J, Hu G, Chen Z, et al. Cost-effectiveness Analysis of Pembrolizumab Plus Axitinib Versus Sunitinib in First-line Advanced Renal Cell Carcinoma in China. Clinical Drug Investigation 2019:1-8.
44. National Institute for Health and Care Excellence. TA215: Pazopanib for the first-line treatment of advanced renal cell carcinoma. 2011.
45. Latimer N. Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. NICE DSU Technical Document 14 2011.
46. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE, London 2013.
47. Merck Sharp & Dohme Corp. asoMC. Protocol of A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426), 2018.
48. National Institute for Health and Care Excellence. TA428. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. 2017.
49. National Institute for Health and Care Excellence. TA366. Pembrolizumab for advanced melanoma not previously treated with ipilimumab. 2017.
50. Hatswell AJ, Pennington B, Pericleous L, et al. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes 2014;**12**:140.
51. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. Discussion paper 172 1999.
52. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health 2010;**13**(5):509-18.
53. Ara R, Wailoo AJ. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. 2011.

54. Joint Formulary Committee. *British National Formulary*: London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2019.
55. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. The lancet oncology 2015;**16**(15):1473-82.
56. National Institute for Health and Care Excellence. TA333: Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. 2015.
57. National Institute for Health and Care Excellence. TA417: Nivolumab for previously treated advanced renal cell carcinoma. 2016.
58. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. The Lancet Oncology 2013;**14**(6):552-62.
59. National Institute for Health and Care Excellence. TA463: Cabozantinib for previously treated advanced renal cell carcinoma. 2017.
60. Motzer RJ, Escudier B, Powles T, et al. Long-term follow-up of overall survival for cabozantinib versus everolimus in advanced renal cell carcinoma. British journal of cancer 2018;**118**(9):1176.
61. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. European journal of cancer 2013;**49**(6):1287-96.
62. National Institute for Health and Care Excellence. TA432: Everolimus for advanced renal cell carcinoma after previous treatment. 2017. https://www.nice.org.uk/guidance/ta432.
63. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology 2014;**32**(8):760.
64. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. New England Journal of Medicine 2007;**356**(22):2271-81.

65. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. Journal of clinical oncology 2010;**28**(13):2137.
66. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New England Journal of Medicine 2019;**380**(12):1116-27.
67. Merck Sharp & Dohme Corp. A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426), 2018.
68. Department of Health. NHS reference costs 2017-2018. http://wwwdhgovuk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803 2018.
69. Curtis L, Burns A. Unit Costs of Health and Social Care 2018. http://wwwpssruacuk/pdf/uc/uc2010/uc2010pdf 2019.
70. National Institute for Health and Care Excellence. TA519 Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. 2018.
71. NICE. TA169: Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE website: NICE, 2009.
72. Gore ME, Szczylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer 2015;**113**(1):12-9.
73. National Institute for Health and Care Excellence. Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547] 2019. (accessed 03/09/2019).
74. Motzer R, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. New England Journal of Medicine 2019;**380**:1103-15.

75. Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. European journal of cancer (Oxford, England : 1990) 2018;**94**:115-25.

9 APPENDICES

9.1 NICE appraisal committee conclusions on equivalence of treatment comparisons in previous appraisals of treatments for first line advanced RCC.

NICE TA215 Pazopanib for the first-line treatment of advanced renal cell carcinoma[44]

"The Committee concluded that pazopanib is likely to be more clinically effective than interferon-α and is probably comparable in its effectiveness to sunitinib. Subsequent publication of the COMPARZ trial in which sunitinib and pazopanib were directly compared confirmed this assertion, though the safety profile and HRQoL was better for patients treated with pazopanib.

NICE TA512 Tivozanib for treating advanced renal cell carcinoma[27]

"The committee concluded that it had seen no evidence to suggest that tivozanib was more effective than sunitinib or pazopanib in extending overall and progression-free survival. What evidence there was suggested that, at best, tivozanib may have a similar effect to sunitinib or pazopanib".

NICE TA542 Cabozantinib for untreated advanced renal cell carcinoma[24]

"The committee recalled that pazopanib and sunitinib can be considered equally clinically effective. Therefore, it concluded that an indirect treatment comparison was not needed, and did not consider it further".

NICE TA581 Nivolumab with ipilimumab for untreated advanced renal cell carcinoma[41]

"The committee recalled that pazopanib and sunitinib can be considered equally clinically effective. It concluded that an indirect treatment comparison was not needed and did not consider it further".

(NB. Nivolumab with ipilimumab is not a comparator in this current appraisal).

9.2 ERG critical appraisal of relevant comparator treatment trials included in network meta-analysis

Critical appraisal of the CABOSUN trial[11]

NICE quality assessment criteria for RCT	Judgement
1. Was the method used to generate random allocations adequate?	Unclear risk of bias
Comments: Stratified randomisation using a dynamic allocation method to balance prognostic factors between treatment groups, no further details.	
2. Was the allocation adequately concealed?	Unclear risk of bias
Comments: The method of allocation concealment is not reported in the trial publication or study protocol	
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes (low risk of bias)
Comments: The publication states that overall, the treatment groups were balanced with respect to baseline demographic and disease characteristics.	
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No (high risk of bias)
Comments: Open label trial.	
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear risk of bias
Comments: drop out balanced for withdrawal due to progression and AEs but there were differences between the study arms in the number of patients who did not receive the study drug and in the number of patients who withdrew consent.	
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (low risk of bias)
Comments: There are no deviations from the trial protocol with regard to outcomes.	
7. 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 (low risk of bias) Yes Yes
Comments: ITT approach (all patients who were randomised) for all but safety data (the safety analysis population was patients who received ≥1 dose of study drug).	

Critical appraisal of the COMPARZ trial[12]

NICE quality assessment criteria for RCT	Judgement
1. Was the method used to generate random allocations adequate?	Unclear risk of bias
Comments: States patients were randomly assigned to one of the two study drugs in a 1:1 ratio in permuted blocks of four but method used to generate the schedule not reported.	
2. Was the allocation adequately concealed?	Yes (low risk of bias)
Comments: Interactive voice response system used.	

3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes (low risk of bias)
Comments: No notable differences between the groups in demographic or clinical characteristics	
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No (high risk of bias)
Comments: The trial was open-label. Imaging data were re-evaluated by an independent review committee who were unaware of the treatment assignments to assess the primary end point and tumour response.	
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No (low risk of bias)
Comments: The number of treatment discontinuations was similar between the two groups	
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (low risk of bias)
Comments: Outcome data are reported for each of the stated outcomes.	
7. 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 (low risk of bias) Yes Unclear
Comments: Efficacy data were analysed in the ITT population (all patients who underwent randomisation). However, the ERG notes that for patient-reported outcomes (HRQoL and symptoms) the number of patients analysed is lower than the number randomised. It is not clear how missing data were handled.	

Critical appraisal of the TIVO-1 trial[13, 21]

NICE quality assessment criteria for RCT	Judgement
1. Was the method used to generate random allocations adequate?	Unclear risk of bias
Comments: States that randomisation was stratified (geographical region, number of prior treatments for metastatic disease, number of metastatic sites/ organs) but no details of the method to generate the sequence	
2. Was the allocation adequately concealed?	Unclear risk of bias
Comments: Not reported	
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Unclear risk of bias
Comments: Study reports some imbalance between groups for ECOG performance status 0 or 1 which may be prognostic.	
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No (High risk of bias)
Comments: open label trial, response and progression outcomes were evaluated by a blinded independent radiology reviewer but other outcomes were not assessed blind.	

5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear risk of bias
Comments: Numbers discontinuing treatment differed but no details of numbers discontinuing the study were reported.	
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (Low risk of bias)
Comments: All outcomes stated in the methods are reported	
7. 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 (Low risk of bias) Yes Unclear
Comments: No details reported	

9.3 Differences in source data and results of constant hazards NMA: CS vs ERG analysis

Differences in NMA source data between CS and ERG

		Data as reported in CS Tables 22, 24, 26, 28			Data as reported in trial publications (extracted by ERG). KEYNOTE-426 taken from CS					
Trial ID	**Comparison**	**HR**	**LHR**	**LSE**	**HR**	**LCI**	**UCI**	**LHR**	**LSE**	**Notes**
Base case PFS										
COMPARZ	pazopanib vs sunitinib	1.05	0.05	0.08	1.05	0.9	1.22	0.05	0.08	
Escudier et al 2009	sorafenib vs INFα	1.14	0.13	0.19	1.14	0.79	1.64	0.13	0.22	calculated reciprocal
	INFα vs sorafenib				0.88	0.61	1.27	-0.13	0.17	Pre-crossover data (Period 1)
KEYNOTE-426	Pembrolizumab+axitinib vs sunitinib	0.69	-0.37	0.1				-0.37	0.1	
Motzer et al 2007	INFα vs sunitinib	1.86	0.62	0.09	2.38	1.85	3.13	0.87	0.32	calculated reciprocal
	sunitinib vs INFα				0.42	0.32	0.54	-0.87	0.06	
TIVO-1	tivozanib vs sorafenib	0.76	-0.28	0.14	0.756	0.58	0.985	-0.28	0.10	Treatment naïve subgroup
Base case OS										
COMPARZ	pazopanib vs sunitinib	0.92	-0.08	0.07	0.91	0.76	1.08	-0.09	0.08	
KEYNOTE-426	Pembrolizumab+axitinib vs sunitinib	0.53	-0.63	0.17				-0.63	0.17	
Intermediate / poor risk subgroup PFS										
CABOSUN	cabozantinib vs sunitinib	0.48	-0.73	0.22	0.66	0.46	0.95	-0.42	0.13	CS used independent committee PFS;[75] ERG used investigator PFS (primary outcome)[11]
KEYNOTE-426	Pembrolizumab+axitinib vs sunitinib	0.67	-0.4	0.12				-0.4	0.12	
Intermediate / poor risk subgroup OS										
CABOSUN	cabozantinib vs sunitinib	0.8	-0.22	0.21	0.8	0.53	1.21	-0.22	0.17	Updated paper (Choueiri, 2018)

KEYNOTE-426	Pembrolizumab+axitinib vs sunitinib	0.52	-0.65	0.18				-0.65	0.18	

HR = Hazard ratio; LHR = log hazard ratio; LSE = log standard error; LCI = lower confidence interval; UCI = upper confidence interval; Shaded cells indicate disagreement between CS and ERG data estimates

Comparison of CS and ERG results: constant HRs (vs sunitinib)

	CS Tables 23,25,27,29)		ERG scenario	
	HR	**95% CrI**	**HR**	**95% CrI**
Base case PFS				
pazopanib	1.05	0.90,1.23	1.05	0.90, 1.23
sorafenib	2.11	1.40,3.18	2.74	1.92, 3.81
INFα	1.85	1.55, 2.22	2.38	2.13,2.66
Pembrolizumab+axitinib	0.69	0.57,0.84	0.69	0.57,0.84
tivozanib	1.6	0.98, 2.59	2.08	1.37, 3.05
Base case OS				
pazopanib	0.92	0.80, 1.07	0.91	0.78, 1.07
Pembrolizumab+axitinib	0.53	0.38, 0.74	0.54	0.38, 0.74
Intermediate / poor risk subgroup PFS				
cabozantinib	0.48	0.31, 0.74	0.67	0.52,0.84
Pembrolizumab+axitinib	0.67	0.53,0.85	0.67	0.53,0.85
Intermediate / poor risk subgroup OS				
cabozantinib	0.8	0.53,1.21	0.81	0.57,1.21
Pembrolizumab+axinib	0.52	0.37,0.74	0.53	0.37,0.74

Shaded cells indicate disagreement between CS and ERG results

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 7 October 2019** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10, KEYNOTE-426 trial results, bullet point number 6: This section which refers to both OS and PFS subgroup analyses later presents a HR based on the January 2019 data-cut without specifying which outcome the ERG is referring to	Proposed revision to the existing text as follows: "…Except for IMDC risk category at the January 2019 data-cut **where** the **OS** HR for the IMDC risk category "Favourable" is higher…"	It should be clarified that the HR result presented refers to the OS endpoint. As both PFS and OS are mentioned at the beginning of the bullet point, the current wording does not make clear which outcome the ERG is referring to	Corrected

Issue 2 Section 1 Introduction to the ERG Report, and Section 3.1.3 Identified studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1, page 20, paragraph 1; and section 3.1.3, page 27, paragraph 1: The Company name is misspelt as "Merck Sharp**e** & Dohme"	Please correct the spelling to: "Merck Sharp & Dohme"	The company name has been incorrectly spelt, hence the need for a correction.	Corrected

Issue 3 Section 2.4. Critique of company's overview of decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22, paragraph 1: Currently states that "The CS decision problem also introduces	Proposed revision to the existing text as follows: "The CS decision problem also introduces a	MSD considers that the requirement to include the subgroup of people with intermediate / poor risk	Not a factual error. And the point made about cabozantinib being only of

a subgroup that was not noted in the NICE scope (there were no subgroups in the NICE scope). This was people with intermediate / poor risk category as defined by IMDC. The rationale for this addition is not made explicitly clear in the CS"	subgroup **(people with intermediate / poor risk category as defined by IMDC)** that was not **explicitly** noted in the NICE scope **as a separate subgroup; however cabozantinib was included in the NICE final scope as a comparator only of relevance for this specific subgroup of patients, and therefore the inclusion of this subgroup is reasonable**."	category as defined by IMDC was implicit, given that cabozantinib was included as a comparator of relevance in the NICE scope but only for this subgroup of patients. MSD's intended approach of included clinical and cost-effectiveness analyses for the subgroup of people with intermediate / poor risk category as defined by IMDC was also discussed and agreed as appropriate by NICE during the Decision Problem meeting which took place on 21 May 2019, prior to submission.	relevance for patients with intermediate / poor risk undermines the company's argument in point 14 below that the comparators in the intermediate / poor subgroup are sunitinib, pazopanib, tivozanib and cabozantinib.

Issue 4 Section 3.1.5 Description and critique of company's outcome selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33, paragraph 3, row 12: Currently states "…however only selected scales are presented in CS Appendix L and the CSR (physical functioning, role functioning, nausea/vomiting, diarrhoea) (the ERG requested results for all scales, clarification question A7)"	Proposed revision to the existing text as follows: "…however only selected scales are presented in CS Appendix L and the CSR (physical functioning, role functioning, nausea/vomiting, diarrhoea). The ERG requested results for all scales (clarification question A7) **and these were subsequently provided by the company**."	The ERG statement as currently written does not make clear that all scales for HRQoL were provided by the company upon the request from the ERG during clarification questions. MSD has proposed the suggested amendment to the wording for consistency with other sections of the ERG report, where the ERG have made clear that the company submitted data in response to a	Amended

		request.	

Issue 5 Section 3.1.7.2 Evidence network

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43, paragraph 2, row 1: Currently states: "Outcome-specific networks are depicted in CS Figure 11 (PFS) and Figure 12 (OS). These networks contain fewer trials and relevant treatments than depicted in **Error! Reference source not found.** (CS Figure 10) due to the lack of available HR and Kaplan-Meier data needed for the constant HR and the time-varying hazard analyses, respectively"	Proposed revision to the existing text as follows: "Outcome-specific networks are depicted in CS Figure 11 (PFS) and Figure 12 (OS). **The OS network contains** fewer trials and relevant treatments than depicted in **Error! Reference source not found.** (CS Figure 10) due to the lack of available HR and Kaplan-Meier data needed for the constant HR and the time-varying hazard analyses, respectively".	The PFS network (CS Figure 11) is identical to Figure 1 (Figure 10 in the CS). The only difference in terms of network (as reported in table 7 of the ERG report) is for the OS network, whereby tivozanib could not be connected to the network.	Corrected
Page 44, under Subgroups section: Currently states: "The NICE scope for this appraisal did not specify any subgroups of relevance. However, the company conducted separate NMAs for RCC risk subgroups: intermediate/poor and favourable."	"Proposed revision to the existing text as follows: "The NICE scope for this appraisal did not **explicitly** specify any subgroups of relevance **(although cabozantinib was listed as a comparator only of relevance to the intermediate / poor risk category as defined by IMDC).** However, the company conducted separate NMAs for RCC risk subgroups: intermediate/poor and favourable."	MSD considers that the requirement to include the subgroup of people with intermediate / poor risk category as defined by IMDC was implicit, given that cabozantinib was included as a comparator of relevance in the NICE scope but only for this subgroup of patients. MSD's intended approach of included clinical and cost-effectiveness analyses for the subgroup of people with intermediate / poor risk category as	Not a factual inaccuracy – see our response to issue 3.

		defined by IMDC was also discussed and agreed as appropriate by NICE during the Decision Problem meeting which took place on 21 May 2019, prior to submission.	

Issue 6 Section 3.1.7.7 Statistical NMA approaches used – fractional polynomials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52, Model fitting section, paragraph 2, row 6: Currently states: "However, the company do not elaborate on this process and whether/how it informed their choice of model."	Proposed revision to the existing text as follows: "However, the company do not elaborate **further** on this process."	MSD response to clarification question A13 clearly stated that "In general, the best-fitting fractional polynomial model was chosen based on the lowest DIC value; however, clinical plausibility was **also** considered insofar as checking if time-varying HR results were relatively stable across fractional polynomial models and cross-referencing time-varying HRs with published constant HRs for included studies." So, clinical plausibility was also used as the choice of the model.	Amended

Issue 7 Section 3.1.7.8 Choice between random effects and fixed effect models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54, row 7: Currently states: "The company	Proposed revision to the existing text as follows: "The company responded that **there is no**	MSD response to clarification question A10 clearly stated that two factors play a great role for not	Not a factual inaccuracy. The ERG's sentence is not

responded that collection and validation of meta-epidemiologic data as proposed by Zondervan-Zwijnenburg (2017) would not have been possible within the time frame"	**meta-epidemiologic data for 1LCC mRCC that can be used at this point in time to determine what informative prior distributions are best for OS and PFS outcomes in the ITT and intermediate/poor risk populations. Additionally**, collection and validation of **such** meta-epidemiologic data as proposed by Zondervan-Zwijnenburg (2017)[30] would not have been possible within the time frame"	using an informative prior: availability of meta-epidemiological data and their validation by researchers, clinical experts. Since meta-epidemiological data are not available and collection of such data would not have been feasible within the timelines permitted for responding to the ERG questions, the NMA could not be re-run. The current wording in the ERG report omits that there is no meta-epidemiological data currently available in the literature.	in accurate as it stands.

Issue 8 Section 3.2 Summary statement of company's approach to evidence synthesis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57, Table 10, row1: In this table, against item 1 "Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?", the ERG response is "Uncertain. The eligibility criteria used for population includes a narrower population of RCC with clear cell component."	Proposed revision to the existing text as follows: "**Yes. Although** the eligibility criteria used for population includes a narrower population of RCC with clear cell component, **this is consistent with patient population included in the pivotal phase III trials of comparator treatments which have been previously appraised and recommended by NICE in the patient population covered by this submission**"	The inclusion/exclusion criteria reported by MSD in the CS are clearly related to the primary studies which address the review question. Question 1 within Table 10 is not related to the generalisability of the population but only to the inclusion/exclusion criteria. The ERG has acknowledged (page 17 and 116) that the information presented is consistent with the approach taken in previous NICE appraisals in this patient population.	We have amended to say: "Yes, although the eligibility criteria used for population includes a narrower population of RCC with clear cell component."

Issue 9 Section 3.3.4 Sub-group analyses for overall survival and PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61, row 5: Currently states: "..the ERG notes that HR for the IMDC Risk Category 'favourable' is higher…"	Proposed revision to the existing text as follows: ..the ERG notes that **the OS** HR for the IMDC Risk category 'favourable' is higher…'	The HR results presented should be accurately reflective of the endpoint/outcome under discussion (OS); since both PFS and OS are mentioned in the Section title, it is not clear which outcome the ERG is referring to.	Corrected
Page 62, under ERG conclusion, row 8: Currently states "…except for IMDC risk category at the January 2019 data-cut."	Proposed revision to the existing text as follows: "…except for IMDC risk category '**favourable'** at the January 2019 data-cut."	Within the same section 3.3.4, the ERG noted a difference in the January 2019 data-cut for the 'favourable' IMDC risk category only. This should be reflected in the ERG conclusion, since the intermediate/poor risk category provided similar results to those at IA.1	Corrected

Issue 10 3.3.5.1 Progression free survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63, row 5: Currently states "Results using the January 2019 KEYNOTE-426 data-cut show [redacted] results"	Proposed revision to the existing text as follows: "Results using the January 2019 KEYNOTE-426 data-cut show [redacted] results"	The January 2019 data-cut results will not be published and therefore they should be marked as commercial in confidence	Corrected
Page 64, row 5: Currently states: "[redacted] were obtained when using the	Proposed revision to the existing text as follows:		Corrected

January 2019 data cut."	"[redacted] were obtained when using the January 2019 data cut."		

Issue 11 3.3.5.2 Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65, row 5: Currently states "[redacted] were obtained when using the January 2019 data cut"	Proposed revision to the existing text as follows: "[redacted] were obtained when using the January 2019 data cut"	The January 2019 data-cut results will not be published and therefore they should be marked as commercial in confidence	Corrected
Page 66, row 3: Currently states "[redacted] were obtained when using the January 2019 data cut from KEYNOTE-426."	Proposed revision to the existing text as follows: "[redacted] were obtained when using the January 2019 data cut from KEYNOTE-426."		Corrected

Issue 12 3.3.6.4 Safety overview

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, row 5: Currently states that "The CS also states that the safety profile of pembrolizumab plus axitinib is consistent with the safety profile of axitinib monotherapy"	Proposed revision to the existing text as follows: "The CS also states that the safety profile of pembrolizumab plus axitinib is **generally consistent with the established safety profile of pembrolizumab monotherapy in solid tumours and the observed safety profile for** axitinib monotherapy"	The CS clearly states that the overall safety profile of the combination therapy of pembrolizumab + axitinib is consistent to the safety profile observed when using the single agents. This should be reflected in the text.	Amended

Issue 13 4.3 Clarification of comparator wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75, paragraph 2, row 5: Currently states: "Nivolumab plus ipilimumab is not listed as a comparator in the CS but nivolumab is featured as a second line treatment"	Proposed revision to the existing text as follows "Nivolumab plus ipilimumab is not listed as a comparator in the CS **in line with the draft scope** but nivolumab **monotherapy** is featured as a second line treatment"	For clarification between first- and second-line therapies.	Not factual inaccuracy, no change made.

Issue 14 4.3.2 Comparison in intermediate/poor subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 77, final paragraph row 3: Currently states: "For the subgroup population of intermediate / poor RCC risk, pembrolizumab plus axitinib is compared to cabozantinib using effect estimate from the company's NMA, as no head-to-head comparison was available."	Proposed revision to the existing text as follows: "For the subgroup population of intermediate / poor RCC risk, pembrolizumab plus axitinib is compared **to sunitinib, pazopanib and tivozanib using survival data from the KEYNOTE-426 trial and is compared to** cabozantinib using effect estimate from the company's NMA, as no head-to-head comparison was available."	The comparison in the intermediate / poor subgroup is versus sunitinib, pazopanib, tivozanib and cabozantinib; MSD request that the text in the ERG report should be changed to reflect this.	Amended
Page 79, final paragraph: Currently states: "The economic model compares the cost effectiveness of pembrolizumab plus axitinib versus sunitinib, pazopanib, and tivozanib for the overall patient population, and compares against cabozantinib for	Proposed revision to the existing text as follows: "The economic model compares the cost effectiveness of pembrolizumab plus axitinib versus sunitinib, pazopanib, and tivozanib for the overall patient population, and compares against **sunitinib, pazopanib, tivozanib and** cabozantinib for the intermediate / poor RCC		Amended

the intermediate / poor RCC risk group."	risk group."		
Page 85, final paragraph: Currently states: "The company compares pembrolizumab plus axitinib versus sunitinib and cabozantinib for patients with intermediate or poor risk status."	Proposed revision to the existing text as follows: "The company compares pembrolizumab plus axitinib versus sunitinib**, pazopanib, tivozanib** and cabozantinib for patients with intermediate or poor risk status."		Amended

Issue 15 4.3.5.1 Use of COMPARZ trial for comparison versus Real World expectations for OS and PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81, final paragraph: "The ERG compares the long-term OS predictions of sunitinib using the exponential, Weibull and Log-logistic with the trial with the longest follow-up, i.e. the COMPARZ trial (**Error! Reference source not found.**)."	Proposed revision to existing text as follows: "The ERG compares the long-term OS predictions of sunitinib using the exponential, Weibull and Log-logistic with the trial with the longest follow-up, i.e. the COMPARZ trial (**Error! Reference source not found.**). **It should be noted that the COMPARZ trial was conducted before nivolumab monotherapy became established therapy in the second line of treatment. Hence 0% of patients received subsequent therapy with nivolumab monotherapy and, as such, it is expected that OS and PFS estimates from the COMPARZ trial are likely to be underestimated vs current UK clinical practice."**	As the ERG state, the COMPARZ trial does have the longest follow-up and should be used to compare versus model estimates for OS and PFS. However, the COMPARZ trial was conducted before nivolumab monotherapy had become established therapy in the subsequent line, hence MSD suggest that this should be reflected within the text.	Thank you for this observation. We still consider that the Weibull provides the best fit to the COMPARZ trial. Other distributions have been used in scenarios.

Issue 16 4.3.5.1 Justification of OS curve selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83, paragraph 1, row 2: Currently states "The company's justification is that the mode of action of combination of immunotherapy with a TKI is not comparable to the mode of action associated with TKI monotherapy."	Proposed revision to existing text as follows: "The company's justification is that the mode of action of combination of immunotherapy with a TKI is not comparable to the mode of action associated with TKI monotherapy. **The company further justified their choice of OS curve by statistical and visual fit, clinical plausibility based on expert opinion and also cross-validation with different modelling approaches (scenario analysis 1 and 3 in the CS). Scenario 1 investigated the use of the landmark modelling technique (see CS Appendix P) and Scenario 3 used the NMA results to estimate the Sunitinib curve. Both scenario analyses produce similar results to that of the base case, hence adding to the internal validity of the selected method.**"	The ERG report does not fully reflect the justifications used for the selection of separate distributions for each arm in relation to overall survival as presented in the company submission.	We have reported on the company's choice of OS based on statistical and visual fit and clinical plausibility. Cross validation with different modelling approaches has not been discussed in this section of the CS.
Page 107, Table 44, column 2 (relating to OS): Currently states: "Weibull provides best visual fit to data."	Please remove the statement	The Weibull curve is the worst fitting curve to the sunitinib KM data and is not the best or second-best fitting curve to the pembrolizumab/axitinib KM data in terms of AIC/BIC criteria. Furthermore, the curves fit the data poorly by visual inspection for both arms. Therefore, MSD considers this statement to be incorrect and suggest it should be removed.	Not a factual inaccuracy. It is the ERG's view that the Weibull provides the best visual fit to the sunitinib data. This is explained in section 4.3.5.1 of the ERG report. Other distributions have been used in scenario analyses.

Issue 17 4.3.5.1 Reference to immunotherapeutic effect modelled in TA581

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83, paragraph 2, row 4: Currently states: "Finally, the ERG notes that the NICE appraisal committee did not consider that the modelling of the immunotherapeutic effect was substantiated by evidence in TA581[41] for nivolumab plus ipilimumab and that it could not generalise the size of this effect from one cancer to another. It concluded "that there was no robust evidence on the size of the association between a clinically meaningful definition of response and long-term survival for nivolumab and ipilimumab"' The ERG considers the committee's decision is relevant to this current appraisal."	Please remove the statement	MSD feels the statement is not relevant as the method of modelling the immunotherapeutic effect in TA581 was based on manually imputed association between durable response and overall survival. No formal immunotherapeutic effect has been modelled within the economic model for this submission and no justification of model selection is attributed to methods used within TA581, hence MSD deems the statement to be irrelevant and suggest it should be removed.	Not a factual inaccuracy. The ERG included this statement to give context for the modelling of immunotherapies in RCC.

Issue 18 4.3.10.1 MSD response to clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104, paragraph 1, row 6: Currently states: "We felt that these additional analyses by the company are incomplete as some of them do not address the	Please remove this statement	MSD considers that the clarification question B13 was unclear; therefore, we attempted to use the opportunity at the clarification questions teleconference (arranged by NICE) to try to gain further clarity	Not a factual inaccuracy. It is unfortunate the company misinterpreted our clarification question. A senior member of the ERG team explained this

questions raised by the ERG. For instance, the ERG requested a scenario analyses for PFS, OS and time on treatment where the same parametric distributions are used for each treatment arm (clarification question B13). However, the company's response does not answer this question."		on what precisely was required. However, the relevant ERG member who authored this question was not present at the call; therefore, the uncertainty surrounding clarification question B13 remained unresolved. In our response to clarification question B13, MSD presented all clinically plausible distributions using the same curve selection for each treatment arm (within outcome). MSD feels the current wording in the ERG report does not fairly reflect our effort to gain clarity and subsequently answer all clarification questions. Furthermore, the request of question B13 did not require any changes to the submitted cost-effectiveness model; hence the ERG had the capability to perform the analysis.	analysis at the clarification questions teleconference on behalf of the team member who authored the question.

Issue 19 4.4 ToT curve selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107, Table 44 column 4 (relating to Time on Treatment): Currently states: "Should use same distribution for all treatments. Weibull provides best visual fit to data."	Please remove the first sentence	Previous TA's have modelled ToT using different distributions for each therapy and were subsequently accepted by the corresponding ERG[1,2]. Hence MSD believes that the precedent set does not dictate that the same curves necessarily need to be selected to model ToT.	Not a factual inaccuracy. See comment on p82 regarding the use of the same distribution for all treatments as stated in TSD 14.

Issue 20 4.4 Comparison vs cabozantinib used as the base case for Scenario Analyses in the intermediate/poor subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 111, Table 51: The table title is currently stated as "Table 51 Scenario analyses for pembrolizumab + axitinib versus cabozantinib in the intermediate / poor risk population"	Proposed revision to the existing text as follows "Table 51 Scenario analyses for pembrolizumab + axitinib versus **sunitinib** in the intermediate / poor risk population" (Please note this would require the re-running of all analyses in Table 51)	Table 51 in the ERG report presents the scenario analyses in the intermediate / poor subgroup using the comparison versus cabozantinib as the base case. MSD consider the appropriate comparison should be against sunitinib as the base case, as this is the trial comparator and produces the most reliable analysis. This requires the analyses to be re-run versus sunitinib.	We have compared pembrolizumab plus axitinib with cabozantinib as this is the most relevant comparator for this subgroup. No change necessary.
Page 111, Table 51, rows 6 & 7: scenario analyses is currently presented investigating the sensitivity of the ICER to changes	Please remove these analyses	As stated in section 4.3.7.2 of the ERG report, "For the subgroup analysis, for the intermediate/poor risk group... For cabozantinib, the proportion of patients remaining on	Not a factual inaccuracy. The scenario analyses are shown to illustrate the change

in PFS and ToT curve selection		treatment was based on the modelled PFS curve for this treatment arm." Hence MSD consider it inappropriate to present scenario analyses where the choice of PFS and ToT curve selected is altered without giving the reader a full understanding of the impact of the ICER resulting from both a change in PFS but also the associated change in ToT, or similarly the fact that changing ToT curve selection does not impact both intervention and comparator. Therefore, MSD considers it most appropriate to remove these analyses from the table, for the comparison versus cabozantinib.	in ICER with different assumptions.

Issue 21 5 End of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 112, paragraph 1: Currently states: "However, the ERG notes that cabozantinib is the current NICE-recommended treatment in poor (and intermediate) risk patients, based on NICE TA542[24]."	Proposed revision to the existing text as follows: "However, the ERG notes that **sunitinib, pazopanib, tivozanib and** cabozantinib **are** the current NICE-recommended treatment **options** in poor (and intermediate) risk patients, based on NICE **TA169, TA215, TA512 and** TA542[24]."	NICE have recommended multiple therapies as treatment options for advanced RCC covering an all-comer population and restricted intermediate/poor risk group population. MSD suggest that the text in the ERG report should be amended to reflect this.	We have reworded to say the following: "However, the ERG notes that cabozantinib is specifically recommended by NICE in poor (and intermediate) risk patients, based on NICE

			TA542[24] “
Page 113, Table 52 column 3: Currently states: “However, cabozantinib is not included in this study, which is the NICE recommended treatment for patients at intermediate / poor risk.”	Proposed revision to the existing text as follows: “However, cabozantinib is not included in this study, which is **one of** the NICE recommended treatment **options** for patients at intermediate / poor risk.”		Amended
Page 114, paragraph 1 row 5: Currently states: “based on cabozantinib being the NICE recommended standard of care”	Proposed revision to the existing text as follows: “based on **sunitinib, pazopanib, tivozanib and** cabozantinib being the NICE recommended **treatment options**.”		We have amended to say: The ERG disagrees with the company that pembrolizumab plus axitinib meets the first end of life criterion in the poor RCC risk subgroup, based on cabozantinib being specifically recommended by NICE in this subgroup.
Page 113, Table 52 column 3: Currently states: “The median OS of 30.3 months for intermediate / poor risk patients in the CABOSUN trial”	Proposed revision to the existing text as follows: “The median OS of 30.3 months for intermediate / poor risk patients in the CABOSUN trial **(please note that this patient population has a more favourable prognosis in comparison to a solely poor risk patient population)**”	MSD suggest that the proposed revision gives a better reflection of the life expectancy of patients with advanced RCC who have a poor risk score.	Not a factual error. No change made.

Issue 22 6 Innovation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115, paragraph 1, row 6:: Currently states: "The ERG clinical advisors agree there does remain an element of unmet need and that the rationale for the combination in RCC is made, however there are other potential treatments that should be considered in relation to pembrolizumab and axitinib (e.g. avelumab plus axitinib – currently the subject of a separate NICE technology appraisal).[73, 74] "	Please remove the second half of the sentence in the current text, so that this section reads as follows: "The ERG clinical advisors agree there does remain an element of unmet need and that the rationale for the combination in RCC is made."	The ongoing appraisal of avelumab in combination with axitinib is outside the scope of this appraisal; it is therefore not relevant nor requires consideration within the context of this appraisal.	Not a factual error, no change made.

Issue 23 7.2 Incorrect reporting of list price ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 116, paragraph 1, row 6: Currently states: "In the company's analysis, pazopanib and tivozanib were slightly more expensive than sunitinib and when compared with pembrolizumab plus axitinib, there was an ICER of £73,245 and £71,175 per QALY gained for tivozanib and pazopanib."	Proposed revision to the existing text as follows: "In the company's analysis, pazopanib and tivozanib were slightly more expensive than sunitinib and when compared with pembrolizumab plus axitinib, there was **ICER of £57,540 and £56,648 per QALY** gained for tivozanib and pazopanib."	Incorrect reporting of ICER values	Corrected

Issue 24 7.2 Incorrect ICER vs reported therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117, paragraph 3: Currently states: "The ERG-preferred analyses gave higher ICER estimates: … £48,424 per QALY for pembrolizumab plus axitinib compared with sunitinib in intermediate / poor risk subgroup."	Please either report an ICER value of £140,481 or change "sunitinib" to "cabozantinib"	Incorrect ICER value or therapy comparison.	ERG agrees this has been incorrectly reported versus sunitinib and should be versus cabozantinib. ERG response: Change values in text

References

1 NICE, NICE TA557 - Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer. Published January 2019.
Accessed via https://www.nice.org.uk/guidance/ta557/documents/committee-papers

2 NICE, NICE TA519 - Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. Published April 2018.
Accessed via https://www.nice.org.uk/guidance/ta519/documents/committee-papers

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Technical engagement response form

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma ID1426

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Tuesday 10 December 2019**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
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information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Merck Sharp & Dohme**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Extrapolation of overall survival	
What proportion of patients in the pembrolizumab with axitinib arm would you expect to be alive at 5 and 10 years?	***MSD considers a 5-year Overall Survival rate of 50% to be entirely plausible, and the estimation at 5 years made by the Technical Team to be implausibly low.*** MSD's clinical experts suggested that 50% of patients alive at 5 years would be a plausible expectation when treated with pembrolizumab in combination with axitinib. One of the ERG clinical experts suggested that this may be optimistic, however the ERG did not propose any expected overall survival values for pembrolizumab in combination with axitinib. Within the draft Technical Report, the Technical Team consulted a clinical expert who estimated 30% survival at 5 years, plateauing at 25% survival for both 10 and 20 years. MSD considers the estimation at 5 years made by the Technical Team to be implausibly low for the following reasons: • Within the appraisal of TA581 (nivolumab in combination with ipilimumab for untreated advanced renal cell carcinoma) [1], the Committee considered a 5-year overall survival of 43.6% when patients were treated with nivolumab with ipilimumab as clinically plausible; please note that the patient population covered in TA581 had a worse prognosis (intermediate/poor-risk patients only) than those included in our submission, and therefore a higher overall survival rate would be

	expected when treated with pembrolizumab in combination with axitinib in an all-comer population. • The data from KEYNOTE-426 would not suggest such a low overall survival rate at 5 years, considering 89.9% of patients are still alive at 1 year. Therefore, MSD consider a 5-year overall survival rate of 50% to be entirely plausible, and although there is also uncertainty around 10-year survival, MSD agree with the technical team's clinical experts' estimation of a survival plateau*.*
What proportion of patients in the sunitinib arm would you expect to be alive at 5 and 10 years?	***Clinical expert opinion estimates 5- and 10-year survival between 20-25% and 10-15%, respectively.*** MSD's clinical experts suggested that first-line treatment using sunitinib is associated with 5- and 10-year survival between 20-25% and 10-15%, respectively. Neither the ERG nor the Technical Team reported estimations from clinical experts on long-term survival expectations for patients treated with sunitinib. MSD recognises this also as an area of uncertainty within this appraisal, due to the changing landscape of RCC treatment within UK clinical practice. Although the COMPARZ trial has the longest follow-up data

	available, MSD consider this a poor reference point for establishing long-term overall survival expectations in UK clinical practice. This is due to the following: • Subsequent therapy usage within the COMPARZ trial does not accurately reflect that of current UK clinical practice [2]; only 1% of patients who received sunitinib in COMPARZ received subsequent therapy with nivolumab, relative to the 30% expected in clinical practice [3]. • 4-year overall survival data is available from CHECKMATE-025, showing 30.0% of patients treated with nivolumab in the second-line are alive at 4 years [4]. • Longer term follow-up data is available from CHECKMATE-214 [5], which although does not yet have 5 years' worth of follow-up, does show that the sunitinib arm reached median overall survival at 37.9 months in the ITT population. MSD sees no reason to disregard the suggestion by our clinical experts of 5- and 10-year survival between 20-25% and 10-15%, respectively, when treated with sunitinib. However, due to the changing landscape of RCC treatment in the UK, it is plausible these estimates understate actual long-term overall survival**.**
Is there sufficient clinical and/or methodological justification to use different distributions to extrapolate overall survival (OS) for pembrolizumab with axitinib, and the comparator sunitinib? a) If there is sufficient justification to use different distributions to extrapolate OS, which distribution (log-logistic, exponential or Weibull) is most appropriate to use to model pembrolizumab with axitinib, and the comparator sunitinib?	***MSD believes there is sufficient clinical and methodological justification to use different distributions to extrapolate overall survival for pembrolizumab, and the comparator sunitinib. We consider the most appropriate distributions to use are log-logistic (for pembrolizumab in combination with axitinib) and exponential (for the comparator sunitinib. We do not consider the Weibull distribution to be appropriate to model both pembrolizumab with axitinib, and the comparator sunitinib.*** Our rationale for the above position is evidence-based; clinical literature confirms that the mechanism of action of combination therapy with an Immune checkpoint inhibitor (ICI) and a tyrosine-kinase inhibitor (TKI) is substantially different than that of TKI monotherapy. Mollica et al (2019) state that the treatment paradigm for metastatic RCC is entering its third revolution; the first being the introduction of the anti-

b) If there is not sufficient justification to use different distributions to extrapolate OS, is the Weibull distribution the most appropriate distribution to model both pembrolizumab with axitinib, and the comparator sunitinib?	angiogenic targeted therapies with TKI's targeting vascular endothelial growth factor (VEGF), the second consisting of immunotherapy's like ICI's, and the third being the ICI and TKI combination [6]. VEGF inhibitors represented a step change in the treatment of mRCC as described by Mantia et al. (2019) [7]. This is because the development of new blood vessels (angiogenesis) is essential for tumour growth, and RCC is known to be a highly vascular tumour; therefore many strategies aim to inhibit angiogenesis. In RCC, the von Hippel-Lindau (VHL) tumour suppressor gene is frequently mutated [7]. VHL is involved in the pathway that leads to the degradation of hypoxia-inducible factor (HIF). When VHL is mutated, HIF is not degraded and leads to the transcription of many genes, including vascular endothelial growth factor (VEGF), which induces angiogenesis [7]. Over the past decade, treatment of mRCC has focused on inhibiting the VEGF pathway with targeted agents, including tyrosine kinase inhibitors (TKIs), which block VEGF receptors and other receptors involved in angiogenesis, as well as an anti-VEGF monoclonal antibody [7]. However, although the development of VEGF inhibitors has transformed the treatment paradigm in mRCC, and VEGF inhibitors can be used in sequence, the majority of patients need to continue with ongoing therapy and durable responses are very rare [7]. Clinical evidence suggests that resistance to VEGF blockade develops because of changes in the microenvironment which allow the resumption of angiogenesis. This resistance to antiangiogenic agents often occurs after a median of 6 to 15 months [7, 8]. The third revolution of mRCC treatment, as described by Mollica et al (2019) [6], has aimed to curb the resistance by combining VEGF inhibition with ICIs. In addition to stimulating angiogenesis, preliminary data suggest that VEGF may contribute to cancer immune evasion [7]. In the setting of high expression of VEGF, fewer and less differentiated antigen-presenting dendritic cells are found in tumour tissue, and more immunosuppressive myeloid cells are seen in the peripheral blood. Please note the median duration of response in KENYOTE-426 was 15.2 months in patients treated with sunitinib, whereas the median was not reached when treated with pembrolizumab in combination with axitinib [9]. The plethora of evidence presented strongly points towards a different mechanism of action between the ICI-TKI combination therapy, and the TKI monotherapy. TSD 14 states clearly that "*fitting different types of*

	parametric model… to different treatment arms would require substantial justification, as different models allow very different shaped distributions" [10]. MSD believes it is clear from the evidence presented within KEYNOTE-426, alongside the explanation of the different mechanisms of action, that it is fully justifiable to select different parametric distributions to each arm. Furthermore, MSD consider that no selection of individual curves applied to each arm simultaneously produces robust estimates of long-term overall survival for both arms. a) MSD considers that our base case assumptions (using the log-logistic to model overall survival for pembrolizumab in combination with axitinib and the exponential to model overall survival for sunitinib) are the most plausible distributions for each arm. The rationale for this is as follows: *Pembrolizumab in combination with axitinib modelled using the log-logistic:* • The log-logistic provides good visual and statistical fit to the observed data • Clinical experts have suggested that 5-year overall survival for pembrolizumab in combination with axitinib will equal ~50%, whilst also predicting a long-term survival benefit for a proportion of patients. The log-logistic curve correlates with both of these expectations by clinical experts. o Scenario analyses 1 and 3 validate the base case assumptions. Scenario 1 used a landmark analysis approach, whereas scenario 3 used a log-logistic extrapolation for pembrolizumab in combination with axitinib and the time-constant hazard ratio derived from the NMA for sunitinib. Please see Table 1 below for estimated long-term overall survival values for both arms; using alternative approaches, the predicted values are closely replicated, further validating the base-case.

Table 1. Overall survival estimates using alternative approaches

Years	Base Case		Scenario 1: Landmark		Scenario 3: L-L, NMA		Weibull curve	
	P+A	S	P+A	S	P+A	S	P+A	S
1	88.5%	79.9%	88.0%	79.8%	88.5%	79.6%	88.6%	80.1%
2	76.8%	63.9%	78.0%	64.7%	76.8%	60.9%	76.2%	62.6%
5	51.9%	32.5%	57.9%	37.3%	51.9%	29.1%	44.9%	28.2%
10	31.6%	10.6%	37.2%	16.2%	31.6%	11.5%	16.5%	6.9%
20	16.5%	1.1%	15.6%	3.1%	16.5%	3.4%	1.7%	0.3%

Sunitinib modelled using the exponential:

- The exponential provides good visual and statistical fit to the observed data; it is the best fitting statistically compared to the other curves considered plausible
- Clinical experts have suggested 5- and 10-year overall survival between 20-25% and 10-15%, respectively. Although the exponential curve predicts slightly higher values at 5 years, the values produced for 10 years are within the range predicted by clinical experts. Please see Table 1 above for verification. Please also note, due to the changing RCC landscape, long-term overall survival when treated with first-line sunitinib is uncertain; therefore, it is plausible that long-term estimates may be higher in clinical practice, hence why the exponential curve was selected over the Weibull.
- Please see Table 1 which shows how the long-term overall survival estimates are closely replicated between the base case, scenario 1 and scenario 3 approaches.

b) MSD considers the Weibull curve to be an inappropriate choice of overall survival curve for both pembrolizumab in combination with axitinib and sunitinib. The rationale for this is as follows:

- Clinical expert opinion has suggested that 5-year overall survival estimates of 50% to be plausible for patients treated with pembrolizumab in combination with axitinib, as well as expecting a survival plateau. The Weibull distribution underestimates long-term overall

	survival estimates for patients treated with pembrolizumab in combination with axitinib, as reflected in Table 1; this shows a clear underestimation in the 5-year overall survival rate for pembrolizumab in combination with axitinib when applying a Weibull distribution. Furthermore, in a direct contradiction to clinical expert opinion which supports a survival plateau for patients treated with pembrolizumab in combination with axitinib, the Weibull curve (in this instance) has a monotonically increasing hazard rate over time, which results in a huge underestimation of the long-term overall survival benefits when treated with pembrolizumab in combination with axitinib. • The Weibull distribution also underestimates long-term overall survival estimates for patients treated with sunitinib, although there is little difference between the long-term overall survival estimates for sunitinib between the exponential and Weibull distributions. Due to the expanded subsequent treatment landscape in RCC, MSD believes that the Weibull distribution underestimates true long-term overall survival when treated with sunitinib. Latest CHECKMATE-214 data report a median overall survival of 37.9 months in the ITT population [5]. The Weibull distribution predicts a much shorter median of 34.2 months, whereas the exponential distribution predicts median overall survival to be 36.7 months. • The ERG preference is to use the trial with the longest-follow up (COMPARZ [2]) to compare overall survival predictions with each distribution, which is also reflected in the draft Technical Report, stating: "*From inspection of the extrapolated survival curves against the trial with the longest follow-up (i.e. the COMPARZ trial) and consideration of clinical expert opinion, the log-logistic, exponential and Weibull functions appear to all produce optimistic extrapolations.*" The Technical report ultimately concludes that the Weibull distribution is the most appropriate for extrapolation. This approach is flawed, as only 1% of patients treated with sunitinib within this trial receive nivolumab in the subsequent line, which is not reflective of nivolumab treatment as subsequent line therapy in UK clinical practice. • The draft Technical Report states, "*The ERG also noted in TA581 (for nivolumab with ipilimumab) that the committee did not consider the modelling of the immunotherapeutic*

	effect to be substantiated by evidence, and that it could not generalise the size of this effect from one cancer to another." It should be noted that this statement is not relevant to this appraisal. This is due to the method of modelling the immunotherapeutic effect in TA581 being based on a manually imputed association between durable response and overall survival. No formal immunotherapeutic effect has been modelled within the economic model for this submission and no justification of model selection is attributed to methods used within TA581 [1]. • The draft Technical Report states, "*However, both the Weibull and exponential appear to have good fit to the KEYNOTE-426 trial data on inspection of the curves*". It should be noted that the Weibull distribution is the worst fitting curve to the sunitinib Kaplan Meier (KM) data and is not the best nor second-best fitting curve to the pembrolizumab/axitinib KM data in terms of AIC/BIC criteria. Furthermore, the Weibull distribution is a poor fit to the data in both arms, based on visual inspection. As such, there is no reasonable justification to dismiss the plausibility of using the log-logistic distribution to model pembrolizumab in combination with axitinib, as presented in our base case. Based on the above presented rationale, MSD believe that the Weibull distribution is inappropriate to model overall survival for both pembrolizumab in combination with axitinib, and sunitinib. In the event that the Committee are unable to accept the use of separate distributions to each arm, MSD would urge the Committee to give further consideration to Scenario analysis 1 which has investigated the use of a different modelling approach, as described in Appendix P of the company submission.

Issue 2: Treatment waning effect after discontinuation	
In clinical practice, would a reduction in treatment effect be observed after treatment with pembrolizumab has been stopped? If so, at what time point?	***MSD believes that a lifetime treatment effect is the most appropriate duration of treatment effect for patients treated with pembrolizumab in combination with axitinib*** The rational for our above position is outlined below*:* • All clinical expert opinion suggests a lifetime treatment effect is plausible: o MSD's clinical expert suggested a continued treatment effect would be seen due to pembrolizumab sufficiently boosting the immune system, alongside the fact that axitinib as monotherapy is maintained post-discontinuation of pembrolizumab. o The ERG report did not mention consulting clinical opinion around this issue, however the technical team's clinical expert's opinion, as written in the draft Technical Report, states, "a ***clinical expert*** *for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years.*" This statement directly implies a continued treatment benefit with pembrolizumab in combination with axitinib, as the statement reflects an expectation that a considerable proportion of patients would remain alive at both 10 and 20 years. The draft Technical Report also states, "***Two clinical experts*** *have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect.*" This statement is again supportive of our view that there will be no loss of treatment effect post discontinuation with pembrolizumab after 2 years, and a lifetime treatment effect is most plausible. o The two nominated clinical experts for this appraisal, Dr Tom Waddell and Dr Balaji Venugopal, participated in the Technical Engagement teleconference for this appraisal. During the call, both clinicians articulated their view that a lifetime treatment effect is

	considered entirely plausible by the clinical community, regardless of pembrolizumab treatment ceasing at 2 years. • Furthermore, from a biochemical point of view, the mechanism of action of PD-1 inhibitors like pembrolizumab enable cytotoxic CD8+ T-cells avoid an exhausted state, thereby allowing them to keep the disease in a state of cancer-immune equilibrium, which can potentially be maintained for up to several decades even in the absence of continued therapy: o Cytotoxic CD8+ T-cells (CTLs) are considered to be one of the main effector cell types of the adaptive immune system responsible for combating cancer cells. Functional tumour-reactive T-cells are able to proliferate, produce effector cytokines, and differentiate into memory T-cells that can successfully keep tumours dormant/subclinical for long periods of time, without eradicating the malignant cells completely, in a state termed cancer-immune equilibrium which can potentially be maintained for prolonged periods of time, possibly up to several decades[11] [12]. o When effector CTLs enter the tumour microenvironment they encounter a complicated network of cells and cytokines including chronic antigen encounter from the tumour which can induce them to enter an "exhausted state" state in which T-cell effector functions and differentiation into memory T-cells are impaired [13]. PD-L1 is one of the major factors in the tumour microenvironment because of its high expression in many cancer tissues and its capability to down-regulate and induce apoptosis in CTLs, the typical sign of T cell exhaustion is expression of the inhibitory receptor PD-1 and so the PD-1/PD-L1 pathway is a central regulator of T-cell exhaustion[13]. o Blockade of the PD-1:PD-L1 pathway can "reinvigorate" exhausted CTLs, restoring effector functions, increasing cell numbers, and generation of functional memory T-cells that can provide an ongoing anti-tumour effect for months to years, even in the absence of continued therapy[14, 15]. • Although pembrolizumab therapy ceases after 2 years from the start of treatment, patients are expected to continue treatment with axitinib monotherapy beyond 2 years, and it is expected that patients will continue to derive benefit from this treatment. • The draft Technical Report accurately details the treatment waning effect imposed in appraisals of previous pembrolizumab indications (TA428, TA519 and TA600) as well as other IO, non-pembrolizumab, appraisals (TA578 and TA520). However, MSD consider these to be of no relevance in the context of this appraisal and see no rationale for maintaining consistency with

<table>
<tr><td></td><td>approaches adopted in appraisals concerning completely different indications. Instead, we would argue that a greater focus should be placed with maintaining consistency with precedent set in previous appraisals of IO therapies in renal cell carcinoma; specifically, in the appraisals of nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA581) and nivolumab for previously treated advanced renal cell carcinoma (TA417), there was no treatment waning effect imposed on the intervention. As such, MSD would urge the Committee to adopt a consistent approach in this appraisal.</td></tr>
<tr><td>What is the most appropriate duration to apply a treatment effect for people treated with pembrolizumab with axitinib?</td><td>

As stated above, MSD considers that a lifelong duration of treatment effect is most appropriate.

Within the draft Technical Report, the technical team requested analyses exploring a duration treatment effect of 2 and 3 years, from the start of treatment. MSD is very willing to present analyses when requested in order to reduce uncertainty and aid decision making; however, in this case, MSD consider the above-mentioned request would serve neither of these purposes. Furthermore, we do not consider this request to be appropriate, given there is no clinical support for such a limited duration of treatment effect (as indicated by each argument above). This is further supported by the clinically implausible long-term survival estimates when implementing a 2- or 3-year treatment effect cap, as shown in Table 2 below.

Table 2. Overall survival estimates implementing clinically implausible treatment waning assumption

Years	Base Case		2 year treatment waning, MSD base-case curve selection		3 year treatment waning, MSD base-case curve selection		2 year treatment waning, ERG base-case curve selection		3 year treatment waning, ERG base-case curve selection	
	P+A	S	P+A	S	P+A	S	P+A	S	P+A	S
1	88.5%	79.9%	88.5%	79.9%	88.5%	79.9%	88.6%	80.1%	88.6%	80.1%
2	76.8%	63.9%	76.7%	63.9%	76.8%	63.9%	76.0%	62.6%	76.2%	62.6%
5	51.9%	32.5%	39.0%	32.5%	42.6%	32.5%	34.2%	28.2%	37.6%	28.2%
10	31.6%	10.6%	12.7%	10.6%	13.8%	10.6%	8.3%	6.9%	9.2%	6.9%
20	16.5%	1.1%	1.3%	1.1%	1.5%	1.1%	0.4%	0.3%	0.5%	0.3%

The results shown above substantiate MSD's opinion that the implementation of a treatment waning effect at 2 or 3 years produces clinically meaningless results, showing minimal survival benefit when treated with pembrolizumab in combination with axitinib versus sunitinib.

Therefore, it is only reasonable that a lifetime treatment effect is considered plausible.

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Issue 3: Time horizon	
Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice in untreated metastatic renal cancer to materialise?	***MSD considers that, as per the CS base case, a time horizon of 40 years is necessary to ensure all differences in benefits and costs arising as a consequence of treatment are captured.*** The rational for our above position is as follows: • The MSD base-case used a 40-year time horizon to maintain consistency with TA581, where a 40-year time horizon was implemented. Within the MSD base-case, 16.5% of patients in the pembrolizumab in combination with axitinib arm and 1.1% of patients in the sunitinib arm are still alive at 20 years after the start of the model. MSD consider it irresponsible to not consider treatment benefits and costs after 20 years when it is plausible that a significant proportion of patients are still alive at 20 years. • The draft Technical Report states, "***The ERG*** *employs a 20-year time horizon in the ERG base case analysis*". This statement is factually incorrect; the ERG base case used a **40-year time horizon**, with scenario analyses conducted investigating the impact of a shorter time horizon. MSD do not understand the rationale of the NICE Technical Team to deviate from the MSD and ERG base case of a 40-year time horizon. • The draft Technical Report states, "*One clinical expert has estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years for people treated with pembrolizumab with axitinib. This could suggest a time horizon beyond 20 years is appropriate.*" MSD agrees with this statement and considers that if clinical opinion suggests patients would still be alive beyond 20 years from the start of treatment, then there is no rationale for shortening the time horizon to 20 years. MSD believes this issue should be resolved before the Committee Meeting; therefore we urge the NICE Technical Team to revise their preliminary judgement to a 40-year time horizon, in line with the MSD and ERG base case, TA581, and overwhelming clinical opinion**.**

Issue 4: Subsequent treatment after first line treatment has stopped	
In clinical practice, what proportion of people would be expected to have subsequent treatment(s), following first line treatment with pembrolizumab with axitinib, and sunitinib respectively?	***Trial-based distribution of subsequent therapies, to model the cost of subsequent therapy, should still be considered as a relevant scenario.*** As per MSD's base case, 50% of patients who are treated with either pembrolizumab in combination with axitinib or sunitinib are expected to receive subsequent therapy. This was verified by a statement made by Peter Clarke (NHS England Chemotherapy Lead and Clinical Lead for the CDF) within TA581; he stated that he expected 50% of patients treated with immunotherapy (in this case nivolumab/ipilimumab) and TKI therapy to receive subsequent therapy***.*** Furthermore, in KEYNOTE-426, [redacted] and [redacted] of patients treated with pembrolizumab in combination with axitinib and sunitinib, respectively, received active treatment post first-line discontinuation, at the time of the first interim analysis of the study (IA1). There are concerns that by using a real-world distribution of therapy, the efficacy patients derived from treatments received within clinical trials are not accurately modelled. Therefore, it is important to keep in mind the impact of scenario analysis 12 within the company submission, which uses the trial-based distribution of subsequent therapies to model the cost of subsequent therapy.
Which subsequent treatment(s) would be used and in what proportions?	***MSD considers the approach used by the ERG in its' base-case, regarding subsequent therapy distribution, to be reasonable. However, as mentioned above, MSD considers it important to bear in mind scenario analyses considering the trial-based distribution of subsequent therapies, as this better reflects efficacy derived from subsequent therapy within KEYNOTE-426.***
Are there any treatments that are used subsequently to pembrolizumab with axitinib, and/or sunitinib that are of particular note in regard to their treatment related adverse event (TRAE) profile (in particular in terms of the	***MSD considers this question best placed for clinical expert opinion.***

TRAE's expected frequency, cost and impact on health related quality of life)?	
Issue 5: Health related quality of life (HRQoL)	
Is using age-related disutility appropriate within the economic model?	***MSD deems it plausible to remove age-adjusted utility from the base-case assumption.*** MSD considers the ERG approach to be reasonable. MSD's response to question B11 of the clarification questions shows no correlation between age and baseline utility assessment; therefore MSD deems it plausible to remove age-adjusted utility from the base-case assumption.
Is using a time to death approach to estimation of utility for use within the economic model appropriate?	***Both MSD and the ERG use the time-to-death approach to estimate utilities.*** As stated in the company submission, the time-to-death approach is frequently used in the estimation of HRQoL for patients with late stage cancer, as it reflects the known decline in cancer patients' quality of life as patients get closer to death. Furthermore, the health-state based approach has severe limitations considering only one EQ-5D questionnaire was administered per patient, 30 days after disease progression. Therefore, there is limited post-progression data available. The ERG cites the paper by Hatswell et al to justify its' selection of time-to-death utilities within the ERG base case [16]. The ERG reports Hatswell et al noted that disease progression may not fully capture all predictive factors of patient utility, and time-to-death provide a good fit to patient data [16]. The Technical Team also considers the time-to-death approach to be appropriate; however, they have concerns due to there being no change in HRQoL when patients are ≥360 days from death. In our company submission, MSD considered that patients who were ≥360 days from death were in a stable state. To support this assumption, MSD fitted a non-parametric LOESS function to the scatterplot of EQ-5D utility by time to death for all records measured ≥360 days from death. The smoothed curve was approximately horizontal, suggesting there was little change in HRQoL when patients were ≥360 days from death (see Figure 1 below).

	Figure 1. EQ-5D utility by TTD for records measured ≥360 days from death  MSD has conducted further analysis investigating the use of a 'hybrid' approach of time-to-death utilities combined with health-state based utilities. Please see Appendix 1 for a detailed summary of this approach. The model based on TTD is recommended as the base-case because this approach utilized more health states than the model based on PS only, and captured most of the variance in the data.
Are the preferred assumptions found in answer to questions 9 and 10 regarding the estimation of utilities in the main analysis, also the preferred	***MSD considers the same approach between the all-comer and intermediate/poor populations to be most appropriate.***

assumptions in the subgroup analysis of the poor IMDC poor risk subgroup?	
Issue 6: Approach to NMA to inform the economic model subgroup analysis	
Should a constant HR approach NMA (as opposed to a varying hazard approach) be used to inform the economic model?	***MSD believes that the results of the constant HR approach used in the NMA are the most appropriate to inform the subgroup analysis of the intermediate/poor risk group in the economic model.*** MSD's submission presented NMA results of both constant and time-varying HRs for the intermediate/poor risk subgroup analysis in accordance with "*the standard methods as recommended by the NICE DSU*" as also noted by the ERG. Within the company submission, MSD transparently acknowledged violations of the proportional hazards assumption for pembrolizumab in combination with axitinib for OS. Nevertheless, the submission explained that given the low number of events in this subgroup (which contributes to large uncertainty because the 2nd order FP models are more sensitive to fluctuations in observed hazards when sample sizes of the at-risk becomes small over time), the constant HR NMA is still considered to provide stable and appropriate relative treatment effects. It is important to note that the small sample sizes of the at-risk population near the end of follow-up, as well as the short follow-up at the time of IA1, contributed to produce large uncertainty. This in turn translated into wider Credible Intervals (Crs) and model instability in the time-varying HR analyses results. This was more exacerbated in the intermediate/poor risk subgroup analyses which used a smaller portion of each trial population (i.e. even smaller sample sizes). Given the severe limitations and instability in the time-varying HR results, the constant HR NMA results were considered a more appropriate alternative in the absence of strong rationale for another analysis and the possibility to access to patient-level data for all included trials. The Technical Team is of the opinion that all included trials, with the possible exception of CABOSUN [17], are adequately powered for stable estimation of constant hazard ratios for the ITT and the intermediate/poor risk populations (>100 patients in each arm). MSD agrees with the conclusion of the Technical Team, that *"a constant HR NMA approach appears reasonable in the absence of a strong justification to use an alternative approach".*

Issue 7: End of life	
Do patients in the IMDC poor risk subgroup meet the end of life criteria? a) Under standard care/cabozantinib, is the life expectancy of people with poor risk RCC more than 24 months? b) Does pembrolizumab with axitinib extend life for more than 3 months for people with poor risk RCC compared with standard care/cabozantinib?	***As per the company submission, MSD believes that patients with IMDC poor risk subgroup RCC meet the end of life criteria:*** Final results from an extended follow-up of a global, expanded-access trial that, prior to regulatory approval, provided sunitinib to metastatic renal cell carcinoma (mRCC) patients, ineligible for registration-directed trials. Median overall survival was reported for the all comer population of 18.7 months. The sub-populations stratified by risk group of favourable, intermediate and poor reported median overall survival of 56.5 months, 20.0 months and 9.1 months, respectively. The patient population included within this study had a proportion of patients that had received prior systemic therapy.
Issue 8: Cancer Drug Fund	
Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in this population?	***Further data from KEYNOTE-426 will become available in the future*** As stated within MSD's submission, KEYNOTE-426 is an on-going clinical trial and only the results of the planned first interim analysis (IA1) were provided [9]. Longer-term follow-up data from the KEYNOTE-426 study will become available in the future in order to inform a potential Cancer Drugs Fund guidance review.
When will these additional data become available?	In the original submission MSD reported that the estimated completion trial data for KEYNOTE-426 was January 2020. However, recent internal updates confirmed that the actual completion data for KEYNOTE-426 has been postponed to [redacted] due to the initial slow enrolment of the study as well as better efficacy in either or both treatment arms, which has contributed to delay events accruing in this event-driven study.

	In accordance with these new timelines, MSD estimates to receive a Clinical Study Report for KEYNOTE-426 around [redacted], which could then be used to inform a potential Cancer Drug Fund review guidance.
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	***MSD believes that the combination of pembrolizumab and axitinib for treating RCC is a suitable candidate for the Cancer Drug Fund*.** MSD recognises that the limited follow-up based on the first interim analysis of KEYNOTE-426 increases the likelihood of potential uncertainties in relation to the long-term overall survival benefit and consequently the cost-effectiveness results presented in the company base-case. Through data-collection and longer-term follow-up data from KEYNOTE-426, MSD would hope to reduce such uncertainties. If the Committee agrees that pembrolizumab in combination with axitinib has the plausible potential to be a cost-effective treatment option for patients with untreated metastatic renal cell carcinoma, MSD urges the Committee to consider making a recommendation for use within the Cancer Drugs Fund. This would ensure patient access to this combination therapy as early as possible, which we believe would be hugely beneficial when considering the unmet need in this patient population and the scarcity of highly effective alternatives. Data collection to inform a potential future Cancer Drugs Fund guidance review would come from further follow-up data from KEYNOTE-426 trial, which is a phase III randomised, open-label study whose primary endpoints include overall survival and progression free survival in an all-comer population, irrespective of IMDC risk category. As mentioned above, this study will complete in [redacted].

References

1. NICE, TA581: Committee papers. 2019, NICE: NICE website.
2. Motzer, R.J., et al., Pazopanib versus sunitinib in metastatic renal-cell carcinoma. New England Journal of Medicine, 2013. 369(8): p. 722-731.
3. GlaxoSmithKline, Study VEG108844, a Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma: Overall Survival Update. 2014: p. Table 6.18020.
4. Kurt M, M.J., Malcolm B, Gooden KM, Borrill J, Holdgate O, Teitsson S, VALIDATION OF PREDICTED SURVIVAL ESTIMATES FROM PREVIOUS DATA CUTS OF THE PHASE III CHECKMATE 025 STUDY IN ADVANCED RENAL CELL CARCINOMA. 2019-11, ISPOR Europe 2019, Copenhagen, Denmark, 2019.
5. al, R.J.M.e., Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncology 2019, 2019. 20(10): p. 1370-1385.
6. Mollica, V., V. Di Nunno, and F. Massari, Pembrolizumab plus axitinib: a new treatment option for patients with metastatic renal cell carcinoma. Chinese Clinical Oncology, 2019.
7. Mantia, C.M. and D.F. McDermott, Vascular endothelial growth factor and programmed death-1 pathway inhibitors in renal cell carcinoma. Cancer, 2019. 125(23): p. 4148-4157.
8. Rini BI, A.M., Resistance to targeted therapy in renal-cell carcinoma. The Lancet, 2009. 10(10): p. 992-1000.
9. Merck Sharp & Dohme Corp., a.S.o.M.C., A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy
as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426). 2018.
10. NICE, NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA 2013, NICE: NICE website.
11. Gabriel, S.S. and A. Kallies, Tissue-resident memory T cells keep cancer dormant. Cell Research, 2019. 29(5): p. 341-342.
12. Park, S.L., et al., Tissue-resident memory CD8+ T cells promote melanoma–immune equilibrium in skin. Nature, 2019. 565(7739): p. 366-371.
13. Kim PS, A.R., Features of responding T cells in cancer and chronic infection. . Curr Opin Immunol. , 2010. 22(2): p. 223–230.
14. Pauken KE, W.E., Overcoming T cell exhaustion in infection and cancer Trends Immunol, 2015. 36 (4): p. 265–276.
15. Lipson, E.J., et al., Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody. Clinical Cancer Research, 2013. 19(2): p. 462-468.
16. Hatswell, A.J., et al., Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health and Quality of Life Outcomes, 2014. 12(1): p. 140.
17. Choueiri, T.K., et al., Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. Journal of Clinical Oncology, 2017. 35(6): p. 591.

Appendix 1 Utilities by both progression status and time-to-death

In this ad-hoc analysis, utility was estimated by both progression status (PS) and time-to-death (TTD) category adjusting for Grade 3+ AEs. An interaction term was included to estimate whether the utility within the same TTD category varied by PS (or whether the utility within the same PS varied by TTD category).

$$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \beta_2 Progression\ Status_{ij} + \beta_3 Progression\ Status_{ij} * Time\ to\ death_i + \beta_4 AE_{ij} + e_i$$

Table 1. Utility by Progression Status and Time-to-Death Category, accounting for Grade 3+ AE (N=523, n=2670), fixed effects

Parameter	Estimate	Std. Error	P-value
Intercept	[redacted]	[redacted]	[redacted]
180 to 359 days from death	[redacted]	[redacted]	[redacted]
90 to 179 days from death	[redacted]	[redacted]	[redacted]
30 to 89 days from death	[redacted]	[redacted]	[redacted]
0 to 29 days from death	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Grade 3+ AEs	[redacted]	[redacted]	[redacted]
180 to 359 days from death, Progressive disease	[redacted]	[redacted]	[redacted]
90 to 179 days from death, Progressive disease	[redacted]	[redacted]	[redacted]
30 to 89 days from death, Progressive disease	[redacted]	[redacted]	[redacted]
0 to 29 days from death, Progressive disease	[redacted]	[redacted]	[redacted]

Table 2. Type III Analysis of Variance Table with Satterthwaite's method

	Sum Sq	Mean Sq	Num DF	DenDF	F value	Pr(>F)

TTD	[redacted]					
PS						
AE						
Interaction between TTD and PS						

Based on the ANOVA table above, the variance in utility was mostly captured by the TTD category. As for the estimates for the parameters, when including the TTD category in the model, only one estimate of the four interaction parameters was statistically significant.

This approach added significant complexity and uncertainty comparing to a model based on TTD category alone or PS alone. The estimates for certain health status were based on very small sample size (e.g., n=9 for progressive and “0-to-29-days-from-death”) and extreme unbalance between PS status for “>= 360-days-from-death” (n=54 for progressive disease, but n=1978 for Progression-Free, among “>= 360 days from death” patients). The model based on TTD is recommended as the base-case because this approach utilized more health states than the model based on PS only, and captured most of the variance in the data.

R output

[redacted]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma ID1426

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Tuesday 10 December 2019**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Kidney cancer UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Questions for engagement

Issue 1: Extrapolation of overall survival	
What proportion of patients in the pembrolizumab with axitinib arm would you expect to be alive at 5 and 10 years?	Patient testimonies are indicating with this drug combination they are having a greater initial reduction in their tumour and subsequent scans. They believe that due to being given the opportunity of having this treatment it has extended their life expectancy beyond that which was expected as per IMDC. For example, a few of the patients we talked to, who were on this treatment, at presentation to the oncology team were intermediate risk. Therefore predicted life expectancy is 22.5 months, yet 36 months later they are still doing well and have a good outlook.
What proportion of patients in the sunitinib arm would you expect to be alive at 5 and 10 years?	A very small minority.
Is there sufficient clinical and/or methodological justification to use different distributions to extrapolate overall survival (OS) for pembrolizumab with axitinib, and the comparator sunitinib? a) If there is sufficient justification to use different distributions to extrapolate OS, which distribution (log-logistic, exponential or Weibull) is most appropriate to use to model pembrolizumab with axitinib, and the comparator sunitinib?	

b) If there is not sufficient justification to use different distributions to extrapolate OS, is the Weibull distribution the most appropriate distribution to model both pembrolizumab with axitinib, and the comparator sunitinib?	
Issue 2: Treatment waning effect after discontinuation	
In clinical practice, would a reduction in treatment effect be observed after treatment with pembrolizumab has been stopped? If so, at what time point?	
What is the most appropriate duration to apply a treatment effect for people treated with pembrolizumab with axitinib?	
Issue 3: Time horizon	
Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice in untreated metastatic renal cancer to materialise?	
Issue 4: Subsequent treatment after first line treatment has stopped	
In clinical practice, what proportion of people would be expected to have subsequent treatment(s), following first line treatment with	

pembrolizumab with axitinib, and sunitinib respectively?	
Which subsequent treatment(s) would be used and in what proportions?	
Are there any treatments that are used subsequently to pembrolizumab with axitinib, and/or sunitinib that are of particular note in regard to their treatment related adverse event (TRAE) profile (in particular in terms of the TRAE's expected frequency, cost and impact on health related quality of life)?	
Issue 5: Health related quality of life (HRQoL)	
Is using age-related disutility appropriate within the economic model?	
Is using a time to death approach to estimation of utility for use within the economic model appropriate?	
Are the preferred assumptions found in answer to questions 9 and 10 regarding the estimation of utilities in the main analysis, also the preferred assumptions in the subgroup analysis of the poor IMDC poor risk subgroup?	

Issue 6: Approach to NMA to inform the economic model subgroup analysis	
Should a constant HR approach NMA (as opposed to a varying hazard approach) be used to inform the economic model?	
Issue 7: End of life	
Do patients in the IMDC poor risk subgroup meet the end of life criteria? a) Under standard care/carbozantinib, is the life expectancy of people with poor risk RCC more than 24 months? b) Does pembrolizumab with axitinib extend life for more than 3 months for people with poor risk RCC compared with standard care/carbozantinib?	
Issue 8: Cancer Drug Fund	
Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in this population?	

When will these additional data become available?	
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	The cancer drug fund would be a good choice for this technology whilst the clinical trial data matures.

NB: We have commented on the questions we feel a patient perspective would be helpful.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma ID1426

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Ipsen Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Extrapolation of overall survival	
What proportion of patients in the pembrolizumab with axitinib arm would you expect to be alive at 5 and 10 years?	
What proportion of patients in the sunitinib arm would you expect to be alive at 5 and 10 years?	
Is there sufficient clinical and/or methodological justification to use different distributions to extrapolate overall survival (OS) for pembrolizumab with axitinib, and the comparator sunitinib? a) If there is sufficient justification to use different distributions to extrapolate OS, which distribution (log-logistic, exponential or Weibull) is most appropriate to use to model pembrolizumab with axitinib, and the comparator sunitinib? b) If there is not sufficient justification to use different distributions to extrapolate OS, is the	

Weibull distribution the most appropriate distribution to model both pembrolizumab with axitinib, and the comparator sunitinib?	
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Issue 3: Time horizon	
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Should a constant HR approach NMA (as opposed to a varying hazard approach) be used to inform the economic model?	
Issue 7: End of life	
Do patients in the IMDC poor risk subgroup meet the end of life criteria? a) Under standard care/carbozantinib, is the life expectancy of people with poor risk RCC more than 24 months? b) Does pembrolizumab with axitinib extend life for more than 3 months for people with poor risk RCC compared with standard care/carbozantinib?	a) The CS does not appear to have provided specific evidence related to the effectiveness of cabozantinib in the poor-risk population. Further, there is no direct evidence provided of the relative cost-effectiveness of the combination of pembrolizumab+axitinib compared with cabozantinib. Accordingly, there is little formal data which help quantify the life expectancy of people with poor risk RCC. The only study that is presented in the CS as having results specifically from the poor-risk subgroup is the long-term follow up of the sunitinib expanded access programme[1]. The authors have readily acknowledged that the programme is limited in its findings, commenting on both "the limits of the lack of strictly standardised criteria for the timing and methodology of assessment of disease state" and the fact that "the characteristics of these patients, especially those in the intermediate and poor risk groups, may not be entirely equivalent to those in the original Heng *et al* model". It should also be remembered that this study included many pre-treated patients (68% had received cytokines and 10% had received antiangiogenics, including TKIs). The programme itself appears to have opened in 2005 which further compromises its ability to demonstrate the life expectancy of people with poor-risk RCC in the present day. The treatments now available in RCC for 2L and beyond mean that survival estimates from people treated years ago may no

	longer be relevant. Finally, the results from this programme do not support any assertion related to cabozantinib in the 1L poor-risk setting. It is worth noting that the CABOSUN trial was not powered for OS, even in the combined population. Given that CABOSUN included relatively few poor-risk patients (15 cabozantinib, 15 sunitinib), it is not possible to draw any conclusions from this population. This point was made by both the ERG and the Committee during the appraisal (TA542)[2]. Please ensure the spelling of cabozantinib is correct throughout the documentation. 1. Gore, M., Szczylik, C., Porta, C. et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer 113, 12–19 (2015) doi:10.1038/bjc.2015.196 2. https://www.nice.org.uk/guidance/ta542
Issue 8: Cancer Drug Fund	
Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in this population?	

When will these additional data become available?	
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Pembrolizumab in combination with axitinib for untreated advanced renal cell carcinoma

Evidence Review Group's comments on the company's response to the technical report

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Dr Keith Cooper, Senior Research Fellow, SHTAC Mr Olu Onyimadu, Research Fellow, SHTAC Dr Jonathan Shepherd, Principal Research Fellow, SHTAC
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Date completed	18th December 2019

1. Introduction

This document is the ERG's critique of the response by the company (Merck Sharp & Dohme) to the draft technical report for technical engagement issued by NICE to stakeholders on 13th November 2019. The ERG received the company's response on 11th December 2019.

Below we take each of the key issues for consideration and comment on the company's response to them.

Issue 1 – Extrapolation of overall survival

Question	ERG comments
What proportion of patients in the pembrolizumab with axitinib arm would you expect to be alive at 5 and 10 years?	The company maintains their assumption that a 5-year overall survival rate of 50% is clinically plausible. This is based on expert clinical advice given to them. To further support their assumption they cite NICE TA581 (nivolumab in combination with ipilimumab for untreated advanced renal cell carcinoma) in which the Committee considered a 5-year overall survival of 43.6% clinically plausible. The ERG suggests that it may not be meaningful to make this direct comparison with TA581 as in that appraisal treatment was a combination of two immunotherapies, whereas in the current appraisal treatment is combined immune checkpoint inhibitor and TKI tyrosine-kinase inhibitor (TKI) therapy. Thus, the mode of action of the respective drug combinations may not necessarily produce similar 5-year overall survival rates. The ERG also notes that combined nivolumab and ipilimumab treatment can continue for up to 5 years, in contrast to 2 years for pembrolizumab. Due to the immaturity of the overall survival data, the long-term survival rate for patients treated with pembrolizumab combined with axitinib is unclear. Estimates by clinical experts consulted by the technical team, the ERG and the company vary between 30-50% survival at 5-years.
What proportion of patients in the sunitinib arm would you expect to be alive at 5 and 10 years?	The company states that survival rates for patients treated with sunitinib may now be higher than that seen in the trial with the longest follow-up available (the COMPARZ trial, in which the 5-year sunitinib treatment survival rate was 22.8%). This is due to the increase in use of subsequent-line therapies such as nivolumab, which will influence overall survival. The company does not dispute the 5 and 10-year overall survival estimates made by their clinical

	experts (20-25% and 10-15%, respectively), but they acknowledge that these may be underestimates. The ERG agrees with the company's statement, although it is unclear how much higher the 5-year survival would be with increased use of nivolumab as a subsequent-line treatment.
Is there sufficient clinical and/or methodological justification to use different distributions to extrapolate overall survival (OS) for pembrolizumab with axitinib, and the comparator sunitinib? a) If there is sufficient justification to use different distributions to extrapolate OS, which distribution (log-logistic, exponential or Weibull) is most appropriate to use to	The company maintains their justification to use different distributions to extrapolate overall survival for pembrolizumab in combination with axitinib, and the comparator treatment sunitinib (log-logistic and exponential distributions, respectively). They cite published review/editorial articles describing the clinical rationale for combined immune checkpoint inhibitor and TKI therapy, and the different mechanisms of action of these drugs, as providing the "substantial justification" required in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 for fitting different parametric models to different treatment arms. The ERG acknowledges the clinical rationale for combined immune checkpoint inhibitor and TKI therapy, and the different mechanisms of action proposed. However, our view is that there is no robust evidence currently available showing a difference in the underlying hazards for overall survival between pembrolizumab in combination with axitinib and the comparator sunitinib, supporting the use of different survival distributions. We note that the KEYNOTE-426 trial overall survival data are immature. a) The company maintains their assertion that the log-logistic and exponential distributions are the most appropriate to model the long-term survival estimates of pembrolizumab in combination with axitinib and sunitinib, respectively. The company state that the log-logistic provides good visual and statistical fit to the observed data. They present a table (Table 1) comparing survival rates up to 20 years between their base case, two of the scenario

model pembrolizumab with axitinib, and the comparator sunitinib?	analyses from their submission (scenario 1 - landmark analysis; and scenario 3 - fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-constant HR for sunitinib) and the Weibull distribution. They state that the two selected scenario analyses validate their base case (i.e. they provide similar survival rates). For sunitinib, they state that the exponential provides a good visual and statistical fit to the observed data and is the best fitting statistically compared to the other curves considered plausible. They also state that the survival estimates tally with expert opinion at 10 years. We note that the AIC/BIC statistics for pembrolizumab in combination with axitinib show that the log-logistic and the Weibull distributions are similar in their statistical fit to the observed data. The best statistical fit is the exponential distribution. Further, the Weibull and exponential distributions provide good visual fits to the observed data. We agree the exponential distribution provides a good visual and statistical fit to the observed data. The Weibull also provides a good visual fit to the observed data. Whilst the statistical fit for sunitinib is not as good for the Weibull as for the exponential distribution, the ERG considers that the statistical fit with the observed data is less important than validation against long-term data. The Weibull also provides a good visual fit to the observed data for sunitinib. b) The company does not consider the Weibull distribution (favoured by the ERG) to be appropriate to model both pembrolizumab with axitinib, and sunitinib (together or separately). The technical team concluded that the Weibull distribution is the most clinically plausible. The estimate for 5-year overall

b) If there is not sufficient justification to use different distributions to extrapolate OS, is the Weibull distribution the most appropriate distribution to model both pembrolizumab with axitinib, and the comparator sunitinib?	survival using the Weibull distribution provides the closest fit to the COMPARZ trial data for patients receiving sunitinib, even allowing for the fact that few patients in that trial received nivolumab as a subsequent-line treatment (as discussed earlier). Furthermore, the 5-year overall survival estimate (45%) for patients treated with pembrolizumab in combination with axitinib is in the range estimated by clinical experts (30%-50%). We also agree that the "*Weibull and exponential distributions appear to have good fits to the Keynote-426 trial data on inspection of the graphs*", as stated in the technical report.

Issue 2 - Treatment effect waning after pembrolizumab discontinuation

Question	**ERG comments**
In clinical practice, would a reduction in treatment effect be observed after treatment with pembrolizumab has been stopped? If so, at what time point?	The ERG agrees with the statement in the technical report that "*the immaturity of data means that the long term treatment effect of the drug is unclear.*" We also agree with the company's statement (in reference to previous NICE pembrolizumab/immunotherapy-oncology appraisals in which a treatment waning effect had been included) that they "*see no rationale for maintaining consistency with approaches adopted in appraisals concerning completely different indications*" and that "*a greater focus should be placed with maintaining consistency with precedent in previous appraisal of IO therapies for renal cell carcinoma*". As noted by the company, in the appraisal of nivolumab and ipilimumab for untreated advanced renal cell carcinoma (NICE TA581), no reduction in treatment effect was included. For this reason, we did not include treatment waning in the ERG base

case, but included it as a scenario analysis to allow for the possibility that a waning effect could be possible.

The NICE technical team requested the company to provide analyses exploring a treatment effect lasting until 2 years (when pembrolizumab treatment stops) and 3 years (treatment effect ends 1 year after stopping pembrolizumab treatment). The company chose not to provide these analyses, citing no clinical support for such a limited duration of treatment effect. However, they did provide the overall survival estimates for these scenarios according to the company's and the ERG's base case parametric survival curves (Table 2 in the company's response document).

The ERG ran these scenario analyses in the economic model and we provide the cost-effectiveness results below based on drug list prices only (Table 1). These scenarios have a large impact on the results, with the ICERs varying between £184,983 per QALY and £269,968 per QALY.

Table 1 – Treatment effect waning scenario analyses for treatment with pembrolizumab + axitinib compared to sunitinib (list prices)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	£137,537	2.32	£59,292
2-year treatment effect waning[a]	£116,835	0.495	£236,229
3-year treatment waning[a]	£123,483	0.668	£184,983
ERG Base case	£140,895	1.170	£120,455
2-year treatment effect waning[b]	£125,895	0.466	£269,968
3-year treatment effect waning[b]	£131,854	0.626	£210,586

	[a] Using the company's base case fitted parametric survival curves [b] Using the ERG's base case fitted parametric survival curves
What is the most appropriate duration to apply a treatment effect for people treated with pembrolizumab with axitinib?	Please see above.

Issue 3 – Time horizon

Question	**ERG comments**
Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice in untreated metastatic renal cancer to materialise?	The choice of time horizon is linked to preferred assumptions for Issue 1 and 2 above for extrapolation of overall survival and treatment waning. The ERG notes that the technical report incorrectly states that the ERG used a 20-year time horizon, whereas the ERG used a 40-year time horizon in their base case and a 20 year time horizon as a scenario analysis. The ERG agrees that a lifetime time horizon of 40 years is most appropriate because it is able to show the differences in costs and outcomes in all scenarios.

Issue 4 -Subsequent treatment after first line treatment has stopped

Question	**ERG comments**
In clinical practice, what proportion of people would be expected to have subsequent treatment(s), following first line treatment with	The technical team agrees with the proportion of people (50%), suggested by the ERG, who would be expected to have

pembrolizumab with axitinib, and sunitinib respectively?	subsequent-line treatment(s) following first-line treatment with pembrolizumab with axitinib, and sunitinib respectively. The company do not disagree with this but emphasise the importance of keeping in mind the impact of scenario analysis 12 from the CS, which uses the KEYNOTE-426 trial-based distribution of subsequent-line therapies to model the cost of subsequent therapy.
Which subsequent treatment(s) would be used and in what proportions?	As above, the company and technical team are in agreement with the ERG's approach.
Are there any treatments that are used subsequently to pembrolizumab with axitinib, and/or sunitinib that are of particular note in regard to their treatment related adverse event (TRAE) profile (in particular in terms of the TRAE's expected frequency, cost and impact on health related quality of life)?	The company suggests expert clinical opinion is sought on this issue, and the ERG concurs.

Issue 5 - Health related quality of life (HRQoL)

Question	**ERG comments**
Is using age-related disutility appropriate within the economic model?	The ERG agrees with the company's response. As there is no correlation between age and baseline utility assessment in the KEYNOTE-426 trial (clarification question B11), it is unnecessary to include age-related utility.
Is using a time to death approach to estimation of utility for use within the economic model appropriate?	The ERG agrees with the company's response. As stated in the ERG report, we consider that a time to death approach is reasonable, given that inclusion of the

	disease progression state may not fully capture all predictive factors of patient utility and time-to-death provides a good fit to patient data. The technical team were concerned that there was no change in HRQoL when patients are ≥360 days from death. The company's assumption is that patients who are ≥360 days from death are in a stable state. To further support this assumption, the company have fitted a non-parametric LOESS function to the scatterplot of EQ-5D utility by time-to-death for all records measured ≥360 days from death. The smoothed curve generated by this analysis is approximately horizontal, suggesting there was little change in HRQoL when patients were ≥360 days from death (Figure 1 of the company's response document). The ERG agrees with this interpretation of the results. The technical report proposes that pooled health state utilities are used with an age-related utility decrement due to the need to model HRQoL over a time horizon longer than the trial (see preferred assumption 5 in Table 1 of the technical report). The company has conducted a further analysis, which they describe as a 'hybrid' approach of time-to-death utilities combined with health-state based utilities (NB. they do not explain why this analysis was done specifically). The results and a description of the method are shown in the company's Appendix to their technical engagement response. A set of utility values is presented

	but these are not used in any cost effectiveness analysis. The company's interpretation of the results is that the hybrid approach adds significant complexity and uncertainty compared to a model based on time-to-death alone or health state alone.
Are the preferred assumptions found in answer to questions 9 and 10 regarding the estimation of utilities in the main analysis, also the preferred assumptions in the subgroup analysis of the poor IMDC poor risk subgroup?	The ERG agrees that the assumptions for the main analysis should also be applied in the subgroup analysis.

Issue 6 – Approach to NMA to inform the economic model subgroup analysis

Question	**ERG comments**
Should a constant HR approach NMA (as opposed to a varying hazard approach) be used to inform the economic model?	The ERG notes that the technical report incorrectly states that the ERG disagrees with the company that the constant hazard NMA approach produces stable results. We state in the ERG report that the time-varying hazards NMA approach produced unstable results. We are in agreement with the company (and the technical team) that despite the violation of the proportional hazards assumption in some instances, the use of a constant hazards NMA is more appropriate than time-varying fractional polynomials when length of follow-up is short, or sample size is small.

Issue 7 – End of life

Question	**ERG comments**

Do patients in the IMDC poor risk subgroup meet the end of life criteria? a) Under standard care/cabozantinib, is the life expectancy of people with poor risk RCC more than 24 months? b) b) Does pembrolizumab with axitinib extend life for more than 3 months for people with poor risk RCC compared with standard care/cabozantinib?	The company re-iterates the justification provided in the CS for why the poor risk subgroup meets the first end of life criterion (a). They cite final results from an extended follow-up of a global, expanded-access sunitinib trial which reported median overall survival of 56.5 months, 20.0 months and 9.1 months in the favourable, intermediate and poor subgroups respectively. They provide no further data or justification for meeting this criterion or the second end of life criterion (b). The ERG disagrees with the company that pembrolizumab in combination with axitinib meets the first end of life criterion in the poor RCC risk subgroup, given that cabozantinib is recommended by NICE for people with poor / intermediate risk. The median overall survival of 30.3 months for intermediate / poor risk patients in the CABOSUN trial of cabozantinib exceeds the end of life criterion of less than 24 months life expectancy. The ERG would like to reiterate that the company's assessment of clinical effectiveness and cost effectiveness is for the intermediate / poor risk subgroup combined. Thus, it is not possible for the ERG to generate modelled estimates of OS for poor risk subgroup patients to inform end of life assessment.

Issue 8 – Cancer Drug Fund

Question	ERG comments
Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in this population?	The company states the timeframe for further data availability from the KEYNOTE-426 trial, which they propose would support potential inclusion of pembrolizumab in combination with axitinib in the Cancer Drugs Fund. As this is a decision for the NICE appraisal committee the ERG has no additional comments to those stated above in relation to uncertainties around clinical effectiveness and cost-effectiveness.
When will these additional data become available?	
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: January 2020

1. Summary of the key issues

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

1.1 The technical team considered the following:

Issue 1 The use of the Weibull distribution for extrapolation of overall survival (OS) for both the intervention and comparator is methodologically appropriate and produces the most plausible OS extrapolations.

Issue 2 There no evidence to support an infinite treatment effect and therefore a treatment waning effect should be used.

Issue 3 **A time horizon of 40 years should be used to capture all relevant benefits and costs that arise as a result of treatment for untreated metastatic renal cell carcinoma (RCC).**

Issue 4 Treatment following pembrolizumab with axitinib is likely to include cabozantinib within UK clinical practice.

Issue 5 Health related quality of life estimates can be based on health state (reflecting disease progression) and be adjusted according to increasing age.

Issue 6 The subgroup analysis for the intermediate/poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group should be informed by the constant hazard approach network meta-analysis (NMA).

Issue 7 **The intermediate/poor IMDC risk subgroup is not likely to meet the end of life criteria.**

The poor IMDC risk subgroup is not likely to meet the end of life criteria.

Issue 8 It is unclear whether pembrolizumab with axitinib is a suitable candidate for the Cancer Drugs Fund (CDF).

Issue 9 It is unclear if a stopping rule of 35 cycles (24 months) for pembrolizumab is clinically appropriate in the treatment of RCC (new issue at technical engagement).

1.2 The technical team feel the following issues have been resolved at technical engagement:

Issue 3: A time horizon of 40 years should be used to capture all relevant benefits and costs that arise as a result of treatment for untreated metastatic renal cell carcinoma (RCC).

Issue 4: Treatment following pembrolizumab with axitinib is likely to include cabozantinib within UK clinical practice.

Issue 6: The subgroup analysis for the intermediate/poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group should be informed by the constant hazard approach network meta-analysis (NMA).

1.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There is an immature evidence base to inform OS; median survival has not been reached.
- Demographics and clinical characteristics of the KEYNOTE-426 trial population may limit generalisability to the UK RCC patient population.
- Demographics and clinical characteristics of the populations within the studies informing the NMA may limit generalisability to the UK RCC patient population.
- There is use of small datasets and potential heterogeneity in studies used in NMA, which introduces uncertainty due to reduced precision of the NMA findings.

- Adverse events (AEs) in second line treatment were not explicitly modelled meaning that cost-effectiveness results may be over or under-estimated.

1.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £175,316 per quality-adjusted life years (QALY) gained in the main analysis of pembrolizumab with axitinib versus sunitinib (see table 1 and 2). Under the technical team's preferred assumptions, the ICER was £82,488 per QALY gained in the poor/intermediate risk subgroup analysis (see table 3). These estimates do not include the commercial arrangements for pembrolizumab, cabozantinib, axitinib, nivolumab, everolimus, lenvatinib, tivozanib or sunitinib. This is because these are confidential and cannot be reported here. Estimates for the main general RCC population analysis that included these commercial arrangements would be lower than those reported above. However, they would still be above the range normally considered good use of NHS resources. Estimates for the poor/intermediate risk subgroup analysis that included these commercial arrangements would be higher than those reported above.

1.5 Based on the modelling assumptions, the intervention is unlikely to meet the end-of-life criteria for the general RCC population. It is also unlikely that the intervention may meet the end of life criteria for the intermediate/poor risk subgroup. There is insufficient evidence to suggest that the poor risk group would meet end of life criteria (see issue 7).

1.6 The company believes that the combination of pembrolizumab and axitinib for treating RCC is a suitable candidate for the Cancer Drugs Fund and indicated further data will be forthcoming at the conclusion of the KEYNOTE 246 trial (see issue 8).

1.7 The technology is unlikely to be considered innovative.

1.8 No equality issues were identified.

These issues are described in detail in section 3 and 4.

2. Topic background

2.1 Disease background

- RCC accounts for 80% of kidney cancer cases.
- The common subtype of RCC are clear-cell or non-papillary (75% of RCCs); papillary or chromophilic (10-15% of RCCs) and chromophobe (5% of RCCs).
- Early symptoms of RCC include haematuria (blood in the urine) and/or persistent pain in the lower back or side between the ribs and hipbone. Later symptoms include fatigue, weakness, pain, anorexia, nausea, dyspnoea, worry, shortness of breath and irritability.
- RCC tends to affect people over 60 years old and is more common in males, although the incidence has increased more rapidly in females than males since the early 1990s.
- In the UK, there are approximately 12,600 new cases of kidney cancer and 4,500 deaths due to kidney cancer annually.
- Approximately 70% and 50% of people with RCC will live to one and ten years respectively, with survival linked to stage of cancer at diagnosis (with five-year survival estimated at 83% and 6% for stage I and IV respectively).
- In 2015, around 44% of people diagnosed with RCC presented at stage III or IV of disease.
- The IMDC criteria classifies people with metastatic RCC that receive systemic treatment in terms of favourable, intermediate or poor risk.

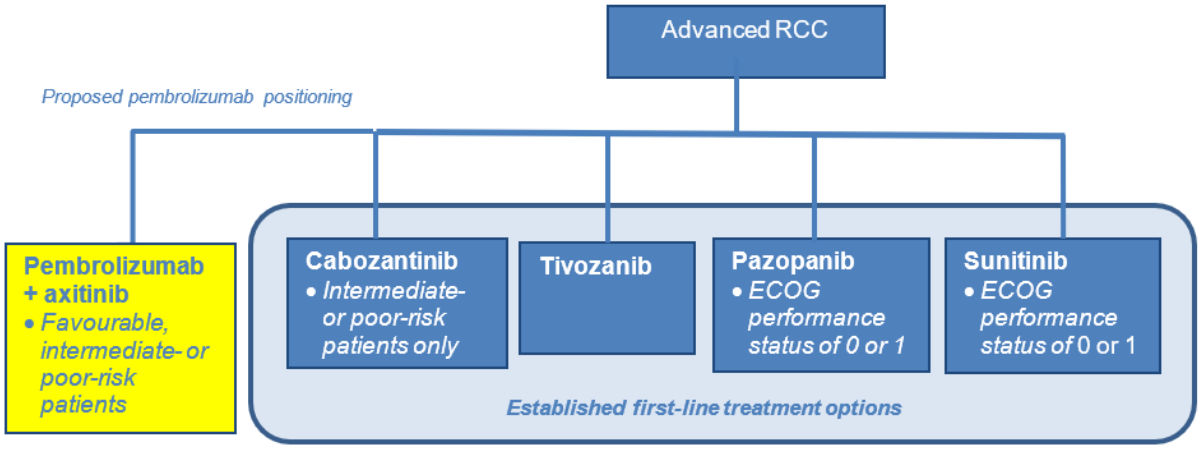
2.2 Pembrolizumab with axitinib

Marketing authorisation	Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults (granted 25 July 2019).
Mechanism of action	Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. Axitinib is a multi-targeted kinase receptor inhibitor with anti-tumour activity. Axitinib inhibits vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet-derived growth factor receptor (PDGFR), and c-kit, which may result in inhibition of angiogenesis in tumours.
Administration	Pembrolizumab 200 mg intravenously every 3 weeks with axitinib 5 mg orally twice daily.
Price	The list price of pembrolizumab is £2,630 per 100 mg vial, the cost of a single administration being £5,260. A commercial access agreement has been arranged with NHS England, with a simple discount in place. The list price of axitinib is £3,517 per 56, 5mg tablets. (The average cost of a course of treatment at list price is: £120,572). Axitinib has a patient access scheme arrangement in place with a simple discount.

2.3 Treatment pathway

- The general approach to treating RCC cancers is surgical resection of localised disease; however, approximately half of patients develop advanced stage disease despite surgery.
- The company proposes that pembrolizumab with axitinib would offer an alternative first-line treatment option to those therapies already recommended for people with advanced RCC (see figure 1).

Figure 1: Proposed treatment pathway which is based on the NICE pathway for RCC and the updated European Association of Urologists guideline*.



*Please note that nivolumab with ipilimumab is recommended for use through the Cancer Drugs Fund (CDF) and therefore cannot be considered as a comparator within the scope of this appraisal to treat adults with untreated advanced renal cell that is intermediate/poor-risk as defined by the IMDC criteria (please see TA581 and the NICE position statement on CDF products as comparators).

2.4 Clinical evidence

- The company systematic review identified four randomised control trials: the pivotal trial for pembrolizumab in combination with axitinib (KEYNOTE-426) and three trials reporting evidence for the relevant comparators (Cabosun, Comparz, Tivo-1). Please see table 1 for study information.
- Findings from KEYNOTE-426 are presented based on a data cut in August 2018, which informed the main analysis in the economic model. The company also presents findings from a subsequent (unplanned) data cut in January 2019 ([redacted]).
- In the absence of direct comparative evidence of pembrolizumab with axitinib versus tivozanib, pazopanib or cabozantinib, a fixed-effects NMA (see figure 2) was undertaken.

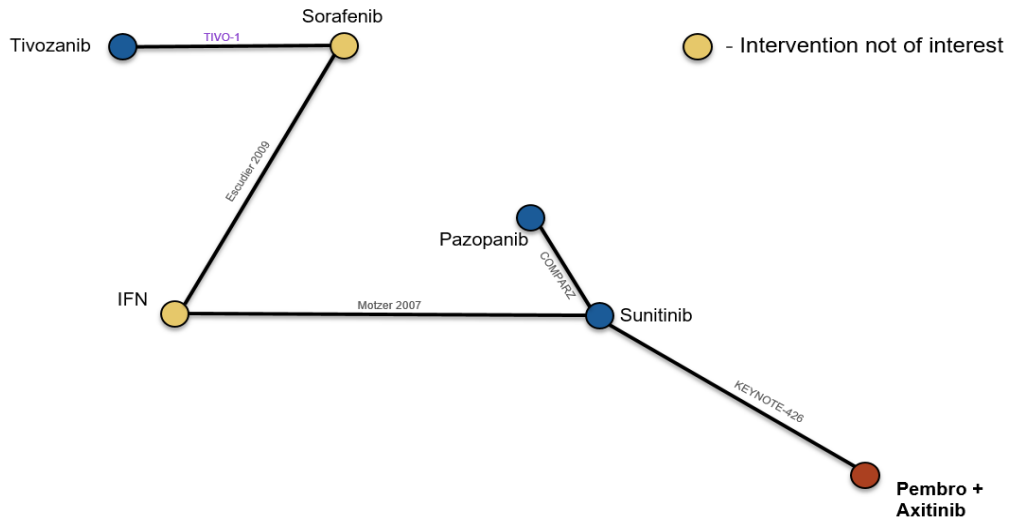
The NMA did not inform the economic base case regarding the general RCC population. Instead, the economic model base case used data from the pivotal data to directly compare pembrolizumab with axitinib and the comparator sunitinib. Tivozanib and pazopanib were assumed to have equal efficacy and safety to sunitinib, which is in line with committee preference in TA512 and TA215 respectively (please also see TA542 and TA581 for cabozantinib and nivolumab respectively, in which the committee also support the assumption of equal clinical efficacy of pazopanib and sunitinib). However, in the absence of direct comparative evidence, the NMA was used to inform the IMDC poor/intermediate risk subgroup analysis within the economic model because sunitinib and cabozantinib could not be assumed equally efficacious.

Table 1: Summary of KEYNOTE-426

Study	KEYNOTE-426: A Phase III Randomised, Open-label Study
Population	Adults with previously untreated advanced clear-cell renal-cell carcinoma
Intervention	Pembrolizumab 200 mg intravenously every 3 weeks with axitinib 5 mg orally twice daily. Pembrolizumab can be continued up to 35 doses (approximately 24 months).
Comparator(s)	Sunitinib monotherapy (50 mg orally once daily for 4 weeks and then off treatment for 2 weeks)
Reported outcomes specified in the decision problem	• **Overall survival (OS)** • **Progression free survival (PFS)** • **Objective response rate (ORR)** • **Adverse effects (AEs) of treatment** • **Health related quality of life (HRQoL)**
All other reported outcomes	• Time to deterioration (TTD) • Duration of response (DOR) • **Patient reported outcomes (PRO)** • Disease control rate (DCR)

Note: Bolded outcomes are included in the economic model

Figure 2: Network of evidence for all included RCTs in untreated RCC (all outcomes)



Note: Interventions not of interest (IFN and sorafenib) were included in the NMA to facilitate an indirect comparison between tivozanib and other interventions of interest. The CABOSUN trial (cabozantinib vs. sunitinib) is not included in this network diagram as this trial included IMDC intermediate/poor risk category patients only

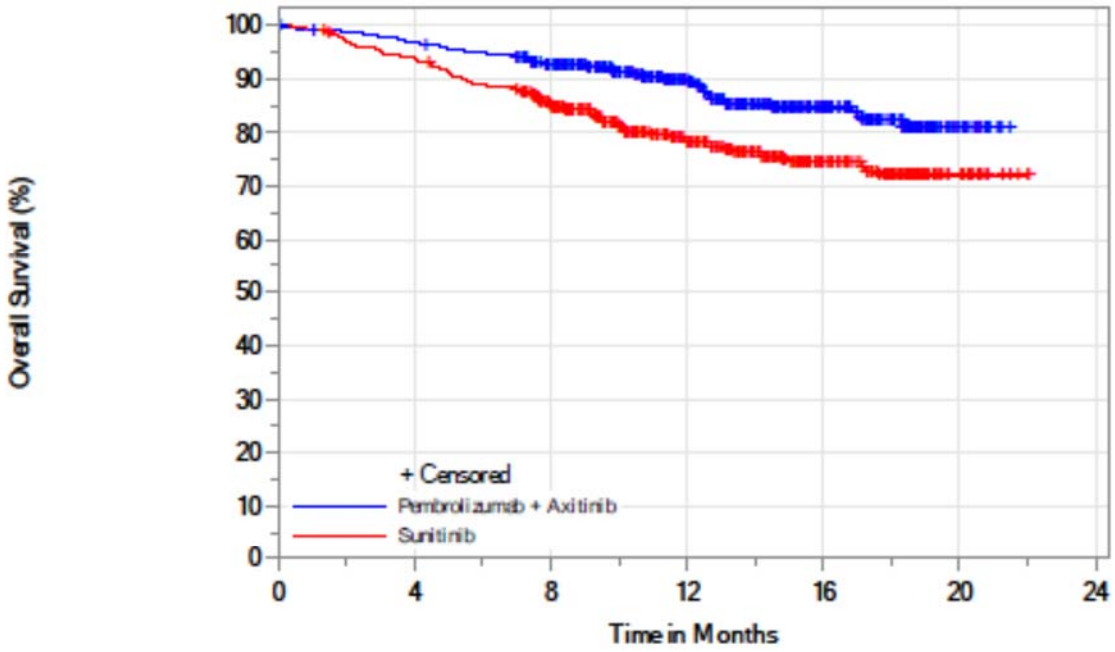
2.5 Key trial results

Using the August 2018 data cut for pembrolizumab with axitinib (intervention) versus sunitinib (comparator):

- Overall survival (OS) hazard ratio (HR): 0.53 (95% CI: 0.38, 0.74; p=0.00005). This represents a 47% reduction in the risk of death in favour of intervention. Median OS was not reached in either group (see figure 2).
- Progression-free survival (PFS) HR: 0.69 (95% CI: 0.57, 0.84; p=0.00014). This represents a 31% reduction in the risk of progression or death in favour of intervention. Median PFS: Intervention: 17.1 months; Comparator: 11.1 months (see figure 3).
- Objective response rate (ORR) (per RECIST 1.1 by blinded independent central review [BICR]): Intervention: 59.3%; Comparator: 35.7%; Difference of 23.6% (95% CI: 17.2, 29.9; p<0.0001).

- EQ-5D-VAS change from baseline to Week 30: The company report no clinically meaningful difference.

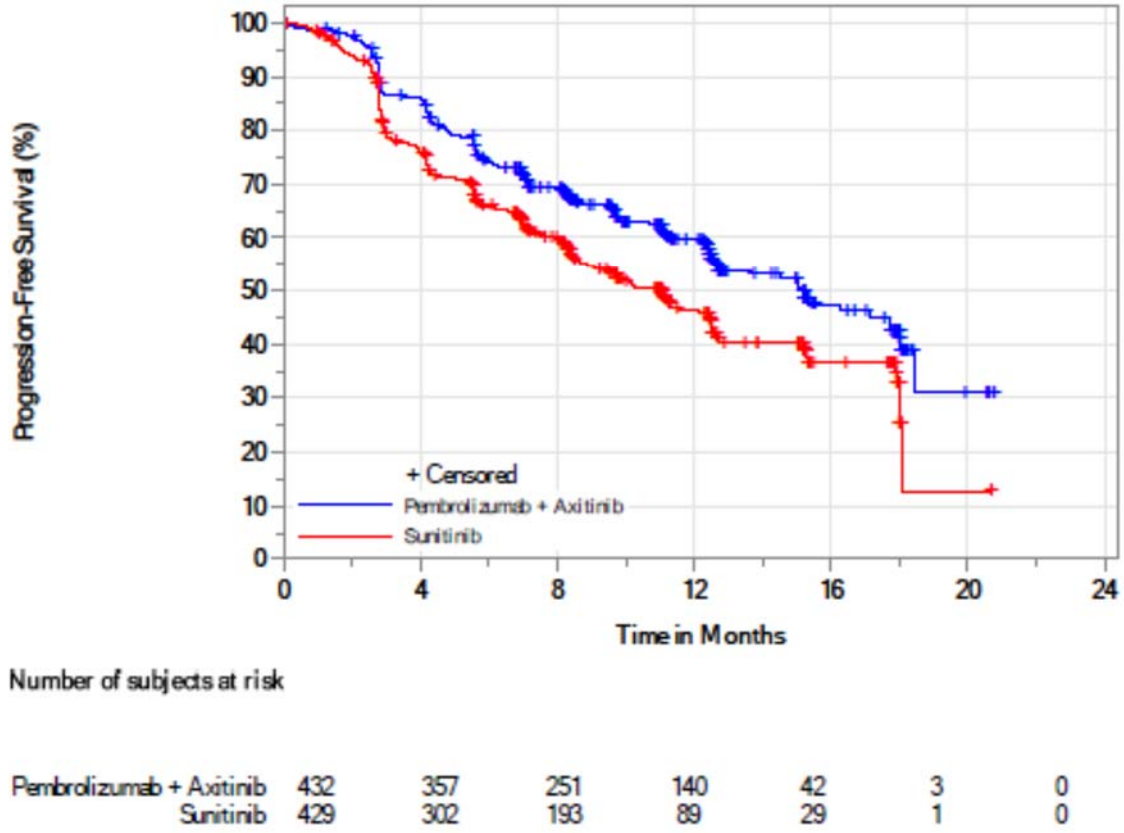
Figure 2: Kaplan Meier Estimates of OS (Intention to treat (ITT))



Number of subjects at risk

Pembrolizumab + Axitinib	432	417	378	256	136	18	0
Sunitinib	429	401	341	211	110	20	0

Figure 3: Kaplan Meier Estimates of PFS (primary censoring rule) based on BICR Assessment per RECIST 1.1 (ITT)



2.6 Findings for the constant HR NMA, August 2018 data cut.

Overall survival

- Pembrolizumab with axitinib resulted in a [redacted] in the duration of OS compared with both pazopanib [redacted] and sunitinib [redacted]. Pazopanib was [redacted] from sunitinib.
- In the intermediate/poor risk subgroup, the results [redacted] pembrolizumab with axitinib [redacted] cabozantinib; however, [redacted]. Pembrolizumab with axitinib was [redacted] to sunitinib [redacted] with respect to OS.

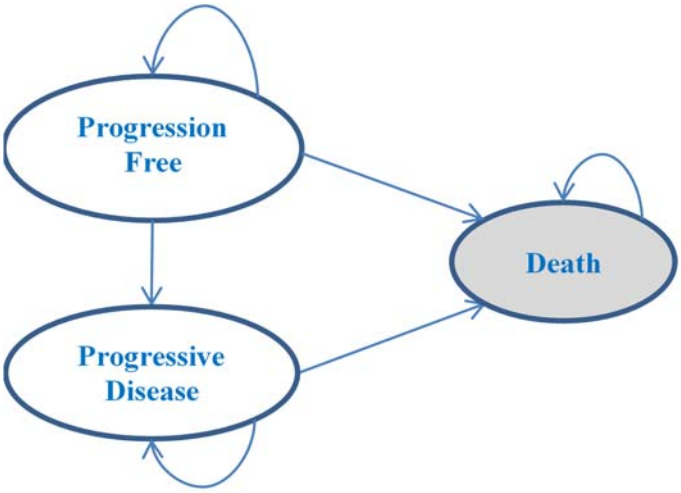
Progression-free survival

- Pembrolizumab with axitinib resulted in a [redacted] in the duration of PFS compared to all competing interventions including tivozanib [redacted], pazopanib [redacted], and sunitinib [redacted].
- In the intermediate/poor risk subgroup, pembrolizumab with axitinib and cabozantinib are [redacted] to sunitinib [HR=[redacted] and HR=[redacted] respectively]. Although the results [redacted] cabozantinib [redacted] pembrolizumab with axitinib, this [redacted].

2.7 Model structure

- Partitioned survival model with 3 health states (see figure 4) and weekly cycle length.
- 40-year time horizon and 3.5% discount rate for costs and benefits.
- Comparators: sunitinib; pazopanib; tivozanib; cabozantinib (in poor/intermediate IMDC risk subgroup only).
- Clinical effectiveness data from KEYNOTE-426 trial, with the exception of the intermediate/poor risk group which came from the NMA.

Figure 4: The economic model structure.



2.8 Key model assumptions

- Population
  - Assumes similar to cohort in KEYNOTE-426 trial (61.5 years old, 71.3% male, 81.5 kg).
- Clinical efficacy:
  - Clinical efficacy of pazopanib and tivozanib is equal to the clinical efficacy of sunitinib for OS, PFS, time on treatment and safety profile (this is in line with previous appraisals in RCC, please see section 1.4).
  - Treatment effect persists throughout lifetime of patient with treatment waning at 10 years tested in a scenario.
  - Once patients progress, they receive subsequent therapies as is experienced in UK clinical practice.
  - To model PFS, KEYNOTE-426 survival data was used for the first 13 weeks, followed by an exponential distribution (for both pembrolizumab with axitinib, and sunitinib).

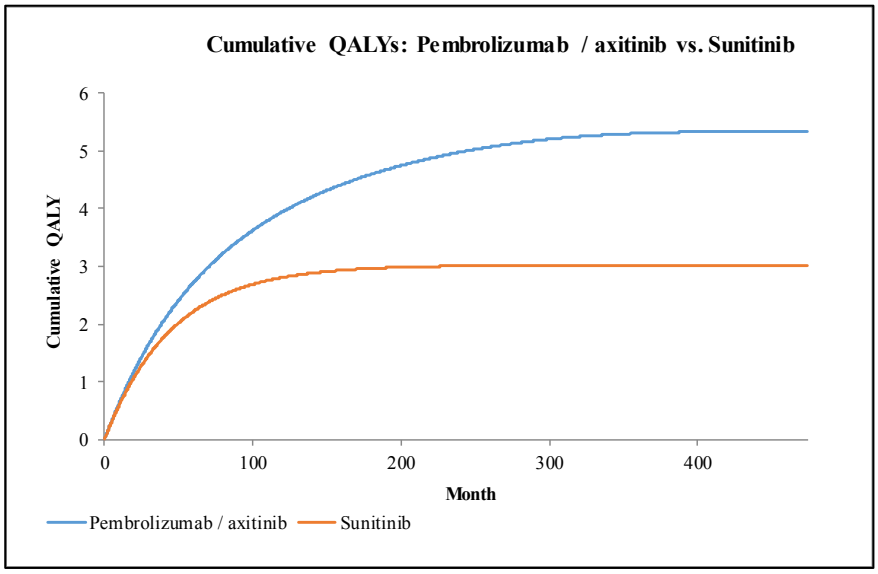
  - To model OS, efficacy log-logistic and exponential distribution were fitted to individual treatment arms from KEYNOTE-426 for pembrolizumab with axitinib, and sunitinib, respectively.
  - Mortality rate is the same before and after disease progression, with adjustment made for age-related mortality.
- Safety:
  - Incidence of AEs informed by KEYNOTE-426 trial, i.e. grade 3-5 AEs (incidence ≥5% in one or more treatment groups, considering any grade) and the published trials on cabozantinib in the intermediate/poor risk group.
  - AEs related to subsequent treatments are not explicitly modelled.
- Health related quality of life:
  - The quality of life of patients is considered using KEYNOTE-426 trial estimates based on time-to-death utilities to capture decline in HRQoL in final months of life.
  - Utility values were adjusted to decease with age.
- Healthcare resource use costs:
  - Resource use is assumed to be equal between pembrolizumab with axitinib and are assumed to be equal per treatment arm in the pre- and post- progression health states.
  - Other costs considered important were acquisition and administration of first and subsequent treatments (adjusted for vial sharing and dose intensity), monitoring and disease management, cost associated with treatment related AEs of first line treatment and end of life care in last cycle before death.
- Stopping rule:

  Pembrolizumab will be administered for a maximum of 35 cycles (24 months), after which axitinib monotherapy will continue until confirmation of disease progression (this reflects the trial protocol).

2.9 Overview of how quality-adjusted life years accrue in the model

- For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period for calculating the cumulative QALYs over the modelled time horizon (see figure 5). An annual rate discount rate of 3.5% was used.

Figure 5: Cumulative QALY gain over the time horizon of the model



- The analysis of the EQ-5D-3L utilities was based on the full analysis set (FAS) population (a total of 850 subjects).
- UK preference-based scores were used and developed using the time trade-off (TTO) technique.
- Estimation of utilities in the base case analysis was based on time-to-death to reflect the decline in health-related quality of life at the terminal phase of disease (see table 2).
- Estimation of utilities based on progression status was also considered, however there was limited post progression utility data available (as this was collected until drug discontinuation or the 30-day post study follow-up).

- Utilities were adjusted for whether the EQ-5D index was measured during a grade 3+ AE using a linear mixed effects model, which also provided estimation of the disutility associated with an adverse event.
- The QALY loss associated with the AE was applied within the first cycle ([redacted] for pembrolizumab in combination with axitinib and [redacted] for sunitinib using the time-to-death regression model).

Table 2. EQ-5D health utility scores by time-to-death

	Pooled (N=532), number of observations: 2,704		
	Estimate	SE	95% confidence interval
≥360 days	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]
90 to 180 days	[redacted]	[redacted]	[redacted]
30 to 90 days	[redacted]	[redacted]	[redacted]
0 to 30 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

3. Key issues for consideration

Issue 1 – Extrapolation of overall survival

Questions for engagement	1. What proportion of patients in the pembrolizumab with axitinib arm would you expect to be alive at 5 and 10 years? 2. What proportion of patients in the sunitinib arm would you expect to be alive at 5 and 10 years? 3. Is there sufficient clinical and/or methodological justification to use different distributions to extrapolate overall survival (OS) for pembrolizumab with axitinib, and the comparator sunitinib? a. If there is sufficient justification to use different distributions to extrapolate OS, which distribution (log-logistic, exponential or Weibull) is most appropriate to use to model pembrolizumab with axitinib, and the comparator sunitinib? b. If there is not sufficient justification to use different distributions to extrapolate OS, is the Weibull distribution the most appropriate distribution to model both pembrolizumab with axitinib, and the comparator sunitinib?
Background/description of issue	The follow-up period in KEYNOTE-426 is shorter than the time horizon in the economic model and therefore extrapolation using parametric curves were used to model OS. The NICE DSU technical support document 14 advises that both arms should have the same extrapolation distribution applied unless substantial justification is given. **The company** used a log-logistic distribution for pembrolizumab with axitinib, and an exponential distribution for sunitinib to model OS. The company's justification for using different distributions for the intervention and comparator is that the mode of action of combination of immunotherapy with a tyrosine kinase inhibitor (TKI) is not comparable to the mode of action associated with TKI monotherapy. The company also states that none of the parametric distributions gave clinically plausible long-term OS estimates for both arms simultaneously. The company justifies use of the exponential distribution to extrapolate OS for the sunitinib arm by stating that the log-cumulative hazard plots showed a constant hazard over time (suggesting that the exponential curve is appropriate), there was close statistical fit to the observed data, and that

	long-term OS estimates were in line with external data and clinical expert opinion. The company justifies use of the log-logistic distribution to extrapolate OS for the pembrolizumab with axitinib arm by stating it had a good statistical fit to the observed data, and that it is clinically credible based on the expectation that a percentage of patients would derive a long-term survival benefit from the combination of an immunotherapy with a TKI. This immunotherapeutic effect would imply a declining, rather than a constant hazard over the long term. **The ERG** considered that both the exponential and Weibull distributions are plausible for OS. The ERG proposed that the Weibull distribution should be used for both the intervention and comparator extrapolation of OS. The ERG suggested that the Weibull distribution was the best fit to sunitinib data, that the underlying hazard for pembrolizumab with axitinib is similar to sunitinib (and either the Weibull or exponential distributions were plausible), and that the data for pembrolizumab with axitinib does not demonstrate an underlying hazard that is similar to the log-logistic. The ERG also noted in TA581 (for nivolumab with ipilimumab) that the committee did not consider the modelling of the immunotherapeutic effect to be substantiated by evidence, and that it could not generalise the size of this effect from one cancer to another. **The technical team** notes that if an exponential distribution is determined to be best fit for sunitinib (i.e. agreement with the company) to model overall survival, and plausible for pembrolizumab with axitinib, then there is potential for the exponential distribution to be used for both the intervention and the comparator. **Two clinical experts** commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only). With regard to long term survival estimates for pembrolizumab with axitinib, the **company clinical experts** estimated a 50% survival at 5 years. An **ERG clinical expert** thought this may be optimistic. A **clinical expert** for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years.
Why this issue is important	The choice of distribution has a large impact on the ICER. Using the exponential distribution to model OS for both intervention and comparator increases the ICER from £59,292 per QALY gained in the company base case to £73,094. Using the Weibull distribution to model OS for both intervention and comparator increases the ICER to £118,931.

Technical team preliminary judgement and rationale	From inspection of the extrapolated survival curves against the trial with the longest follow-up (i.e. the COMPARZ trial) and consideration of clinical expert opinion, the log-logistic, exponential and Weibull functions appear to all produce optimistic extrapolations. However, both the Weibull and exponential appear to have good fit to the Keynote-426 trial data on inspection of the graphs. Overall, the Weibull appears to be most likely to be clinically plausible. Nonetheless, uncertainty regarding the best distribution will remain due to the immaturity of the data.
Summary of comments	***Comments received by the company:*** • A 5-year 50% OS is plausible; recognise uncertainty around 10-year survival and agree with the technical team's clinical experts' estimation of a survival plateau. • The 5-year survival estimation made by the technical team is implausibly low because: o TA581 (nivolumab with ipilimumab) considered a 5-year overall survival of 43.6% as clinically plausible in intermediate/poor-risk patients o In KEYNOTE-426, 89.9% of patients are still alive at 1 year • 5- and 10-year survival between 20-25% and 10-15% may understate the actual long-term survival when treated with sunitinib o the COMPARZ trial provides a poor reference point for survival on standard of care (sunitinib) due to poor applicability of second line treatments to current UK practice. o CHECKMATE-025 shows 30.0% of patients treated with nivolumab in the second-line are alive at 4 years. o CHECKMATE-214 shows that the sunitinib arm reached median overall survival at 37.9 months in the ITT population. • The Weibull distribution is not appropriate to model both pembrolizumab with axitinib, and sunitinib (together or separately). It is the worst fitting curve to the sunitinib Kaplan Meier (KM) data and is not the best nor second-best fitting curve to the pembrolizumab/axitinib KM data in terms of AIC/BIC criteria, as well as having poor visual fit to observed data. • The method of modelling the immunotherapeutic effect in TA581 was based on a manually imputed association between durable response and overall survival, and therefore comparison to TA581 is not applicable

- The Weibull distribution underestimates OS of the comparator: CHECKMATE-214 estimated sunitinib OS at 37.9 months in the ITT population versus an estimated median 34.2 months and 36.7-month OS with a Weibull distribution and exponential distribution.
- For pembrolizumab with axitinib, the Weibull distribution (in this instance) has a monotonically increasing hazard rate over time, which results in a huge underestimation of the long-term OS benefits if there is a survival plateau with this technology as cited by clinical experts.
- The use of different distributions to extrapolate OS for pembrolizumab with axitinib, and sunitinib (log-logistic and exponential distributions, respectively) is "substantially justifiable" based on:
  - Evidence describing the clinical rationale and mechanism of action for combined immune checkpoint inhibitor and TKI therapy
  - The view that distributions selected for company base case have good visual and statistical fit of observed data, as well as expert opinion of OS at 10 years.
- Compared survival rates up to 20 years when estimated by Weibull and those estimated in the company base case, scenario 1(landmark analysis); and scenario 3 (log-logistic OS extrapolation for pembrolizumab with axitinib, time-constant HR for sunitinib). The company claim the values predicted from the scenario analyses are similar to, and validate, the company base case (in contrast to the predicted values using the Weibull distribution).

Table 1 from company response: Overall survival estimates using alternative approaches

Years	Base Case		Scenario 1: Landmark		Scenario 3: L-L, NMA		Weibull curve	
	P+A	S	P+A	S	P+A	S	P+A	S
1	88.5%	79.9%	88.0%	79.8%	88.5%	79.6%	88.6%	80.1%
2	76.8%	63.9%	78.0%	64.7%	76.8%	60.9%	76.2%	62.6%
5	51.9%	32.5%	57.9%	37.3%	51.9%	29.1%	44.9%	28.2%
10	31.6%	10.6%	37.2%	16.2%	31.6%	11.5%	16.5%	6.9%
20	16.5%	1.1%	15.6%	3.1%	16.5%	3.4%	1.7%	0.3%

- Requested further consideration to Scenario analysis 1, as described in Appendix P of the company submission, if the use of separate distributions to each arm is not accepted.

ERG critique:

	• Questioned comparability to TA581, which appraised a combination of two immunotherapies where treatment could continue for up to 5 years; not a combined immune checkpoint inhibitor and TKI tyrosine-kinase inhibitor (TKI) therapy where pembrolizumab is stopped after 2 years. • Noted that estimates of 5-year OS provided by clinical experts for pembrolizumab with axitinib vary between 30-50%. • Agreed with company that OS estimates may be underestimated, although it is unclear how much higher the 5-year survival would be with increased use of nivolumab as a subsequent-line of treatment. • Acknowledged the clinical rationale for combined immune checkpoint inhibitor and TKI therapy, and the different mechanisms of action proposed. However, it states that there is no robust evidence currently showing a difference in the underlying hazards for OS between pembrolizumab with axitinib and the comparator sunitinib, to support the use of different survival distributions. It also notes that the KEYNOTE-426 OS data are immature. • Noted the comparison of survival estimates using the Weibull distribution against estimates produced by the company scenario analyses 1 and 3, however, provided no further comment on whether the comparison with the selected scenarios validated the base case assumptions. • Noted that AIC/BIC statistics for pembrolizumab with axitinib show that the log-logistic and the Weibull are similar in their statistical fit to the observed data. The best statistical fit is the exponential distribution. Weibull and exponential distributions provide good visual fits to the observed data. • Noted that the exponential distribution offers a better statistical fit for sunitinib than the Weibull. The Weibull also provides a good visual fit to the observed data for sunitinib. • Noted that the Weibull distribution provides: - the closest fit to the COMPARZ trial data for sunitinib (allowing that few patients received nivolumab as a subsequent-line treatment) - 5-year OS (45%) for patients treated with pembrolizumab with axitinib is within 30%-50% range estimated by clinical experts. • Commented that the Weibull and exponential distributions appear to have good visual fit to the KEYNOTE-426 trial data on inspection of the graphs.

	• Proposed that the statistical fit with the observed data is less important than validation against long-term data.
	Patient representative: Patients are having a greater initial reduction in their tumour and subsequent scans with pembrolizumab with axitinib, and believe treatment has extended their life expectancy beyond expected, i.e. 36 months survival achieved (with good outlook) versus an expected 22.5 months for intermediate risk.
Technical team judgement after engagement	The technical team maintains that in the absence of robust evidence to justify different distributions for the extrapolation of OS for the intervention and comparator, the Weibull distribution should be applied for the extrapolation of OS for both pembrolizumab with axitinib, and sunitinib. The Weibull distribution offers a good fit to the observed data on visual inspection when considering both the intervention and the comparator data, and it produces OS estimates within the range provided by clinical experts. Nonetheless, the technical team recognise that uncertainty regarding the best distribution will remain due to the immaturity of the data.

Issue 2 – Treatment waning effect after discontinuation

Questions for engagement	4. In clinical practice, would a reduction in treatment effect be observed after treatment with pembrolizumab has been stopped? If so, at what time point? 5. What is the most appropriate duration to apply a treatment effect for people treated with pembrolizumab with axitinib?
Background/description of issue	Due to the immaturity of data, it is unclear whether treatment effect on OS is sustained beyond the 2-year stopping rule for pembrolizumab. Several NICE appraisals have questioned the treatment effect duration used in immune-oncology economic models; committees have generally preferred a 3-year or 5-year treatment effect (whereby effect persists for 1 year or 3 years after stopping

	treatment respectively) rather than a lifetime effect once treatment stops. Further detail regarding these appraisals is given below. **The company** has not included the assumption of treatment effect waning (reducing) in their base case, noting that waning of effect has not been included in previous NICE appraisals for RCC, and that patients continue to be treated with axitinib after the 2-year stopping rule for pembrolizumab. In addition, the company states that it believes a proportion of patients would derive a long-term survival benefit from the combination of an immunotherapy with a TKI. **The ERG** notes that a proportion of patients would receive second-line treatment after disease progression and this second-line treatment would influence their survival. Further, many patients who receive sunitinib as first line treatment would receive nivolumab as second-line therapy and so it may be the case that OS for patients receiving second-line treatment may be similar between treatment arms. However, as the OS data from KEYNOTE-426 is immature, the ERG did not include a treatment waning effect in the ERG base case. **The technical team** questioned the appropriate duration of the treatment effect applied in the model. The technical team notes that once treatment effect of pembrolizumab with axitinib wanes in the company model, no treatment cost of pembrolizumab with axitinib is applied and the PFS and OS probabilities associated with treatment of first line sunitinib are applied instead, until there is movement to second line treatment (i.e. due to disease progression). **The technical team** notes that duration of treatment effect has been a key issue in several previous appraisals. In TA428 (pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy), the committee preferred to assume a 3 to 5 year treatment effect duration, commencing after treatment discontinuation (i.e. 3 years after stopping treatment or 5 years from commencing treatment). Committee members in TA519 (pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) recognised that the duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty for new immunotherapies, but it concluded that a lifetime continued treatment effect was implausible. Committee members in TA600 (pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer) also considered a lifetime treatment effect to be implausible. The technical team recognises that these appraisals ([TA519],

	[TA600], and [TA428]) evaluate pembrolizumab for different indications and populations than that of the current appraisal, and that pembrolizumab was not combined with axitinib. The committee for TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma) agreed that the long term benefit of the immunological therapy had yet to be established and believed that the modelled immunotherapeutic effect relied on speculative assumptions that were not substantiated by evidence (noting that the trial had not employed a stopping rule and the definition of durable response was questionable). **The technical team** also notes that committees for other immuno-oncology appraisals have preferred either a 3-year or 5-year treatment effect (whereby effect persists for 1 year or 3 years after stopping treatment respectively), for example please see TA578 (durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemo radiation) and TA520 (atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy). On balance, **the technical team** are unclear on the most appropriate treatment effect duration, however, believe a lifetime duration is inappropriate. **Two clinical experts** have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect.
Why this issue is important	The length of assumed treatment benefit after discontinuation impacts upon the ICER, with longer treatment effects associated with a lower ICER. This is driven by a health benefit being obtained without treatment costs being incurred. Therefore, the treatment waning effect after discontinuation is an important consideration as it has a large impact on the cost-effectiveness results. The ICER increased from £59,292 in the company base case to £86,712 if the treatment waning effect was 10 years, and £133,900 if the treatment waning effect was 5 years.

<table>
<tr><td></td><td>The ICER increased from £120,455 in the ERG base case to £129,368 if the treatment waning effect was 10 years and £162,424 if the treatment waning effect was 5 years.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>The immaturity of data means that the long-term treatment effect of the drug is unclear. This does not necessarily indicate that there is a waning in treatment effect but equally there is no evidence that there isn't. When considering the analyses provided to date, the technical team prefers the assumption that treatment effect reduces at 5 years. The technical team would like the company to provide analyses exploring a treatment effect of 2 years (that is, no continued benefit after stopping treatment) and 3 years (treatment benefit ends 1 year after stopping treatment).</td></tr>
<tr><td>Summary of comments</td><td>Comments received by the company:
A lifetime treatment effect should be considered as plausible.
Clinical opinion supported the notion that there will be no loss of treatment effect post discontinuation with pembrolizumab after 2 years, and a lifetime treatment effect is plausible.
Referred to publications regarding the biochemical mode of action of the intervention which would suggest a continued treatment effect
Requested consistency of approach with the appraisals of nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA581) and nivolumab for previously treated advanced renal cell carcinoma (TA417) where no treatment waning effect imposed on the intervention.
The request for cost-effectiveness analyses exploring a treatment effect lasting until 2 years (when pembrolizumab treatment stops) and 3 years (treatment effect ends 1 year after stopping pembrolizumab treatment) was considered to be inappropriate: survival estimates indicate such analyses would be clinically implausible (please see below table):
Table 1. Overall survival estimates implementing clinically implausible treatment waning assumption
<table>
<tr><th rowspan="2">Years</th><th colspan="2">Base Case</th><th colspan="2">2-year treatment waning, base-case curve selection</th><th colspan="2">3-year treatment waning, base-case curve selection</th><th colspan="2">2-year treatment waning, ERG base-case curve selection</th><th colspan="2">3-year treatment waning, ERG base-case curve selection</th></tr>
<tr><td>P+A</td><td>S</td><td>P+A</td><td>S</td><td>P+A</td><td>S</td><td>P+A</td><td>S</td><td>P+A</td><td>S</td></tr>
</table></td></tr>
</table>

1	88.5%	79.9%	88.5%	79.9%	88.5%	79.9%	88.6%	80.1%	88.6%	80.1%
2	76.8%	63.9%	76.7%	63.9%	76.8%	63.9%	76.0%	62.6%	76.2%	62.6%
5	51.9%	32.5%	39.0%	32.5%	42.6%	32.5%	34.2%	28.2%	37.6%	28.2%
10	31.6%	10.6%	12.7%	10.6%	13.8%	10.6%	8.3%	6.9%	9.2%	6.9%
20	16.5%	1.1%	1.3%	1.1%	1.5%	1.1%	0.4%	0.3%	0.5%	0.3%

The ERG critique:

- Agreed that "the immaturity of data means that the long-term treatment effect of the drug is unclear."
- Agreed with the company that focus should be on keeping consistency with appraisals for IO therapies in renal cell carcinoma and there is not a rationale for maintaining consistency with approaches adopted in appraisals concerning different indications.
- The ERG decision to not include a treatment effect waning in the ERG base case (and present treatment waning as a scenario) is in line with NICE TA581 where no reduction in treatment effect was included.
- Noted that when the company survival estimates (table 2 in company response document) was ran through the economic model, the ICERs varied between £184,983 per QALY and £269,968 per QALY– see table below:

Table 2 – Treatment effect waning scenario analyses for treatment with pembrolizumab + axitinib compared to sunitinib (list prices)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	£137,537	2.32	£59,292
2-year treatment effect waning[a]	£116,835	0.495	£236,229
3-year treatment waning[a]	£123,483	0.668	£184,983
ERG Base case	£140,895	1.170	£120,455
2-year treatment effect waning[b]	£125,895	0.466	£269,968
3-year treatment effect waning[b]	£131,854	0.626	£210,586

a Using the company's base case fitted parametric survival curves
b Using the ERG's base case fitted parametric survival curves

Technical team judgement after engagement	The technical team recognise that the long-term treatment effect of the intervention is unclear, and therefore a lifetime treatment effect is possible. However, in the absence of mature data to substantiate a lifetime treatment effect, a scenario with a treatment waning effect is preferable to inform decision making. While consistency with TA581 and TA417 should be considered, it is noteworthy that the former did not have a 2-year stopping rule and evaluated combined immunologics which could have an alternative mechanism of action. The latter is in a population who had previously been treated and estimated time to stopping treatment via parametric modelling (median stopping time was under one year), and treatment effect duration was not seen as a key issue in this appraisal. Therefore, for decision making the technical team recommend the consideration of consistency with all relevant appraisals (i.e. those with similar indication, interventions with similar mode of action or those concerning the same drugs as the current appraisal). On balance, the technical team preferred assumption is to employ a treatment waning effect of 5 years and present the ERG and company analyses as alternative scenarios.

Issue 3 – Time horizon

Questions for engagement	6. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice in untreated metastatic renal cancer to materialise?
Background/description of issue	The NICE reference case for economic evaluation notes that the time horizon of an economic model should be "long enough to reflect all important differences in costs or outcomes between the technologies being compared", and as such typically a life time horizon is used. However, where extrapolation is uncertain, a longer than required time horizon may exacerbate any over or underestimation in difference of effect over a longer time period. **The company** employs a 40-year time horizon in the model base case analysis. **The ERG** employs a 40-year time horizon in the ERG base case analysis, citing this horizon has been commonly used in similar appraisals, and a 20-year horizon as a scenario analysis. **One clinical expert** has estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years for people treated with pembrolizumab with axitinib. This could suggest a time horizon beyond 20 years is appropriate.

Why this issue is important	Having a longer time horizon allows for a greater time for benefits to accrue to balance any costs incurred at the start of the model horizon (for example costs associated with adverse events or treatment which subsequently stops), as well as extenuate the balance between costs and effects of continued treatments. The time horizon has a moderate impact on the cost-effectiveness results, whereby a reduction in the time horizon allows for less time for benefits to accrue (and balance the cost of adverse events and pembrolizumab which has a 2-year stopping rule). Further a reduction of the time horizon reduces the overall cost effectiveness of the intervention that may be driven by the balance between costs and effects of ongoing first and second-line treatments (which may be driven by assumptions considered favourable to the intervention). The ICER increased from £59,292 in the company base case to £68,760 when the time horizon was reduced to 20 years.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG scenario analysis that a 20-year time horizon should be sufficient to capture all important benefits and costs arising from choice of treatment for untreated metastatic renal cancer for a population with a mean age of 62 years.
Summary of comments	**Company response:** • Noted that the ERG base case agreed with the company base case of 40 years • A 40-year horizon is consistent with TA581 • Noted, under company preferred assumptions, 16.5% of patients in the pembrolizumab with axitinib arm and 1.1% of patients in the sunitinib arm were expected to be alive at 20 years • Referred to clinical opinion within the technical report that expressed a plateau of 25% survival could be plausible at 10 and 20 years **ERG critique:** • Agreed that the choice of time horizon is linked to preferred assumptions for Issue 1 and 2 above for extrapolation of overall survival and treatment waning. • Noted that technical report needed correction to state that the ERG used a 40-year time horizon in their base case and a 20-year time horizon as a scenario analysis. • Agreed that a lifetime time horizon of 40 years is most appropriate because it is able to show the differences in costs and outcomes in all scenarios.
Technical team judgement after engagement	The technical team have corrected the technical report in line with ERG and company comments (amended text underlined above). The technical team note the absence of robust evidence to

	suggest survival beyond 20 years for a population with a mean age of 62 years. Additional survival estimates by the company in response to engagement (see issue 2) indicate that with a treatment waning effect a 20-year horizon is a plausible time frame to capture all important benefits and costs arising from choice of treatment for untreated metastatic renal cancer within the economic model. The technical team also recognises other scenarios may indicate that a longer horizon is appropriate, however, these scenarios are not based on the preferred assumptions of the technical team and result in projections that are believed to be either optimistic or highly uncertain. Notwithstanding committee judgement regarding expected survival and in recognition of the uncertainty in survival estimates and treatment effect duration, the technical team have modified the time horizon in their analysis to 40 years. As the technical team, ERG and company are aligned in their viewpoint, and no further comments were made on this key issue, this issue is viewed to have been resolved at technical engagement.

Issue 4 – Subsequent treatment after first line treatment has stopped

Questions for engagement	7. In clinical practice, what proportion of people would be expected to have subsequent treatment(s), following first line treatment with pembrolizumab with axitinib, and sunitinib respectively? 8. Which subsequent treatment(s) would be used and in what proportions? 9. Are there any treatments that are used subsequently to pembrolizumab with axitinib, and/or sunitinib that are of particular note in regard to their treatment related adverse event (TRAE) profile (in particular in terms of the TRAE's expected frequency, cost and impact on health related quality of life)?
Background/description of issue	The company economic model allows for people who have stopped first-line treatment to move to second-line treatment. However, the second-line therapies used in the KEYNOTE trial were not considered to be relevant to UK clinical practice and were therefore not considered in the economic modelling; these included cytokines (interferon), temsirolimus and everolimus. Further, lenvatinib/everolimus was not considered in the ERG or the company base case. In addition, it is unclear whether the proportion of people receiving a given second-line treatment within the model is reflective of current UK practice. When considering this issue, it

should be kept in mind that OS is in part determined by second-line therapies which were given in the pivotal trial.

The company base case assumes that 50% of patients who had progressed on first-line treatment for RCC receive second-line treatment (as per the NHS England submission in TA581). The company base-case model assumes people who receive pembrolizumab with axitinib as first-line treatment would receive the second-line treatment of pazopanib (30%) or sunitinib (20%)

The ERG noted that they had received expert clinical opinion that a higher proportion (55%-70%) of people who progress on first-line therapy could receive subsequent therapy. An alternative ERG scenario is also run where a higher proportion (60%) of patients receive second-line treatment. The ERG also believed that a higher proportion of people (20%) who receive pembrolizumab with axitinib as first-line treatment would receive the second-line treatment of cabozantinib.

Table 1 below shows the distributions found in the KEYNOTE-426 trial, the company base case and the ERG base case and scenario analysis.

The technical team notes that no adverse events are associated with subsequent treatment within the model and therefore alterations in the proportion of people receiving subsequent treatment will alter overall cost of the strategy, but not quality of life. Cabozantinib has the highest drug acquisition cost of all of the subsequent therapies, and therefore increasing the proportion of people that would have this therapy as second line to pembrolizumab with axitinib, would favour the comparator.

Clinical experts estimated that 70% to 80% of people get second-line treatment after treatment with pembrolizumab with axitinib (and that 60% to 80% of people get second line therapy with sunitinib). **Clinical experts** estimated that 40% to 60% of people who have pembrolizumab with axitinib would have cabozantinib as a second-line therapy.

Table 1. Total acquisition cost and proportion of patients on subsequent-line treatment (list price)

	Total drug acquisition cost	KEYNOTE-426 trial	Company base case	ERG base case	ERG scenario analysis

Subsequent treatment	**(2018 GBP list price)**	**Pembro' + axitinib**	**Sunitinib**	**Pembro' + axitinib**	**Sunitinib**	**Pembro' + axitinib**	**Sunitinib**	**Pembro' + axitinib**	**Sunitinib**
Best supportive care		[redacted]	[redacted]	50%	50%	50%	50%	40%	40%
Lenvatinib/ everolimus	42,856.12	[redacted]	[redacted]	0%	0%	0%	0%	0%	0%
Axitinib	46,133.02	[redacted]	[redacted]	0%	8%	0%	8%	0%	8%
Cabozantinib	63,235.08	[redacted]	[redacted]	0%	13%	20%	13%	20%	13%
Nivolumab	41,804.38	[redacted]	[redacted]	0%	30%	0%	30%	0%	40%
Pazopanib	20,884.69	[redacted]	[redacted]	30%	0%	20%	0%	25%	0%
Sunitinib	18,140.54	[redacted]	[redacted]	20%	0%	10%	0%	15%	0%

Reproduced from ERG report Table 37, Table 36 and Table 47. Data regarding second line therapies not considered relevant to UK practice in KEYNOTE-426 included: cytokines (interferon), temsirolimus and everolimus, and as such are not considered within this table.

Why this issue is important	Consideration of subsequent treatments can have a substantial effect on cost-effectiveness estimates. Greater health gains can be expected along with increased costs, if the proportion of people assumed to receive subsequent treatments is increased. Further, if more people progress to expensive second line treatments, the overall costs of the strategy will increase. Changing the proportion of people on subsequent treatment in line with the ERG base case and scenario analysis increases the company base case ICER from £59,292 to £62,910, and £61,720 respectively.
Technical team preliminary judgement and rationale	It is appropriate to include cabozantinib as a second-line treatment for pembrolizumab with axitinib. This allows the model to be in line with clinical expert opinion sourced by the ERG and the technical team, as well as with the findings of the pivotal trial (where approximately [redacted] of patients had cabozantinib as subsequent treatment). Therefore, the ERG base case distribution of people on specific subsequent treatment, including best supportive care, is the technical team's preferred assumption (please see Table 1 within the "Background/description of issue" section above).
Summary of comments	**Comments received by the company:** • Considers approach used by ERG in its base case to be reasonable.

	• Emphasises that scenario analysis 12 from the CS, which uses the KEYNOTE-426 trial-based distribution of subsequent-line therapies to model the cost of subsequent therapy, should be considered as a relevant scenario. **ERG critique:** • Reiterated what was stated in the technical report and in the company response.
Technical team judgement after engagement	The company does not disagree with the technical team or ERG preferred assumptions, but request that scenario 12 in the company submission is considered as a relevant scenario. Therefore, the technical team maintains their judgement that the scenario proposed in the ERG base case should hold as a preferred assumption. As the technical team, ERG and company are aligned in their viewpoint, and no further comments were made on this key issue, this issue is viewed to have been resolved at technical engagement.

Issue 5 – Health related quality of life (HRQoL)

Questions for engagement	10. Is using age-related disutility appropriate within the economic model? 11. Is using a time to death approach to estimation of utility for use within the economic model appropriate? 12. Are the preferred assumptions found in answer to questions 9 and 10 regarding the estimation of utilities in the main analysis, also the preferred assumptions in the subgroup analysis of the poor IMDC poor risk subgroup?
	Two key assumptions underpin the company model's estimation of HRQoL. 1. Age related disutility **The company** uses age-related disutility in the economic model, and thereby there is an implicit assumption that HRQoL will decrease with age regardless of treatment choice for untreated metastatic renal cancer. **The ERG** acknowledges that that including age-adjusted utility is recommended by NICE DSU Technical Support Document, however, disagrees that an age-related disutility should be used because the company found that the utility values derived from the trial data were not associated with age.

	The technical team disagrees with the ERG that an age-related disutility should not be considered given the long time horizon of the company model. However, if a shorter time horizon is preferred, then the technical team recognises that the disutility associated with age may already be accounted for through use of the trial data. **Clinical experts** indicated that performance and control of disease would be a better indicator of HRQoL than age**. One expert** commented that the effect of age over a median survival period of 2-3 years is negligible. 2. Time to death approach to estimation of utility **The company** uses a time to death approach in estimation of utility values from the trial. This assumes that the proximity in time to death has a greater influence on HRQoL than state of disease. **The ERG** considers that a health state or a time to death approach to utility estimation is reasonable, noting that disease progression may not fully capture all predictive factors of patient utility and time to death provides a reasonable fit to patient data. The ERG noted that the company scenario analysis suggested that the approach to utility estimation did not have a large impact on results. **The technical team** recognises that time to death may be an appropriate approach. However, this approach implies no change in HRQoL ≥360 days from death. It is unclear if clinical opinion supports this assumption. This assumption has particular relevance if OS is overestimated, as a higher estimation HRQoL may be sustained over a longer period, regardless of disease progression and age (if no age-related disutility is applied). **Clinical experts** commented that both control of disease and time until death were important factors in determining HRQoL. One expert concluded that HRQoL is most associated with the patient's disease status. When disease progression begins to occur, patients move closer to death and may experience stepwise deterioration as the time period shortens (unless subsequent therapy is again able to achieve good disease control).
Why this issue is important	The preferred approach to estimation of utility may have greater importance and impact on the ICER dependent on which preferred assumptions are used. It is currently unclear if the approach taken has clinical plausibility and therefore this is a potentially important issue.

	The company base case ICER rises to £60,876 when health state-based utilities are treatment specific and £63,400 when pooled, with an age-related utility decrement applied. To note, use of utility values from previous appraisals (tivozanib [TA512] and pazopanib [TA215]) in this topic area has a large impact on the ICER. However, the ERG and the technical team agree that the company's use of the KEYNOTE-426 data is preferable to other sources.
Technical team preliminary judgement and rationale	The technical team are unclear if there is justification for a time to death approach to estimation of utility to be used in the model, and notes that its use may exacerbate any bias introduced by optimistic OS of the intervention. The technical team note that age may have greater impact on HRQoL if people with RCC are expected to have a longer life expectancy due to new treatment. Therefore, the technical team proposes that pooled health state utilities are used with an age-related utility decrement due to the need to model HRQoL over a time horizon longer than the trial.
Summary of comments	**Comments received by the company:** • Deemed it plausible to remove age-adjusted utility from the base-case assumption • The health-state based approach has severe limitations considering only one EQ-5D questionnaire was administered per patient, 30 days after disease progression, limiting post-progression. • To support the assumption that patients who were ≥360 days from death were in a stable state, the company fitted a non-parametric LOESS function to the scatterplot of EQ-5D utility by time to death for all records measured ≥360 days from death (Figure 1, company response). • Conducted a further analysis, which was described as a 'hybrid' approach of time-to-death utilities combined with health-state based utilities, and stated that this approach adds significant complexity and uncertainty compared to a model based on time-to-death alone or health state alone because of small sample size and extreme unbalance between

	progression status for "≥360-days-from-death" (n=54 for progressive disease, but n=1978 for progression-free, among "≥ 360 days from death" patients). • Recommended time to death approach as it utilised more health states than the model based on progression status only, and captured most of the variance in the data. **ERG critique:** • Agreed with the company that because there was no correlation between age and baseline utility assessment in the KEYNOTE-426 trial (clarification question B11), it was unnecessary to include age-related utility. • Agreed with the company that a time to death approach is reasonable, given that inclusion of the disease progression state may not fully capture all predictive factors of patient utility and time-to-death provides a good fit to patient data. • Agreed with the company there was little change in HRQoL when patients were ≥360 days from death in the KEYNOTE 246 trial (based on the analysis presented in figure 1 of the company response document) • Noted the additional analysis undertaken by the company which presented a hybrid method combining time to death and health state utilities, noting that the utilities derived from this analysis were not applied in the cost-effectiveness model. The ERG notes a rationale was not given for the analysis, but does not comment on the validity of the method. Both the **ERG** and the **company** agreed that the assumptions for the main analysis should also be applied in the subgroup analysis for the intermediate/poor risk group.
Technical team judgement after engagement	The technical team recognises that there appears to be no correlation between age and baseline utility (i.e. prior to treatment for metastatic RCC) in the KEYNOTE-426 trial, however, does not believe that HRQoL will not decline with age over a 40-year horizon, and there is no evidence presented to suggest that no correlation will be observed after treatment is given. Therefore, the technical team agrees with the approach in the company submission to adjust HRQoL with age in the economic model. The technical team, although recognising HRQoL appears constant in the duration of the KEYNOTE-426 trial ≥360 days from death, still remain uncertain whether patients who are ≥360

	days from death are in a stable state over a 40-year horizon (also noting that extrapolations of the timing of disease progression suggest a change in disease status prior to 360 days before death). The time to death approach, as applied in the company model, means that the cumulative QALY gain is closely tied to the expected survival of the population, rather than based on the expected time of disease progression. The technical team also note that the timing of a change in HRQoL using the time to death approach in the model is based on OS data (which is immature) rather than on the PFS data (which is mature). The technical team agree with the company that the hybrid approach to utility derivation (presented by the company in response to engagement) adds complexity and uncertainty, and running an analysis with these utilities would not reduce uncertainty. The technical team have opted to maintain their preliminary judgement regarding the application of utilities based on disease progression, and as such prefer to use pooled health state utilities to keep consistency with the three health state modelling approach. However, the technical team agree with the ERG report in that either method may be valid, and recognise that the small sample size informing utilities for the post progression state introduces uncertainty in the HRQoL estimation. As such, a scenario analysis using a time to death approach to estimate utilities should be considered; notwithstanding that the application of such an approach within the economic model will likely overestimate the QALY gain if survival is also overestimated.

Issue 6 – Approach to NMA to inform the economic model subgroup analysis

Questions for engagement	13. Should a constant HR approach NMA (as opposed to a varying hazard approach) be used to inform the economic model?
Background/description of issue	The company economic model uses the NMA results to inform a subgroup analysis for the intermediate/poor RCC subgroup. **The company** stated that a constant HR NMA produced more stable results than the use of a time varying hazards approach in the NMA which informed the subgroup analysis for the intermediate/ poor risk subgroup. **The ERG** notes that the constant hazards NMA was conducted according to standard methods as recommended by the NICE DSU, and noted the time-varying hazards NMA approach produced

	unstable results. Noting that the appraisal committee in NICE TA512 (tivozanib) had raised concerns that the choice of fractional polynomial model had a substantial impact on the cost-effectiveness results, the ERG undertook a scenario analysis on the NMA approach which demonstrated a large variability in cost effectiveness results. For the two time varying hazard fractional polynomial models used, the ICER varies between £117,279 and £149,347 per QALY gained in the ERG scenario analysis, which is substantially higher than the ERG base case ICER of £48,424.
Why this issue is important	The method of the approach taken in the NMA that informs the subgroup economic analysis has a large impact on the ICER.
Technical team preliminary judgement and rationale	The uncertainty on conclusions introduced by the method of undertaking the subgroup NMA is acknowledged by the technical team. However, a constant HR NMA approach appears reasonable in the absence of a strong justification to use an alternative approach.
Summary of comments	**Comments received by the company:** • Maintained that the constant HR approach used in the NMA are the most appropriate to inform the subgroup analysis of the intermediate/poor risk group in the economic model. **ERG critique:** • Clarified that the draft technical report required amendment, noting that the ERG did not disagree with the approach taken and that the time-varying hazards NMA approach produced unstable results. • The ERG agrees with the company (and the technical team) that despite the violation of the proportional hazards assumption in some instances, the use of a constant hazards NMA is more appropriate than time-varying fractional polynomials when length of follow-up is short, or sample size is small.
Technical team judgement after engagement	The technical team have amended the technical report in line with ERG comments (amended text underlined above). As the technical team, ERG and company are aligned in their viewpoint, and no further comments were made on this key issue, this issue is viewed to have been resolved at technical engagement.

Issue 7 – End of life

Questions for engagement	14. Do patients in the IMDC poor risk subgroup meet the end of life criteria? a. Under standard care/cabozantinib, is the life expectancy of people with poor risk RCC more than 24 months? b. Does pembrolizumab with axitinib extend life for more than 3 months for people with poor risk RCC compared with standard care/cabozantinib?
Background/description of issue	In its submission, **the company** does not consider pembrolizumab with axitinib to meet the NICE end of life criteria for the overall RCC patient population. The **technical team** and **ERG** note that estimates of OS for sunitinib in pivotal phase III RCTs are in excess of 24 months and therefore agree with the company that criterion 1 (which states that the treatment is indicated for patients with a short life expectancy, normally less than 24 months) would not be met for the overall RCC patient population. • A randomised, phase III trial of sunitinib compared with interferon alfa as first-line treatment for metastatic RCC reported median OS of 26.4 months in the sunitinib arm (Motzer et al 2009). • A randomised, open-label, phase III trial of pazopanib versus sunitinib reported median OS as 29.3 months in the sunitinib group and 28.4 months in the pazopanib group (Motzer et al 2013). However, **the company** considers that patients in the poor risk subgroup (as defined by the IMDC criterion) would meet end of life criteria with a life expectancy of less than 24 months, and an expected increase in life expectancy of greater than 3 months. The company cites the following evidence in support that patients in the poor risk subgroup (as defined by the IMDC criterion) would meet end of life criterion 1 (that the treatment is indicated for patients with a short life expectancy, normally less than 24 months): • A randomised, open label phase II trial comparing cabozantinib with standard-of-care sunitinib in IMDC intermediate and poor risk patients with advanced RCC in the first-line setting reported median OS of 21.8 months with sunitinib and 30.3 months with cabozantinib

	(Choueiri et al 2017). This patient population has inferior clinical outcomes compared to an all-comer population. • Final results from an extended follow-up of a global, expanded-access trial that, prior to regulatory approval, provided sunitinib to metastatic RCC patients, ineligible for registration-directed trials. Median OS was reported for the all-comer population of 18.7 months. The subpopulations stratified by risk group of favourable, intermediate and poor reported median OS of 56.5 months, 20.0 months and 9.1 months, respectively. The patient population included within this study had a proportion of patients that had received prior systemic therapy (Gore et al 2015). **The company** states that there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment: • Median OS does not accurately capture the OS benefit in patients treated with pembrolizumab in combination with axitinib; instead, the mean provides a more reliable statistical measure for estimated OS in patients treated with pembrolizumab in combination with axitinib, due to the longevity of the benefit observed in some patients. • Median OS was not reached in KEYNOTE426; however, there was an improvement in 12 months OS rate with pembrolizumab with axitinib versus sunitinib of 11.6% (89.9% vs 78.3%). • Based on economic modelling there is an estimated improvement in 2 years OS rate of 14.1% (78.0% vs 63.9%) and 3 years OS rate of 17.7% (68.8% vs 51.1%). In summary**, the company** claims that people with IMDC poor risk RCC would meet the end of life criteria as they have a life expectancy of less than 24 months, and would have an expected increase in life expectancy of greater than 3 months with pembrolizumab with axitinib. The company cites pivotal phase III trials of first line RCC treatments, including CABOSUN (median OS was 30.3 months for cabozantinib, and 21.8 months for sunitinib), which included intermediate/poor RCC risk patients. Other trial estimates of OS for sunitinib were in excess of 24 months (though not restricted to intermediate/poor risk patients). The company also notes final results from extended follow-up of a global, expanded-access trial of sunitinib treatment in 4543 patients with metastatic RCC ineligible for registration trials. Median OS stratified by risk group was 56.5 months (favourable risk), 20.0 months (intermediate risk), and 9.1 months (poor risk). The distribution of patients across

	IMDC risk categories was 22%, 48% and 20%, respectively. However, this study did not include cabozantinib. **The ERG** had concerns that the company appears to have used sunitinib as the standard of care arm instead of cabozantinib (which is currently recommended for this group, please see NICE TA542) in the end of life consideration in the poor RCC risk subgroup. The ERG noted that no rationale was provided by the company as to why the poor risk subgroup was chosen, when in their assessment of clinical and cost-effectiveness, the subgroup considered is intermediate/poor risk. The ERG was therefore unable to generate modelled estimates of OS for the poor risk subgroup patients to inform end of life assessment. The ERG disagreed with the company that pembrolizumab with axitinib meets the first end of life criterion (treatment is indicated in patients with a short life expectancy, normally less than 24 months) in the poor risk RCC subgroup. **The technical team** notes that the committee for TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma) considered that the end of life criteria in the intermediate-poor risk group had not been met because the median overall survival in the sunitinib arm of CheckMate 214 was 25.9 months.
Why this issue is important	The appraisal committee's judgements about the acceptability of the technology as an effective use of NHS resources will take into account whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'. A technology which meets the NICE end of life criteria has an increased maximum acceptable ICER.
Technical team preliminary judgement and rationale	It appears that pembrolizumab with axitinib meets the second end of life criterion (expected increase in life expectancy of greater than 3 months) for the poor/intermediate risk group. However, there is no supportive evidence presented that the first criterion is met in this subgroup for whom cabozantinib is the recommended first-line treatment. Based on evidence presented in TA581, the technical team considers it unlikely that end of life criteria is met for this indication. It is not clear if the end of life criteria are fully met for the poor risk subgroup and whether pembrolizumab with axitinib should be considered as a life-extending treatment for people with a short life expectancy in this subgroup in particular.

Summary of comments	**Comments received by the company:** • Patients in the IMDC poor risk subgroup meet the end of life criteria. The company reiterated the rationale provided within its submission. **ERG critique:** • Noted that the company reiterated arguments provided in the company submission and did not provide further data or justification for meeting the first or second end of life criterion • Disagreed with the company that pembrolizumab with axitinib meets the first end of life criterion in the poor risk subgroup, because the overall survival of 30.3 months for intermediate/poor risk patients in the CABOSUN trial of cabozantinib exceeds the end of life criterion of less than 24 months life expectancy. • Reiterated that the ERG could not generate modelled estimates of OS for poor risk subgroup because the company's assessment of clinical effectiveness and cost effectiveness is for the intermediate/poor risk subgroup combined. **A commentator** noted the lack of direct comparative data between pembrolizumab with axitinib and cabozantinib in the poor risk group. They also noted the limitations of using Gore et al (2015) to estimate survival in this group, and in particular noted issues in specification of baseline characteristics and applicability of findings to the present day. They noted that the CABOSUN trial was not powered for OS and included few poor-risk patients (15 cabozantinib, 15 sunitinib), which was noted by both the ERG and the committee during the appraisal of cabozantinib (TA542).
Technical team judgement after engagement	The technical team maintains that it is unlikely that end of life criteria is met for this indication in the poor risk subgroup, the intermediate/poor risk subgroup and in the general population of metastatic RCC.

Issue 8 – Cancer Drug Fund

Questions for engagement	13. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in this population? 14. When will these additional data become available? 15. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?

Background/description of issue	The overall survival data is immature. Overall, there is no long-term data available to understand duration of treatment effect. Longer term follow-up data may provide greater certainty regarding the duration of sustained effect of pembrolizumab with axitinib (taking into account the 35-dose stopping rule of pembrolizumab), as well as, the overall survival of people with untreated metastatic RCC who have pembrolizumab with axitinib. The KEYNOTE-426 trial is currently ongoing, with an estimated end date of January 2020. **The company** has noted a preference for routine commissioning in the NHS in England and did not comment on the suitability of pembrolizumab with axitinib for the CDF within the main submission. **The ERG** has made no comment on the suitability of pembrolizumab with axitinib for funding through the CDF as the company have not expressed any intention to pursue it in its submission. **The technical team** notes that the available KEYNOTE-426 OS data is immature. If there was a plausible potential for the technology to be cost-effective, further data from KEYNOTE-426 trial may help to reduce uncertainty regarding overall survival extrapolation (issue 1), treatment effect of pembrolizumab with axitinib (issue 2) and the most appropriate time horizon to use in the economic model (issue 3).
Why this issue is important	The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid delaying patient access, but would require further information on its effectiveness before it can be considered for routine commissioning when the guidance is reviewed.
Technical team preliminary judgement and rationale	The technical team is aware of the high level of uncertainty resulting from the immature data presented from the KEYNOTE-426 trial and that overall survival estimates impact substantially on cost-effectiveness estimates. Additionally, it is unclear whether pembrolizumab with axitinib has a sustained treatment effect (taking into account the potential impact of stopping pembrolizumab after 2 years). Duration of treatment effect also has a large impact on the expected cost effectiveness of the intervention.

	The technical team would like input from the company regarding the timescale of when further data from KEYNOTE-426 is likely to become available, what this additional data will be, and whether any uncertainty around the company's assumed lifetime treatment effect and duration of response can be resolved. Therefore, the drug may be a candidate for the CDF, but there is uncertainty regarding its suitability.
Summary of comments	**Comments received by the company:** • The combination of pembrolizumab and axitinib for treating RCC is a suitable candidate for the Cancer Drug Fund. The completion of KEYNOTE-426 has been postponed to [redacted] and a Clinical Study Report for KEYNOTE-426 is expected in [redacted] **ERG critique:** • **The ERG** had no additional comments to those stated in this report in relation to uncertainties around clinical effectiveness and cost-effectiveness **A patient representative** commented that the Cancer Drug Fund would be a good choice for this technology while the clinical trial data matures.
Technical team judgement after engagement	At the current value proposition and using the technical team's preferred assumptions, pembrolizumab with axitinib does not appear to have plausible potential for cost-effectiveness with ICERs all above the £20,000–£30,000 per QALY gained range (when commercial arrangements are considered). It is therefore unlikely to meet the criteria for inclusion in the Cancer Drugs Fund. The available KEYNOTE-426 data are immature. If there was a plausible potential for the technology to be cost-effective, further data collection in the Cancer Drugs Fund may help to reduce uncertainty; however, it is uncertain whether the data will become sufficiently mature within the proposed timeframe to resolve uncertainties in the evidence base.

Issue 9 – Stopping rule in the treatment of pembrolizumab at 2 years

Questions for engagement	16. Are treatment stopping rules appropriate in the treatment of RCC? 17. Would the 2-year stopping rule for pembrolizumab be implemented in clinical practice for RCC?
Background/description of issue	The KEYNOTE 426 trial protocol states that patients in the combination arm must discontinue pembrolizumab after receiving 35 doses but may continue receiving axitinib until disease progression. 35 doses equate to approximately 2 years of treatment. **The company** comment that, as per the anticipated licensed indication, patients treated with pembrolizumab with axitinib were expected to be treated until disease progression or unacceptable toxicity. In line with the KEYNOTE-426 protocol, a stopping rule was implemented in the economic model whereby patients did not receive pembrolizumab therapy beyond 2 years (and no costs for pembrolizumab were applied beyond 2 years). Patients discontinuing pembrolizumab after 24 months could continue treatment with axitinib, as per KEYNOTE-426 protocol, until disease progression or unacceptable toxicity. In the company scenario analysis 13, patients also discontinued treatment with axitinib after a maximum of 2 year, resulting in an ICER of £50,436. **One clinical expert** commented that stopping rules for the combination therapy would be according to patient tolerance. Following a very good response then pembrolizumab and axitinib could be stopped after 2 years of therapy with the expectation of continued treatment effect. Another **clinical expert** commented that the company had set a stopping rule of a maximum of 35 infusions for pembrolizumab, which would be followed in clinical practice. During the process of technical engagement, **the technical team** questioned whether a 2-year stopping rule for pembrolizumab would be clinically appropriate for untreated metastatic RCC. A stopping rule (to stop treatment after 5 years) was not accepted in TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma); however, the pivotal trial supporting this appraisal did not have a specified stopping rule (in contrast to KEYNOTE-426).
Why this issue is important	In the economic model, the stopping rule stops the accrual of treatment costs of pembrolizumab for all patients after 2 years. However, it is assumed in the company base case that there is a continued lifetime treatment effect. If the stopping rule in the model was removed, it is likely that the ICER would increase.

Technical team preliminary judgement and rationale	The application of a stopping rule for pembrolizumab, in the combination treatment of pembrolizumab with axitinib for untreated metastatic RCC, is appropriately applied within the company economic model given that a stopping rule was implemented within the pivotal trial informing the economic model. As such, no cost-effectiveness evidence was submitted for this appraisal without the stopping rule for pembrolizumab applied; therefore, the cost-effectiveness for this scenario cannot be determined. Further clinical expert input would be required to determine whether the 2-year stopping rule for pembrolizumab would be clinically appropriate in the treatment of RCC.

4. Issues for information

Tables 1 to 5 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab with axitinib versus sunitinib for untreated metastatic renal cell carcinoma (estimates are based on list price of all treatments and apply to the overall RCC population).

Alteration	Technical team rationale	ICER	Change from base case
Company base case		£59,292	
1. Extrapolation of overall survival to use the Weibull distribution for both intervention and comparator	The technical team agree with the ERG that the Weibull distribution is the best fit (see issue 1).	£118,931	£59,639
2. A treatment waning effect of 5 years is used.	The technical team questioned if treatment effect was likely to extend beyond 5 years (see issue 2).	£133,900	£74,608
3. Likelihood of subsequent treatment is in line with the ERG preferred assumption and includes cabozantinib as a valid second line treatment for the intervention.	The technical team believe the ERG preferred assumptions regarding likelihood of subsequent treatment are preferable given clinical opinion and the distribution of people	£62,678	£3,385

Alteration	Technical team rationale	ICER	Change from base case
	taking subsequent therapy in the pivotal trial (see issue 4).		
4. Pooled health state utilities are used instead of time to death estimated utilities with an age-related decrement (i.e. company submission scenario 7).	The technical team notes that the ERG believe both methods of utility estimation are acceptable, however, the technical team believe that using time to death utilities may overestimate the benefit of OS (which is uncertain and possibly overestimated in the model due to immature data) and underestimate the difference in benefit observed with PFS. The technical team agree with the company and ERG that the same utilities can be used for the different treatment arms. In line with methodological guidance and due to health state utilities employed, an age-related decrement is used (see issue 5).	£63,400	£4,107
5. Estimation of time on treatment (ToT) to be estimated using a Weibull distribution.	The technical team agreed with the ERG that the Weibull distribution should be used to extrapolate treatment for pembrolizumab, axitinib and sunitinib because there is not substantial justification presented for a different distribution (exponential) to be used for axitinib and sunitinib. The Weibull gives estimates which are similar to the company's clinical experts and in line with methodological advice in DSU 14.	£58,671	-£621
6. Cost of terminal care to £8,073 (the company model cost was £6,789.76)	The technical team considers the ERG estimate to be more comprehensive and in line with TA542.	£59,235	-£58

Alteration	Technical team rationale	ICER	Change from base case
7. Administration costs of oral treatment set to £0 (The company includes a £174.40 administration cost for IV and oral treatments in the model.)	The technical team recognises that the company may have double counted the cost of oral drug administration given a follow-up outpatient consultation is included (equating to approximately 1 consultation every 4 weeks). The technical team therefore agrees with the ERG base case assumption of zero cost for the administration of oral drugs.	£59,488	£196
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate		£175,316[a]	£116,024[b]

a) Updated from previously reported ICER of £150,257; b) Updated from previously reported change of base-case of £90,064

Table 2: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab with axitinib versus the comparator in the main general RCC population analysis (estimates are based on list price for all treatments)[a]

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
Company base case	£59,292	£56,648	£57,540	Not applicable				Not applicable
1. Weibull distribution to model OS	£118,931	£113,472	£115,314		£59,639	£56,824	£57,774	
2. A treatment waning effect of 5 years	£133,900	£127,687	£129,783		£74,608	£71,039	£72,243	
3. Likelihood of subsequent treatment is in line with the ERG assumption	£62,678	£60,033	£60,925		£3,385	£3,385	£3,385	

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
4. Pooled health state utilities with an age-related decrement	£63,400	£60,572	£61,526		£4,107	£3,924	£3,986	
5. Weibull distribution to model ToT	£58,671	£55,895	£56,829		-£621	-£753	-£711	
6. Cost of terminal care: £8073	£59,235	£56,590	£57,483		-£58	-£58	-£58	
7. Administration costs of oral treatment set to £0	£59,488	£57,136	£58,029		£196	£489	£489	
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate [a]	£175,316	£168,173	£170,877		£116,024	£111,525	£113,337	

a) Table correction: Respectively for sunitinib, tivozanib and pazopanib, previous ICERs were £150,257, £144,425 and £146.638; previous changes from ICER were £90,064, £87,777 and £89,098.

Table 3: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab with axitinib versus the comparator for the intermediate/poor risk subgroup analysis (estimates are based on list price of all treatments)[a]

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
Company base case	£59,766	£57,611	£58,350	£21,452				
1. Weibull distribution to model OS	£134,527	£129,524	£131,241	£35,338	£74,761	£71,913	£72,890	£13,886
2. A treatment waning effect of 5 years	£125,775	£121,043	£122,667	£54,108	£66,009	£63,432	£64,316	£32,657

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
3. Likelihood of subsequent treatment is in line with the ERG assumption	£63,244	£61,089	£61,829	£26,931	£3,478	£3,478	£3,478	£5,479
4. Pooled health state utilities with an age-related decrement	£63,837	£61,535	£62,325	£23,351	£4,071	£3,924	£3,975	£1,899
5. Weibull distribution to model ToT	£60,513	£58,305	£59,061	£22,874	£747	£694	£711	£1,422
6. Cost of terminal care: £8073	£59,709	£57,554	£58,293	£21,395	-£57	-£57	-£57	-£57
7. Administration costs of oral treatment set to £0	£59,902	£57,988	£58,727	£23,176	£136	£377	£377	£1,724
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate[a]	£179,701	£173,921	£176,150	£82,488	£119,935	£116,310	£117,800	£61,036

a) Table correction: Respectively for sunitinib, tivozanib, pazopanib and cabozantinib, previous ICERs were £141,025, £136,590, £138,304 and £75,589; previous changes from ICER were £81,259; £78,979; £79,953 and £54,137.

Table 4: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
There is an immature evidence base to inform overall survival.	The KEYNOTE-426 trial showed statistically significant improvement in both co-primary endpoints and key secondary endpoint. Efficacy testing was therefore stopped at an interim time point. The median duration of follow-up at this time was 13.2 months	It is unknown what impact this could have on the cost-effectiveness results as survival estimates may be overestimated for both intervention and comparator.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	(pembrolizumab with axitinib) and 12.1 months (sunitinib). The early stopping of trials can lead to overestimation of treatment effect. Median overall survival in the trial had not yet been reached and analyses are based on extrapolated mean values.	

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Demographics and clinical characteristics of the KEYNOTE 426 trial population. The pivotal trial population may not be representative of the people with untreated metastatic renal cancer in the UK. The trial population may be younger and fitter than people in the UK with untreated metastatic RCC.	Findings of the trial and economic model may have limited applicability to the UK NHS. 63% of trial participants were from outside of Europe, and the number of participants randomised in the UK was unclear. The median age of the trial population was 62 years (range 26 to 90 years), with 38% of the trial population greater than 65 years of age, and 73% were men. In the UK, estimates suggest 65% of new cases of kidney cancer are in people greater than 65 years of age (data from years 2014 to 2016). The trial population had locally advanced or metastatic RCC with clear cell component ± sarcomatoid features. The population may therefore not be generalisable to the wider RCC population. Additionally, there were some participants who had recurrent disease which may have been treated at the advanced stage.	Younger people are likely to have better outcomes so if the trial population is younger than the people whom will be seen in clinical practice in the UK, then the survival estimates from the trial could be overestimated. The impact of this area of uncertainty on cost effectiveness is not clear.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Demographics and clinical characteristics of the populations within the studies informing the NMA.	The populations of the studies included within the NMA may not be representative of the people with untreated metastatic renal cancer in the UK and therefore findings of NMA may have limited applicability to the UK NHS. The evidence used in the NMA reflects the decision problem with the exception of the population having a more precise definition for clear cell (± sarcomatoid features) and some participants may have been treated at an advanced stage previously.	In the economic model, only the subgroup analysis for intermediate/poor risk subgroup was informed by the NMA. The impact of this area of uncertainty on cost effectiveness is not clear.
Small datasets and potential heterogeneity in studies used in NMA	The subgroup NMA analyses are based on subsets of randomised patients in the KEYNOTE 426 trial. The use of subsets and smaller samples of patients within the analysis can increase uncertainty about the precision of treatment effects.	The impact of this area of uncertainty on cost effectiveness is not clear.
Adverse events in second-line treatment were not explicitly modelled.	This assumption will have more importance if the it is assumed a higher proportion of patients have active second-line treatment and/or the safety profile of those treatments result in high cost or HRQoL reducing adverse events.	The impact of this area of uncertainty on cost effectiveness is not clear.

Table 5: Other issues for information

Issue	Comments
A separate subgroup analysis was performed for the IMDC poor/intermediate risk subgroup	The NICE scope for this appraisal did not specify any subgroups of relevance. However, the company conducted separate NMAs for the RCC risk subgroups: intermediate/poor and favourable. The company also performed a separate subgroup analysis in the economic model for the IMDC poor/intermediate risk subgroup using the findings of the associated NMA. The company and ERG agree that the RCC risk score is an effect modifier in the treatment of RCC. Further, cabozantinib is only indicated in the intermediate/poor risk subgroup of patients. Therefore, the technical team agree that it is appropriate to undertake a subgroup analysis in the intermediate/poor risk group.
Use of fully parametric modelling instead of the NMA to inform the economic model	The company, ERG and technical team agree that the use of parametric modelling using data from the KEYNOTE-426 trial in the main base case analysis is appropriate. This assumes that pazopanib and tivozanib are clinically equivalent to sunitinib. In previous NICE appraisals of first-line treatments for advanced RCC, the appraisal committees have agreed, based on expert clinical opinion, that sunitinib, pazopanib and tivozanib are broadly similar to each other in efficacy and safety, and therefore have not considered indirect comparisons as a key factor in their decision making. However, the current appraisal includes cabozantinib as a comparator, and it cannot be assumed that it is similar in efficacy and safety to the existing comparators. It is therefore appropriate that indirect comparison methods, in the absence of head to head trials, were used to inform the economic subgroup analysis of the intermediate/poor risk subgroup of people with untreated RCC.
Innovation	The company considers the drug to be innovative. One clinical expert, in support that the intervention was innovative, commented on the proportion of patients that may achieve a durable response without the significant adverse events noticed with ipilimumab or nivolumab. They also stated this technology would be first of its kind to combine immune checkpoint inhibitor and VEGF TKI. Another clinical expert supported the notion that the intervention was innovative due to the potential durability of response and improved survival. However, the technical team believes that all relevant benefits associated with the drug are adequately captured in the model and the QALY calculation.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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Issue date: January 2020

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: January 2020

1. Summary of the key issues

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in bold below.

1.1 The technical team considered the following:

Issue 1 The use of the Weibull distribution for extrapolation of overall survival (OS) for both the intervention and comparator is methodologically appropriate and produces the most plausible OS extrapolations.

Issue 2 There no evidence to support an infinite treatment effect and therefore a treatment waning effect should be used.

Issue 3 **A time horizon of 40 years should be used to capture all relevant benefits and costs that arise as a result of treatment for untreated metastatic renal cell carcinoma (RCC).**

Issue 4 Treatment following pembrolizumab with axitinib is likely to include cabozantinib within UK clinical practice.

Issue 5 Health related quality of life estimates can be based on health state (reflecting disease progression) and be adjusted according to increasing age.

Issue 6 The subgroup analysis for the intermediate/poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group should be informed by the constant hazard approach network meta-analysis (NMA).

Issue 7 **The intermediate/poor IMDC risk subgroup is not likely to meet the end of life criteria.**

The poor IMDC risk subgroup is not likely to meet the end of life criteria.

Issue 8 It is unclear whether pembrolizumab with axitinib is a suitable candidate for the Cancer Drugs Fund (CDF).

Issue 9 It is unclear if a stopping rule of 35 cycles (24 months) for pembrolizumab is clinically appropriate in the treatment of RCC (new issue at technical engagement).

1.2 The technical team feel the following issues have been resolved at technical engagement:

Issue 3: A time horizon of 40 years should be used to capture all relevant benefits and costs that arise as a result of treatment for untreated metastatic renal cell carcinoma (RCC).

Issue 4: Treatment following pembrolizumab with axitinib is likely to include cabozantinib within UK clinical practice.

Issue 6: The subgroup analysis for the intermediate/poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group should be informed by the constant hazard approach network meta-analysis (NMA).

1.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There is an immature evidence base to inform OS; median survival has not been reached.
- Demographics and clinical characteristics of the KEYNOTE-426 trial population may limit generalisability to the UK RCC patient population.
- Demographics and clinical characteristics of the populations within the studies informing the NMA may limit generalisability to the UK RCC patient population.
- There is use of small datasets and potential heterogeneity in studies used in NMA, which introduces uncertainty due to reduced precision of the NMA findings.

- Adverse events (AEs) in second line treatment were not explicitly modelled meaning that cost-effectiveness results may be over or under-estimated.

1.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £175,316 per quality-adjusted life years (QALY) gained in the main analysis of pembrolizumab with axitinib versus sunitinib (see table 1 and 2). Under the technical team's preferred assumptions, the ICER was £82,488 per QALY gained in the poor/intermediate risk subgroup analysis (see table 3). These estimates do not include the commercial arrangements for pembrolizumab, cabozantinib, axitinib, nivolumab, everolimus, lenvatinib, tivozanib or sunitinib. This is because these are confidential and cannot be reported here. Estimates for the main general RCC population analysis that included these commercial arrangements would be lower than those reported above. However, they would still be above the range normally considered good use of NHS resources. Estimates for the poor/intermediate risk subgroup analysis that included these commercial arrangements would be higher than those reported above.

1.5 Based on the modelling assumptions, the intervention is unlikely to meet the end-of-life criteria for the general RCC population. It is also unlikely that the intervention may meet the end of life criteria for the intermediate/poor risk subgroup. There is insufficient evidence to suggest that the poor risk group would meet end of life criteria (see issue 7).

1.6 The company believes that the combination of pembrolizumab and axitinib for treating RCC is a suitable candidate for the Cancer Drugs Fund and indicated further data will be forthcoming at the conclusion of the KEYNOTE 246 trial (see issue 8).

1.7 The technology is unlikely to be considered innovative.

1.8 No equality issues were identified.

These issues are described in detail in section 3 and 4.

2. Topic background

2.1 Disease background

- RCC accounts for 80% of kidney cancer cases.
- The common subtype of RCC are clear-cell or non-papillary (75% of RCCs); papillary or chromophilic (10-15% of RCCs) and chromophobe (5% of RCCs).
- Early symptoms of RCC include haematuria (blood in the urine) and/or persistent pain in the lower back or side between the ribs and hipbone. Later symptoms include fatigue, weakness, pain, anorexia, nausea, dyspnoea, worry, shortness of breath and irritability.
- RCC tends to affect people over 60 years old and is more common in males, although the incidence has increased more rapidly in females than males since the early 1990s.
- In the UK, there are approximately 12,600 new cases of kidney cancer and 4,500 deaths due to kidney cancer annually.
- Approximately 70% and 50% of people with RCC will live to one and ten years respectively, with survival linked to stage of cancer at diagnosis (with five-year survival estimated at 83% and 6% for stage I and IV respectively).
- In 2015, around 44% of people diagnosed with RCC presented at stage III or IV of disease.
- The IMDC criteria classifies people with metastatic RCC that receive systemic treatment in terms of favourable, intermediate or poor risk.

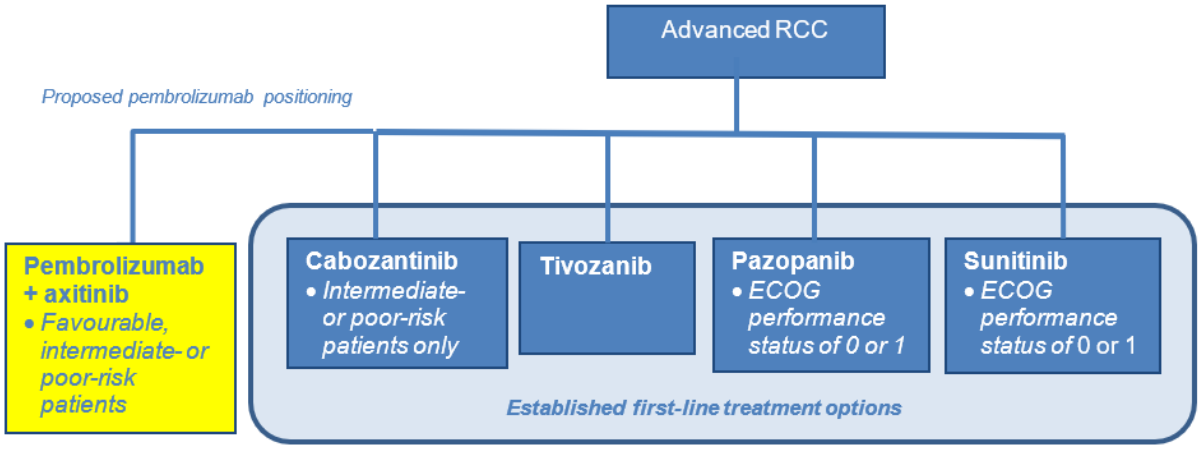
2.2 Pembrolizumab with axitinib

Marketing authorisation	Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults (granted 25 July 2019).
Mechanism of action	Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. Axitinib is a multi-targeted kinase receptor inhibitor with anti-tumour activity. Axitinib inhibits vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet-derived growth factor receptor (PDGFR), and c-kit, which may result in inhibition of angiogenesis in tumours.
Administration	Pembrolizumab 200 mg intravenously every 3 weeks with axitinib 5 mg orally twice daily.
Price	The list price of pembrolizumab is £2,630 per 100 mg vial, the cost of a single administration being £5,260. A commercial access agreement has been arranged with NHS England, with a simple discount in place. The list price of axitinib is £3,517 per 56, 5mg tablets. (The average cost of a course of treatment at list price is: £120,572). Axitinib has a patient access scheme arrangement in place with a simple discount.

2.3 Treatment pathway

- The general approach to treating RCC cancers is surgical resection of localised disease; however, approximately half of patients develop advanced stage disease despite surgery.
- The company proposes that pembrolizumab with axitinib would offer an alternative first-line treatment option to those therapies already recommended for people with advanced RCC (see figure 1).

Figure 1: Proposed treatment pathway which is based on the NICE pathway for RCC and the updated European Association of Urologists guideline*.



*Please note that nivolumab with ipilimumab is recommended for use through the Cancer Drugs Fund (CDF) and therefore cannot be considered as a comparator within the scope of this appraisal to treat adults with untreated advanced renal cell that is intermediate/poor-risk as defined by the IMDC criteria (please see TA581 and the NICE position statement on CDF products as comparators).

2.4 Clinical evidence

- The company systematic review identified four randomised control trials: the pivotal trial for pembrolizumab in combination with axitinib (KEYNOTE-426) and three trials reporting evidence for the relevant comparators (Cabosun, Comparz, Tivo-1). Please see table 1 for study information.
- Findings from KEYNOTE-426 are presented based on a data cut in August 2018, which informed the main analysis in the economic model. The company also presents findings from a subsequent (unplanned) data cut in January 2019 ([redacted]).
- In the absence of direct comparative evidence of pembrolizumab with axitinib versus tivozanib, pazopanib or cabozantinib, a fixed-effects NMA (see figure 2) was undertaken.

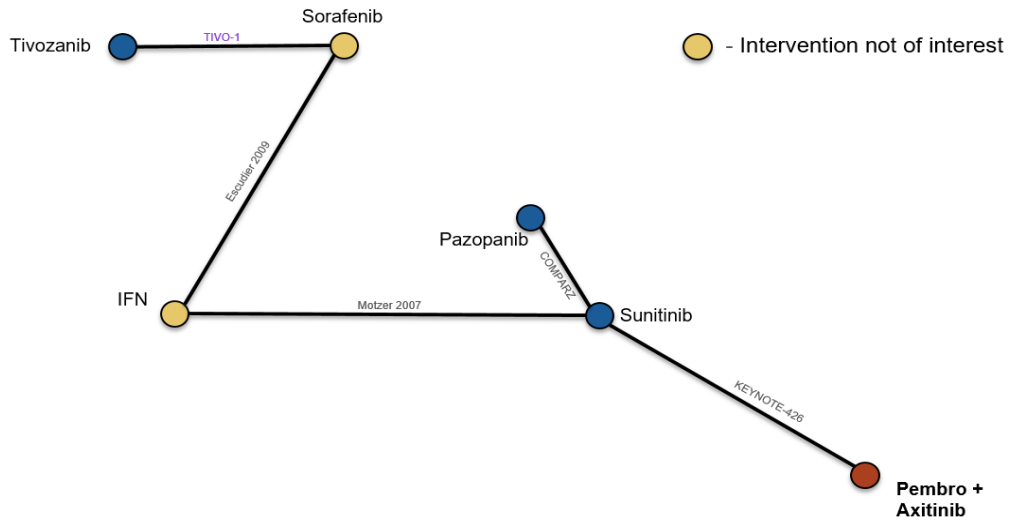
The NMA did not inform the economic base case regarding the general RCC population. Instead, the economic model base case used data from the pivotal data to directly compare pembrolizumab with axitinib and the comparator sunitinib. Tivozanib and pazopanib were assumed to have equal efficacy and safety to sunitinib, which is in line with committee preference in TA512 and TA215 respectively (please also see TA542 and TA581 for cabozantinib and nivolumab respectively, in which the committee also support the assumption of equal clinical efficacy of pazopanib and sunitinib). However, in the absence of direct comparative evidence, the NMA was used to inform the IMDC poor/intermediate risk subgroup analysis within the economic model because sunitinib and cabozantinib could not be assumed equally efficacious.

Table 1: Summary of KEYNOTE-426

Study	KEYNOTE-426: A Phase III Randomised, Open-label Study
Population	Adults with previously untreated advanced clear-cell renal-cell carcinoma
Intervention	Pembrolizumab 200 mg intravenously every 3 weeks with axitinib 5 mg orally twice daily. Pembrolizumab can be continued up to 35 doses (approximately 24 months).
Comparator(s)	Sunitinib monotherapy (50 mg orally once daily for 4 weeks and then off treatment for 2 weeks)
Reported outcomes specified in the decision problem	• **Overall survival (OS)** • **Progression free survival (PFS)** • **Objective response rate (ORR)** • **Adverse effects (AEs) of treatment** • **Health related quality of life (HRQoL)**
All other reported outcomes	• Time to deterioration (TTD) • Duration of response (DOR) • **Patient reported outcomes (PRO)** • Disease control rate (DCR)

Note: Bolded outcomes are included in the economic model

Figure 2: Network of evidence for all included RCTs in untreated RCC (all outcomes)



Note: Interventions not of interest (IFN and sorafenib) were included in the NMA to facilitate an indirect comparison between tivozanib and other interventions of interest. The CABOSUN trial (cabozantinib vs. sunitinib) is not included in this network diagram as this trial included IMDC intermediate/poor risk category patients only

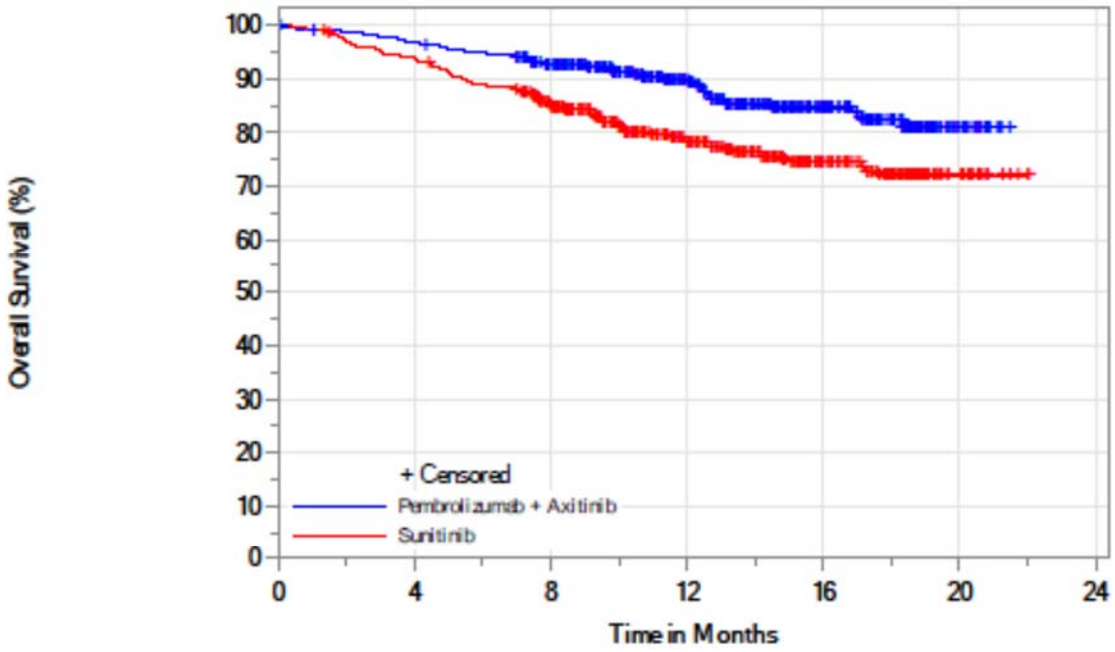
2.5 Key trial results

Using the August 2018 data cut for pembrolizumab with axitinib (intervention) versus sunitinib (comparator):

- Overall survival (OS) hazard ratio (HR): 0.53 (95% CI: 0.38, 0.74; p=0.00005). This represents a 47% reduction in the risk of death in favour of intervention. Median OS was not reached in either group (see figure 2).
- Progression-free survival (PFS) HR: 0.69 (95% CI: 0.57, 0.84; p=0.00014). This represents a 31% reduction in the risk of progression or death in favour of intervention. Median PFS: Intervention: 17.1 months; Comparator: 11.1 months (see figure 3).
- Objective response rate (ORR) (per RECIST 1.1 by blinded independent central review [BICR]): Intervention: 59.3%; Comparator: 35.7%; Difference of 23.6% (95% CI: 17.2, 29.9; p<0.0001).

- EQ-5D-VAS change from baseline to Week 30: The company report no clinically meaningful difference.

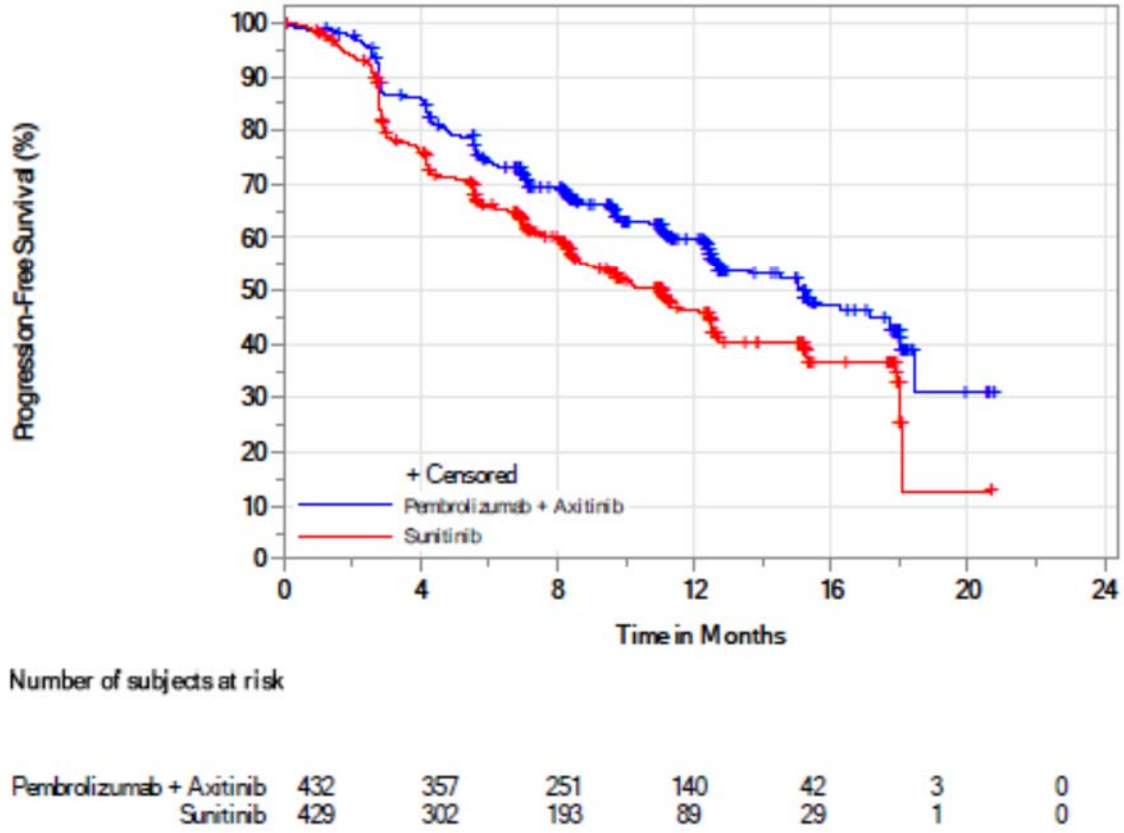
Figure 2: Kaplan Meier Estimates of OS (Intention to treat (ITT))



Number of subjects at risk

Pembrolizumab + Axitinib	432	417	378	256	136	18	0
Sunitinib	429	401	341	211	110	20	0

Figure 3: Kaplan Meier Estimates of PFS (primary censoring rule) based on BICR Assessment per RECIST 1.1 (ITT)



2.6 Findings for the constant HR NMA, August 2018 data cut.

Overall survival

- Pembrolizumab with axitinib resulted in a [redacted] in the duration of OS compared with both pazopanib [redacted] and sunitinib [redacted]. Pazopanib was [redacted] from sunitinib.
- In the intermediate/poor risk subgroup, the results [redacted] pembrolizumab with axitinib [redacted] cabozantinib; however, [redacted]. Pembrolizumab with axitinib was [redacted] to sunitinib [redacted] with respect to OS.

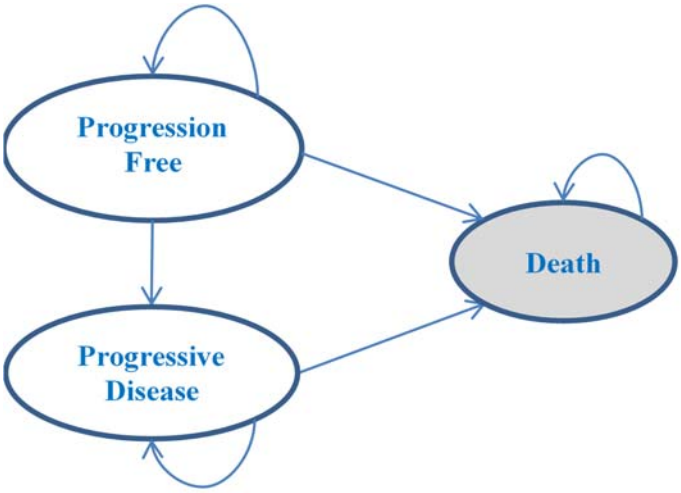
Progression-free survival

- Pembrolizumab with axitinib resulted in a [redacted] in the duration of PFS compared to all competing interventions including tivozanib [redacted], pazopanib [redacted], and sunitinib [redacted].
- In the intermediate/poor risk subgroup, pembrolizumab with axitinib and cabozantinib are [redacted] to sunitinib [HR=[redacted] and HR=[redacted] respectively]. Although the results [redacted] cabozantinib [redacted] pembrolizumab with axitinib, this [redacted].

2.7 Model structure

- Partitioned survival model with 3 health states (see figure 4) and weekly cycle length.
- 40-year time horizon and 3.5% discount rate for costs and benefits.
- Comparators: sunitinib; pazopanib; tivozanib; cabozantinib (in poor/intermediate IMDC risk subgroup only).
- Clinical effectiveness data from KEYNOTE-426 trial, with the exception of the intermediate/poor risk group which came from the NMA.

Figure 4: The economic model structure.



2.8 Key model assumptions

- Population
  - Assumes similar to cohort in KEYNOTE-426 trial (61.5 years old, 71.3% male, 81.5 kg).
- Clinical efficacy:
  - Clinical efficacy of pazopanib and tivozanib is equal to the clinical efficacy of sunitinib for OS, PFS, time on treatment and safety profile (this is in line with previous appraisals in RCC, please see section 1.4).
  - Treatment effect persists throughout lifetime of patient with treatment waning at 10 years tested in a scenario.
  - Once patients progress, they receive subsequent therapies as is experienced in UK clinical practice.
  - To model PFS, KEYNOTE-426 survival data was used for the first 13 weeks, followed by an exponential distribution (for both pembrolizumab with axitinib, and sunitinib).

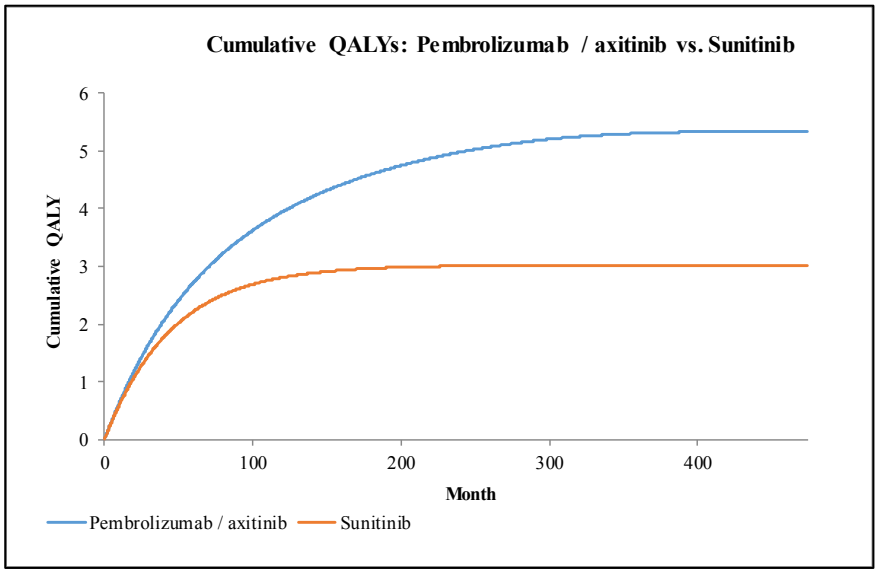
  - To model OS, efficacy log-logistic and exponential distribution were fitted to individual treatment arms from KEYNOTE-426 for pembrolizumab with axitinib, and sunitinib, respectively.
  - Mortality rate is the same before and after disease progression, with adjustment made for age-related mortality.
- Safety:
  - Incidence of AEs informed by KEYNOTE-426 trial, i.e. grade 3-5 AEs (incidence ≥5% in one or more treatment groups, considering any grade) and the published trials on cabozantinib in the intermediate/poor risk group.
  - AEs related to subsequent treatments are not explicitly modelled.
- Health related quality of life:
  - The quality of life of patients is considered using KEYNOTE-426 trial estimates based on time-to-death utilities to capture decline in HRQoL in final months of life.
  - Utility values were adjusted to decease with age.
- Healthcare resource use costs:
  - Resource use is assumed to be equal between pembrolizumab with axitinib and are assumed to be equal per treatment arm in the pre- and post- progression health states.
  - Other costs considered important were acquisition and administration of first and subsequent treatments (adjusted for vial sharing and dose intensity), monitoring and disease management, cost associated with treatment related AEs of first line treatment and end of life care in last cycle before death.
- Stopping rule:

  Pembrolizumab will be administered for a maximum of 35 cycles (24 months), after which axitinib monotherapy will continue until confirmation of disease progression (this reflects the trial protocol).

2.9 Overview of how quality-adjusted life years accrue in the model

- For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period for calculating the cumulative QALYs over the modelled time horizon (see figure 5). An annual rate discount rate of 3.5% was used.

Figure 5: Cumulative QALY gain over the time horizon of the model



- The analysis of the EQ-5D-3L utilities was based on the full analysis set (FAS) population (a total of 850 subjects).
- UK preference-based scores were used and developed using the time trade-off (TTO) technique.
- Estimation of utilities in the base case analysis was based on time-to-death to reflect the decline in health-related quality of life at the terminal phase of disease (see table 2).
- Estimation of utilities based on progression status was also considered, however there was limited post progression utility data available (as this was collected until drug discontinuation or the 30-day post study follow-up).

- Utilities were adjusted for whether the EQ-5D index was measured during a grade 3+ AE using a linear mixed effects model, which also provided estimation of the disutility associated with an adverse event.
- The QALY loss associated with the AE was applied within the first cycle ([redacted] for pembrolizumab in combination with axitinib and [redacted] for sunitinib using the time-to-death regression model).

Table 2. EQ-5D health utility scores by time-to-death

	Pooled (N=532), number of observations: 2,704		
	Estimate	SE	95% confidence interval
≥360 days	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]
90 to 180 days	[redacted]	[redacted]	[redacted]
30 to 90 days	[redacted]	[redacted]	[redacted]
0 to 30 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

3. Key issues for consideration

Issue 1 – Extrapolation of overall survival

Questions for engagement	1. What proportion of patients in the pembrolizumab with axitinib arm would you expect to be alive at 5 and 10 years? 2. What proportion of patients in the sunitinib arm would you expect to be alive at 5 and 10 years? 3. Is there sufficient clinical and/or methodological justification to use different distributions to extrapolate overall survival (OS) for pembrolizumab with axitinib, and the comparator sunitinib? a. If there is sufficient justification to use different distributions to extrapolate OS, which distribution (log-logistic, exponential or Weibull) is most appropriate to use to model pembrolizumab with axitinib, and the comparator sunitinib? b. If there is not sufficient justification to use different distributions to extrapolate OS, is the Weibull distribution the most appropriate distribution to model both pembrolizumab with axitinib, and the comparator sunitinib?
Background/description of issue	The follow-up period in KEYNOTE-426 is shorter than the time horizon in the economic model and therefore extrapolation using parametric curves were used to model OS. The NICE DSU technical support document 14 advises that both arms should have the same extrapolation distribution applied unless substantial justification is given. **The company** used a log-logistic distribution for pembrolizumab with axitinib, and an exponential distribution for sunitinib to model OS. The company's justification for using different distributions for the intervention and comparator is that the mode of action of combination of immunotherapy with a tyrosine kinase inhibitor (TKI) is not comparable to the mode of action associated with TKI monotherapy. The company also states that none of the parametric distributions gave clinically plausible long-term OS estimates for both arms simultaneously. The company justifies use of the exponential distribution to extrapolate OS for the sunitinib arm by stating that the log-cumulative hazard plots showed a constant hazard over time (suggesting that the exponential curve is appropriate), there was close statistical fit to the observed data, and that

	long-term OS estimates were in line with external data and clinical expert opinion. The company justifies use of the log-logistic distribution to extrapolate OS for the pembrolizumab with axitinib arm by stating it had a good statistical fit to the observed data, and that it is clinically credible based on the expectation that a percentage of patients would derive a long-term survival benefit from the combination of an immunotherapy with a TKI. This immunotherapeutic effect would imply a declining, rather than a constant hazard over the long term. **The ERG** considered that both the exponential and Weibull distributions are plausible for OS. The ERG proposed that the Weibull distribution should be used for both the intervention and comparator extrapolation of OS. The ERG suggested that the Weibull distribution was the best fit to sunitinib data, that the underlying hazard for pembrolizumab with axitinib is similar to sunitinib (and either the Weibull or exponential distributions were plausible), and that the data for pembrolizumab with axitinib does not demonstrate an underlying hazard that is similar to the log-logistic. The ERG also noted in TA581 (for nivolumab with ipilimumab) that the committee did not consider the modelling of the immunotherapeutic effect to be substantiated by evidence, and that it could not generalise the size of this effect from one cancer to another. **The technical team** notes that if an exponential distribution is determined to be best fit for sunitinib (i.e. agreement with the company) to model overall survival, and plausible for pembrolizumab with axitinib, then there is potential for the exponential distribution to be used for both the intervention and the comparator. **Two clinical experts** commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only). With regard to long term survival estimates for pembrolizumab with axitinib, the **company clinical experts** estimated a 50% survival at 5 years. An **ERG clinical expert** thought this may be optimistic. A **clinical expert** for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years.
Why this issue is important	The choice of distribution has a large impact on the ICER. Using the exponential distribution to model OS for both intervention and comparator increases the ICER from £59,292 per QALY gained in the company base case to £73,094. Using the Weibull distribution to model OS for both intervention and comparator increases the ICER to £118,931.

Technical team preliminary judgement and rationale	From inspection of the extrapolated survival curves against the trial with the longest follow-up (i.e. the COMPARZ trial) and consideration of clinical expert opinion, the log-logistic, exponential and Weibull functions appear to all produce optimistic extrapolations. However, both the Weibull and exponential appear to have good fit to the Keynote-426 trial data on inspection of the graphs. Overall, the Weibull appears to be most likely to be clinically plausible. Nonetheless, uncertainty regarding the best distribution will remain due to the immaturity of the data.
Summary of comments	***Comments received by the company:*** • A 5-year 50% OS is plausible; recognise uncertainty around 10-year survival and agree with the technical team's clinical experts' estimation of a survival plateau. • The 5-year survival estimation made by the technical team is implausibly low because: o TA581 (nivolumab with ipilimumab) considered a 5-year overall survival of 43.6% as clinically plausible in intermediate/poor-risk patients o In KEYNOTE-426, 89.9% of patients are still alive at 1 year • 5- and 10-year survival between 20-25% and 10-15% may understate the actual long-term survival when treated with sunitinib o the COMPARZ trial provides a poor reference point for survival on standard of care (sunitinib) due to poor applicability of second line treatments to current UK practice. o CHECKMATE-025 shows 30.0% of patients treated with nivolumab in the second-line are alive at 4 years. o CHECKMATE-214 shows that the sunitinib arm reached median overall survival at 37.9 months in the ITT population. • The Weibull distribution is not appropriate to model both pembrolizumab with axitinib, and sunitinib (together or separately). It is the worst fitting curve to the sunitinib Kaplan Meier (KM) data and is not the best nor second-best fitting curve to the pembrolizumab/axitinib KM data in terms of AIC/BIC criteria, as well as having poor visual fit to observed data. • The method of modelling the immunotherapeutic effect in TA581 was based on a manually imputed association between durable response and overall survival, and therefore comparison to TA581 is not applicable

- The Weibull distribution underestimates OS of the comparator: CHECKMATE-214 estimated sunitinib OS at 37.9 months in the ITT population versus an estimated median 34.2 months and 36.7-month OS with a Weibull distribution and exponential distribution.
- For pembrolizumab with axitinib, the Weibull distribution (in this instance) has a monotonically increasing hazard rate over time, which results in a huge underestimation of the long-term OS benefits if there is a survival plateau with this technology as cited by clinical experts.
- The use of different distributions to extrapolate OS for pembrolizumab with axitinib, and sunitinib (log-logistic and exponential distributions, respectively) is "substantially justifiable" based on:
  - Evidence describing the clinical rationale and mechanism of action for combined immune checkpoint inhibitor and TKI therapy
  - The view that distributions selected for company base case have good visual and statistical fit of observed data, as well as expert opinion of OS at 10 years.
- Compared survival rates up to 20 years when estimated by Weibull and those estimated in the company base case, scenario 1(landmark analysis); and scenario 3 (log-logistic OS extrapolation for pembrolizumab with axitinib, time-constant HR for sunitinib). The company claim the values predicted from the scenario analyses are similar to, and validate, the company base case (in contrast to the predicted values using the Weibull distribution).

Table 1 from company response: Overall survival estimates using alternative approaches

Years	Base Case		Scenario 1: Landmark		Scenario 3: L-L, NMA		Weibull curve	
	P+A	S	P+A	S	P+A	S	P+A	S
1	88.5%	79.9%	88.0%	79.8%	88.5%	79.6%	88.6%	80.1%
2	76.8%	63.9%	78.0%	64.7%	76.8%	60.9%	76.2%	62.6%
5	51.9%	32.5%	57.9%	37.3%	51.9%	29.1%	44.9%	28.2%
10	31.6%	10.6%	37.2%	16.2%	31.6%	11.5%	16.5%	6.9%
20	16.5%	1.1%	15.6%	3.1%	16.5%	3.4%	1.7%	0.3%

- Requested further consideration to Scenario analysis 1, as described in Appendix P of the company submission, if the use of separate distributions to each arm is not accepted.

ERG critique:

	• Questioned comparability to TA581, which appraised a combination of two immunotherapies where treatment could continue for up to 5 years; not a combined immune checkpoint inhibitor and TKI tyrosine-kinase inhibitor (TKI) therapy where pembrolizumab is stopped after 2 years. • Noted that estimates of 5-year OS provided by clinical experts for pembrolizumab with axitinib vary between 30-50%. • Agreed with company that OS estimates may be underestimated, although it is unclear how much higher the 5-year survival would be with increased use of nivolumab as a subsequent-line of treatment. • Acknowledged the clinical rationale for combined immune checkpoint inhibitor and TKI therapy, and the different mechanisms of action proposed. However, it states that there is no robust evidence currently showing a difference in the underlying hazards for OS between pembrolizumab with axitinib and the comparator sunitinib, to support the use of different survival distributions. It also notes that the KEYNOTE-426 OS data are immature. • Noted the comparison of survival estimates using the Weibull distribution against estimates produced by the company scenario analyses 1 and 3, however, provided no further comment on whether the comparison with the selected scenarios validated the base case assumptions. • Noted that AIC/BIC statistics for pembrolizumab with axitinib show that the log-logistic and the Weibull are similar in their statistical fit to the observed data. The best statistical fit is the exponential distribution. Weibull and exponential distributions provide good visual fits to the observed data. • Noted that the exponential distribution offers a better statistical fit for sunitinib than the Weibull. The Weibull also provides a good visual fit to the observed data for sunitinib. • Noted that the Weibull distribution provides: - the closest fit to the COMPARZ trial data for sunitinib (allowing that few patients received nivolumab as a subsequent-line treatment) - 5-year OS (45%) for patients treated with pembrolizumab with axitinib is within 30%-50% range estimated by clinical experts. • Commented that the Weibull and exponential distributions appear to have good visual fit to the KEYNOTE-426 trial data on inspection of the graphs.

	• Proposed that the statistical fit with the observed data is less important than validation against long-term data.
	Patient representative: Patients are having a greater initial reduction in their tumour and subsequent scans with pembrolizumab with axitinib, and believe treatment has extended their life expectancy beyond expected, i.e. 36 months survival achieved (with good outlook) versus an expected 22.5 months for intermediate risk.
Technical team judgement after engagement	The technical team maintains that in the absence of robust evidence to justify different distributions for the extrapolation of OS for the intervention and comparator, the Weibull distribution should be applied for the extrapolation of OS for both pembrolizumab with axitinib, and sunitinib. The Weibull distribution offers a good fit to the observed data on visual inspection when considering both the intervention and the comparator data, and it produces OS estimates within the range provided by clinical experts. Nonetheless, the technical team recognise that uncertainty regarding the best distribution will remain due to the immaturity of the data.

Issue 2 – Treatment waning effect after discontinuation

Questions for engagement	4. In clinical practice, would a reduction in treatment effect be observed after treatment with pembrolizumab has been stopped? If so, at what time point? 5. What is the most appropriate duration to apply a treatment effect for people treated with pembrolizumab with axitinib?
Background/description of issue	Due to the immaturity of data, it is unclear whether treatment effect on OS is sustained beyond the 2-year stopping rule for pembrolizumab. Several NICE appraisals have questioned the treatment effect duration used in immune-oncology economic models; committees have generally preferred a 3-year or 5-year treatment effect (whereby effect persists for 1 year or 3 years after stopping

	treatment respectively) rather than a lifetime effect once treatment stops. Further detail regarding these appraisals is given below. **The company** has not included the assumption of treatment effect waning (reducing) in their base case, noting that waning of effect has not been included in previous NICE appraisals for RCC, and that patients continue to be treated with axitinib after the 2-year stopping rule for pembrolizumab. In addition, the company states that it believes a proportion of patients would derive a long-term survival benefit from the combination of an immunotherapy with a TKI. **The ERG** notes that a proportion of patients would receive second-line treatment after disease progression and this second-line treatment would influence their survival. Further, many patients who receive sunitinib as first line treatment would receive nivolumab as second-line therapy and so it may be the case that OS for patients receiving second-line treatment may be similar between treatment arms. However, as the OS data from KEYNOTE-426 is immature, the ERG did not include a treatment waning effect in the ERG base case. **The technical team** questioned the appropriate duration of the treatment effect applied in the model. The technical team notes that once treatment effect of pembrolizumab with axitinib wanes in the company model, no treatment cost of pembrolizumab with axitinib is applied and the PFS and OS probabilities associated with treatment of first line sunitinib are applied instead, until there is movement to second line treatment (i.e. due to disease progression). **The technical team** notes that duration of treatment effect has been a key issue in several previous appraisals. In TA428 (pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy), the committee preferred to assume a 3 to 5 year treatment effect duration, commencing after treatment discontinuation (i.e. 3 years after stopping treatment or 5 years from commencing treatment). Committee members in TA519 (pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) recognised that the duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty for new immunotherapies, but it concluded that a lifetime continued treatment effect was implausible. Committee members in TA600 (pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer) also considered a lifetime treatment effect to be implausible. The technical team recognises that these appraisals ([TA519],

	[TA600], and [TA428]) evaluate pembrolizumab for different indications and populations than that of the current appraisal, and that pembrolizumab was not combined with axitinib. The committee for TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma) agreed that the long term benefit of the immunological therapy had yet to be established and believed that the modelled immunotherapeutic effect relied on speculative assumptions that were not substantiated by evidence (noting that the trial had not employed a stopping rule and the definition of durable response was questionable). **The technical team** also notes that committees for other immuno-oncology appraisals have preferred either a 3-year or 5-year treatment effect (whereby effect persists for 1 year or 3 years after stopping treatment respectively), for example please see TA578 (durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemo radiation) and TA520 (atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy). On balance, **the technical team** are unclear on the most appropriate treatment effect duration, however, believe a lifetime duration is inappropriate. **Two clinical experts** have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect.
Why this issue is important	The length of assumed treatment benefit after discontinuation impacts upon the ICER, with longer treatment effects associated with a lower ICER. This is driven by a health benefit being obtained without treatment costs being incurred. Therefore, the treatment waning effect after discontinuation is an important consideration as it has a large impact on the cost-effectiveness results. The ICER increased from £59,292 in the company base case to £86,712 if the treatment waning effect was 10 years, and £133,900 if the treatment waning effect was 5 years.

<table>
<tr><td></td><td>The ICER increased from £120,455 in the ERG base case to £129,368 if the treatment waning effect was 10 years and £162,424 if the treatment waning effect was 5 years.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>The immaturity of data means that the long-term treatment effect of the drug is unclear. This does not necessarily indicate that there is a waning in treatment effect but equally there is no evidence that there isn't. When considering the analyses provided to date, the technical team prefers the assumption that treatment effect reduces at 5 years. The technical team would like the company to provide analyses exploring a treatment effect of 2 years (that is, no continued benefit after stopping treatment) and 3 years (treatment benefit ends 1 year after stopping treatment).</td></tr>
<tr><td>Summary of comments</td><td>Comments received by the company:
A lifetime treatment effect should be considered as plausible.
Clinical opinion supported the notion that there will be no loss of treatment effect post discontinuation with pembrolizumab after 2 years, and a lifetime treatment effect is plausible.
Referred to publications regarding the biochemical mode of action of the intervention which would suggest a continued treatment effect
Requested consistency of approach with the appraisals of nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA581) and nivolumab for previously treated advanced renal cell carcinoma (TA417) where no treatment waning effect imposed on the intervention.
The request for cost-effectiveness analyses exploring a treatment effect lasting until 2 years (when pembrolizumab treatment stops) and 3 years (treatment effect ends 1 year after stopping pembrolizumab treatment) was considered to be inappropriate: survival estimates indicate such analyses would be clinically implausible (please see below table):
Table 1. Overall survival estimates implementing clinically implausible treatment waning assumption
<table>
<tr><th rowspan="2">Years</th><th colspan="2">Base Case</th><th colspan="2">2-year treatment waning, base-case curve selection</th><th colspan="2">3-year treatment waning, base-case curve selection</th><th colspan="2">2-year treatment waning, ERG base-case curve selection</th><th colspan="2">3-year treatment waning, ERG base-case curve selection</th></tr>
<tr><td>P+A</td><td>S</td><td>P+A</td><td>S</td><td>P+A</td><td>S</td><td>P+A</td><td>S</td><td>P+A</td><td>S</td></tr>
</table></td></tr>
</table>

1	88.5%	79.9%	88.5%	79.9%	88.5%	79.9%	88.6%	80.1%	88.6%	80.1%
2	76.8%	63.9%	76.7%	63.9%	76.8%	63.9%	76.0%	62.6%	76.2%	62.6%
5	51.9%	32.5%	39.0%	32.5%	42.6%	32.5%	34.2%	28.2%	37.6%	28.2%
10	31.6%	10.6%	12.7%	10.6%	13.8%	10.6%	8.3%	6.9%	9.2%	6.9%
20	16.5%	1.1%	1.3%	1.1%	1.5%	1.1%	0.4%	0.3%	0.5%	0.3%

The ERG critique:

- Agreed that "the immaturity of data means that the long-term treatment effect of the drug is unclear."
- Agreed with the company that focus should be on keeping consistency with appraisals for IO therapies in renal cell carcinoma and there is not a rationale for maintaining consistency with approaches adopted in appraisals concerning different indications.
- The ERG decision to not include a treatment effect waning in the ERG base case (and present treatment waning as a scenario) is in line with NICE TA581 where no reduction in treatment effect was included.
- Noted that when the company survival estimates (table 2 in company response document) was ran through the economic model, the ICERs varied between £184,983 per QALY and £269,968 per QALY– see table below:

Table 2 – Treatment effect waning scenario analyses for treatment with pembrolizumab + axitinib compared to sunitinib (list prices)

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	£137,537	2.32	£59,292
2-year treatment effect waning[a]	£116,835	0.495	£236,229
3-year treatment waning[a]	£123,483	0.668	£184,983
ERG Base case	£140,895	1.170	£120,455
2-year treatment effect waning[b]	£125,895	0.466	£269,968
3-year treatment effect waning[b]	£131,854	0.626	£210,586

a Using the company's base case fitted parametric survival curves
b Using the ERG's base case fitted parametric survival curves

Technical team judgement after engagement	The technical team recognise that the long-term treatment effect of the intervention is unclear, and therefore a lifetime treatment effect is possible. However, in the absence of mature data to substantiate a lifetime treatment effect, a scenario with a treatment waning effect is preferable to inform decision making. While consistency with TA581 and TA417 should be considered, it is noteworthy that the former did not have a 2-year stopping rule and evaluated combined immunologics which could have an alternative mechanism of action. The latter is in a population who had previously been treated and estimated time to stopping treatment via parametric modelling (median stopping time was under one year), and treatment effect duration was not seen as a key issue in this appraisal. Therefore, for decision making the technical team recommend the consideration of consistency with all relevant appraisals (i.e. those with similar indication, interventions with similar mode of action or those concerning the same drugs as the current appraisal). On balance, the technical team preferred assumption is to employ a treatment waning effect of 5 years and present the ERG and company analyses as alternative scenarios.

Issue 3 – Time horizon

Questions for engagement	6. Over what time horizon would you expect all differences in benefits and costs that arise as a consequence of treatment choice in untreated metastatic renal cancer to materialise?
Background/description of issue	The NICE reference case for economic evaluation notes that the time horizon of an economic model should be "long enough to reflect all important differences in costs or outcomes between the technologies being compared", and as such typically a life time horizon is used. However, where extrapolation is uncertain, a longer than required time horizon may exacerbate any over or underestimation in difference of effect over a longer time period. **The company** employs a 40-year time horizon in the model base case analysis. **The ERG** employs a 40-year time horizon in the ERG base case analysis, citing this horizon has been commonly used in similar appraisals, and a 20-year horizon as a scenario analysis. **One clinical expert** has estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years for people treated with pembrolizumab with axitinib. This could suggest a time horizon beyond 20 years is appropriate.

Why this issue is important	Having a longer time horizon allows for a greater time for benefits to accrue to balance any costs incurred at the start of the model horizon (for example costs associated with adverse events or treatment which subsequently stops), as well as extenuate the balance between costs and effects of continued treatments. The time horizon has a moderate impact on the cost-effectiveness results, whereby a reduction in the time horizon allows for less time for benefits to accrue (and balance the cost of adverse events and pembrolizumab which has a 2-year stopping rule). Further a reduction of the time horizon reduces the overall cost effectiveness of the intervention that may be driven by the balance between costs and effects of ongoing first and second-line treatments (which may be driven by assumptions considered favourable to the intervention). The ICER increased from £59,292 in the company base case to £68,760 when the time horizon was reduced to 20 years.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG scenario analysis that a 20-year time horizon should be sufficient to capture all important benefits and costs arising from choice of treatment for untreated metastatic renal cancer for a population with a mean age of 62 years.
Summary of comments	**Company response:** • Noted that the ERG base case agreed with the company base case of 40 years • A 40-year horizon is consistent with TA581 • Noted, under company preferred assumptions, 16.5% of patients in the pembrolizumab with axitinib arm and 1.1% of patients in the sunitinib arm were expected to be alive at 20 years • Referred to clinical opinion within the technical report that expressed a plateau of 25% survival could be plausible at 10 and 20 years **ERG critique:** • Agreed that the choice of time horizon is linked to preferred assumptions for Issue 1 and 2 above for extrapolation of overall survival and treatment waning. • Noted that technical report needed correction to state that the ERG used a 40-year time horizon in their base case and a 20-year time horizon as a scenario analysis. • Agreed that a lifetime time horizon of 40 years is most appropriate because it is able to show the differences in costs and outcomes in all scenarios.
Technical team judgement after engagement	The technical team have corrected the technical report in line with ERG and company comments (amended text underlined above). The technical team note the absence of robust evidence to

	suggest survival beyond 20 years for a population with a mean age of 62 years. Additional survival estimates by the company in response to engagement (see issue 2) indicate that with a treatment waning effect a 20-year horizon is a plausible time frame to capture all important benefits and costs arising from choice of treatment for untreated metastatic renal cancer within the economic model. The technical team also recognises other scenarios may indicate that a longer horizon is appropriate, however, these scenarios are not based on the preferred assumptions of the technical team and result in projections that are believed to be either optimistic or highly uncertain. Notwithstanding committee judgement regarding expected survival and in recognition of the uncertainty in survival estimates and treatment effect duration, the technical team have modified the time horizon in their analysis to 40 years. As the technical team, ERG and company are aligned in their viewpoint, and no further comments were made on this key issue, this issue is viewed to have been resolved at technical engagement.

Issue 4 – Subsequent treatment after first line treatment has stopped

Questions for engagement	7. In clinical practice, what proportion of people would be expected to have subsequent treatment(s), following first line treatment with pembrolizumab with axitinib, and sunitinib respectively? 8. Which subsequent treatment(s) would be used and in what proportions? 9. Are there any treatments that are used subsequently to pembrolizumab with axitinib, and/or sunitinib that are of particular note in regard to their treatment related adverse event (TRAE) profile (in particular in terms of the TRAE's expected frequency, cost and impact on health related quality of life)?
Background/description of issue	The company economic model allows for people who have stopped first-line treatment to move to second-line treatment. However, the second-line therapies used in the KEYNOTE trial were not considered to be relevant to UK clinical practice and were therefore not considered in the economic modelling; these included cytokines (interferon), temsirolimus and everolimus. Further, lenvatinib/everolimus was not considered in the ERG or the company base case. In addition, it is unclear whether the proportion of people receiving a given second-line treatment within the model is reflective of current UK practice. When considering this issue, it

should be kept in mind that OS is in part determined by second-line therapies which were given in the pivotal trial.

The company base case assumes that 50% of patients who had progressed on first-line treatment for RCC receive second-line treatment (as per the NHS England submission in TA581). The company base-case model assumes people who receive pembrolizumab with axitinib as first-line treatment would receive the second-line treatment of pazopanib (30%) or sunitinib (20%)

The ERG noted that they had received expert clinical opinion that a higher proportion (55%-70%) of people who progress on first-line therapy could receive subsequent therapy. An alternative ERG scenario is also run where a higher proportion (60%) of patients receive second-line treatment. The ERG also believed that a higher proportion of people (20%) who receive pembrolizumab with axitinib as first-line treatment would receive the second-line treatment of cabozantinib.

Table 1 below shows the distributions found in the KEYNOTE-426 trial, the company base case and the ERG base case and scenario analysis.

The technical team notes that no adverse events are associated with subsequent treatment within the model and therefore alterations in the proportion of people receiving subsequent treatment will alter overall cost of the strategy, but not quality of life. Cabozantinib has the highest drug acquisition cost of all of the subsequent therapies, and therefore increasing the proportion of people that would have this therapy as second line to pembrolizumab with axitinib, would favour the comparator.

Clinical experts estimated that 70% to 80% of people get second-line treatment after treatment with pembrolizumab with axitinib (and that 60% to 80% of people get second line therapy with sunitinib). **Clinical experts** estimated that 40% to 60% of people who have pembrolizumab with axitinib would have cabozantinib as a second-line therapy.

Table 1. Total acquisition cost and proportion of patients on subsequent-line treatment (list price)

	Total drug acquisition cost	KEYNOTE-426 trial	Company base case	ERG base case	ERG scenario analysis

Subsequent treatment	**(2018 GBP list price)**	**Pembro' + axitinib**	**Sunitinib**	**Pembro' + axitinib**	**Sunitinib**	**Pembro' + axitinib**	**Sunitinib**	**Pembro' + axitinib**	**Sunitinib**
Best supportive care		[redacted]	[redacted]	50%	50%	50%	50%	40%	40%
Lenvatinib/ everolimus	42,856.12	[redacted]	[redacted]	0%	0%	0%	0%	0%	0%
Axitinib	46,133.02	[redacted]	[redacted]	0%	8%	0%	8%	0%	8%
Cabozantinib	63,235.08	[redacted]	[redacted]	0%	13%	20%	13%	20%	13%
Nivolumab	41,804.38	[redacted]	[redacted]	0%	30%	0%	30%	0%	40%
Pazopanib	20,884.69	[redacted]	[redacted]	30%	0%	20%	0%	25%	0%
Sunitinib	18,140.54	[redacted]	[redacted]	20%	0%	10%	0%	15%	0%

Reproduced from ERG report Table 37, Table 36 and Table 47. Data regarding second line therapies not considered relevant to UK practice in KEYNOTE-426 included: cytokines (interferon), temsirolimus and everolimus, and as such are not considered within this table.

Why this issue is important	Consideration of subsequent treatments can have a substantial effect on cost-effectiveness estimates. Greater health gains can be expected along with increased costs, if the proportion of people assumed to receive subsequent treatments is increased. Further, if more people progress to expensive second line treatments, the overall costs of the strategy will increase. Changing the proportion of people on subsequent treatment in line with the ERG base case and scenario analysis increases the company base case ICER from £59,292 to £62,910, and £61,720 respectively.
Technical team preliminary judgement and rationale	It is appropriate to include cabozantinib as a second-line treatment for pembrolizumab with axitinib. This allows the model to be in line with clinical expert opinion sourced by the ERG and the technical team, as well as with the findings of the pivotal trial (where approximately [redacted] of patients had cabozantinib as subsequent treatment). Therefore, the ERG base case distribution of people on specific subsequent treatment, including best supportive care, is the technical team's preferred assumption (please see Table 1 within the "Background/description of issue" section above).
Summary of comments	**Comments received by the company:** • Considers approach used by ERG in its base case to be reasonable.

	• Emphasises that scenario analysis 12 from the CS, which uses the KEYNOTE-426 trial-based distribution of subsequent-line therapies to model the cost of subsequent therapy, should be considered as a relevant scenario. **ERG critique:** • Reiterated what was stated in the technical report and in the company response.
Technical team judgement after engagement	The company does not disagree with the technical team or ERG preferred assumptions, but request that scenario 12 in the company submission is considered as a relevant scenario. Therefore, the technical team maintains their judgement that the scenario proposed in the ERG base case should hold as a preferred assumption. As the technical team, ERG and company are aligned in their viewpoint, and no further comments were made on this key issue, this issue is viewed to have been resolved at technical engagement.

Issue 5 – Health related quality of life (HRQoL)

Questions for engagement	10. Is using age-related disutility appropriate within the economic model? 11. Is using a time to death approach to estimation of utility for use within the economic model appropriate? 12. Are the preferred assumptions found in answer to questions 9 and 10 regarding the estimation of utilities in the main analysis, also the preferred assumptions in the subgroup analysis of the poor IMDC poor risk subgroup?
	Two key assumptions underpin the company model's estimation of HRQoL. 1. Age related disutility **The company** uses age-related disutility in the economic model, and thereby there is an implicit assumption that HRQoL will decrease with age regardless of treatment choice for untreated metastatic renal cancer. **The ERG** acknowledges that that including age-adjusted utility is recommended by NICE DSU Technical Support Document, however, disagrees that an age-related disutility should be used because the company found that the utility values derived from the trial data were not associated with age.

	The technical team disagrees with the ERG that an age-related disutility should not be considered given the long time horizon of the company model. However, if a shorter time horizon is preferred, then the technical team recognises that the disutility associated with age may already be accounted for through use of the trial data. **Clinical experts** indicated that performance and control of disease would be a better indicator of HRQoL than age**. One expert** commented that the effect of age over a median survival period of 2-3 years is negligible. 2. Time to death approach to estimation of utility **The company** uses a time to death approach in estimation of utility values from the trial. This assumes that the proximity in time to death has a greater influence on HRQoL than state of disease. **The ERG** considers that a health state or a time to death approach to utility estimation is reasonable, noting that disease progression may not fully capture all predictive factors of patient utility and time to death provides a reasonable fit to patient data. The ERG noted that the company scenario analysis suggested that the approach to utility estimation did not have a large impact on results. **The technical team** recognises that time to death may be an appropriate approach. However, this approach implies no change in HRQoL ≥360 days from death. It is unclear if clinical opinion supports this assumption. This assumption has particular relevance if OS is overestimated, as a higher estimation HRQoL may be sustained over a longer period, regardless of disease progression and age (if no age-related disutility is applied). **Clinical experts** commented that both control of disease and time until death were important factors in determining HRQoL. One expert concluded that HRQoL is most associated with the patient's disease status. When disease progression begins to occur, patients move closer to death and may experience stepwise deterioration as the time period shortens (unless subsequent therapy is again able to achieve good disease control).
Why this issue is important	The preferred approach to estimation of utility may have greater importance and impact on the ICER dependent on which preferred assumptions are used. It is currently unclear if the approach taken has clinical plausibility and therefore this is a potentially important issue.

	The company base case ICER rises to £60,876 when health state-based utilities are treatment specific and £63,400 when pooled, with an age-related utility decrement applied. To note, use of utility values from previous appraisals (tivozanib [TA512] and pazopanib [TA215]) in this topic area has a large impact on the ICER. However, the ERG and the technical team agree that the company's use of the KEYNOTE-426 data is preferable to other sources.
Technical team preliminary judgement and rationale	The technical team are unclear if there is justification for a time to death approach to estimation of utility to be used in the model, and notes that its use may exacerbate any bias introduced by optimistic OS of the intervention. The technical team note that age may have greater impact on HRQoL if people with RCC are expected to have a longer life expectancy due to new treatment. Therefore, the technical team proposes that pooled health state utilities are used with an age-related utility decrement due to the need to model HRQoL over a time horizon longer than the trial.
Summary of comments	**Comments received by the company:** • Deemed it plausible to remove age-adjusted utility from the base-case assumption • The health-state based approach has severe limitations considering only one EQ-5D questionnaire was administered per patient, 30 days after disease progression, limiting post-progression. • To support the assumption that patients who were ≥360 days from death were in a stable state, the company fitted a non-parametric LOESS function to the scatterplot of EQ-5D utility by time to death for all records measured ≥360 days from death (Figure 1, company response). • Conducted a further analysis, which was described as a 'hybrid' approach of time-to-death utilities combined with health-state based utilities, and stated that this approach adds significant complexity and uncertainty compared to a model based on time-to-death alone or health state alone because of small sample size and extreme unbalance between

	progression status for "≥360-days-from-death" (n=54 for progressive disease, but n=1978 for progression-free, among "≥ 360 days from death" patients). • Recommended time to death approach as it utilised more health states than the model based on progression status only, and captured most of the variance in the data. **ERG critique:** • Agreed with the company that because there was no correlation between age and baseline utility assessment in the KEYNOTE-426 trial (clarification question B11), it was unnecessary to include age-related utility. • Agreed with the company that a time to death approach is reasonable, given that inclusion of the disease progression state may not fully capture all predictive factors of patient utility and time-to-death provides a good fit to patient data. • Agreed with the company there was little change in HRQoL when patients were ≥360 days from death in the KEYNOTE 246 trial (based on the analysis presented in figure 1 of the company response document) • Noted the additional analysis undertaken by the company which presented a hybrid method combining time to death and health state utilities, noting that the utilities derived from this analysis were not applied in the cost-effectiveness model. The ERG notes a rationale was not given for the analysis, but does not comment on the validity of the method. Both the **ERG** and the **company** agreed that the assumptions for the main analysis should also be applied in the subgroup analysis for the intermediate/poor risk group.
Technical team judgement after engagement	The technical team recognises that there appears to be no correlation between age and baseline utility (i.e. prior to treatment for metastatic RCC) in the KEYNOTE-426 trial, however, does not believe that HRQoL will not decline with age over a 40-year horizon, and there is no evidence presented to suggest that no correlation will be observed after treatment is given. Therefore, the technical team agrees with the approach in the company submission to adjust HRQoL with age in the economic model. The technical team, although recognising HRQoL appears constant in the duration of the KEYNOTE-426 trial ≥360 days from death, still remain uncertain whether patients who are ≥360

	days from death are in a stable state over a 40-year horizon (also noting that extrapolations of the timing of disease progression suggest a change in disease status prior to 360 days before death). The time to death approach, as applied in the company model, means that the cumulative QALY gain is closely tied to the expected survival of the population, rather than based on the expected time of disease progression. The technical team also note that the timing of a change in HRQoL using the time to death approach in the model is based on OS data (which is immature) rather than on the PFS data (which is mature). The technical team agree with the company that the hybrid approach to utility derivation (presented by the company in response to engagement) adds complexity and uncertainty, and running an analysis with these utilities would not reduce uncertainty. The technical team have opted to maintain their preliminary judgement regarding the application of utilities based on disease progression, and as such prefer to use pooled health state utilities to keep consistency with the three health state modelling approach. However, the technical team agree with the ERG report in that either method may be valid, and recognise that the small sample size informing utilities for the post progression state introduces uncertainty in the HRQoL estimation. As such, a scenario analysis using a time to death approach to estimate utilities should be considered; notwithstanding that the application of such an approach within the economic model will likely overestimate the QALY gain if survival is also overestimated.

Issue 6 – Approach to NMA to inform the economic model subgroup analysis

Questions for engagement	13. Should a constant HR approach NMA (as opposed to a varying hazard approach) be used to inform the economic model?
Background/description of issue	The company economic model uses the NMA results to inform a subgroup analysis for the intermediate/poor RCC subgroup. **The company** stated that a constant HR NMA produced more stable results than the use of a time varying hazards approach in the NMA which informed the subgroup analysis for the intermediate/ poor risk subgroup. **The ERG** notes that the constant hazards NMA was conducted according to standard methods as recommended by the NICE DSU, and noted the time-varying hazards NMA approach produced

	unstable results. Noting that the appraisal committee in NICE TA512 (tivozanib) had raised concerns that the choice of fractional polynomial model had a substantial impact on the cost-effectiveness results, the ERG undertook a scenario analysis on the NMA approach which demonstrated a large variability in cost effectiveness results. For the two time varying hazard fractional polynomial models used, the ICER varies between £117,279 and £149,347 per QALY gained in the ERG scenario analysis, which is substantially higher than the ERG base case ICER of £48,424.
Why this issue is important	The method of the approach taken in the NMA that informs the subgroup economic analysis has a large impact on the ICER.
Technical team preliminary judgement and rationale	The uncertainty on conclusions introduced by the method of undertaking the subgroup NMA is acknowledged by the technical team. However, a constant HR NMA approach appears reasonable in the absence of a strong justification to use an alternative approach.
Summary of comments	**Comments received by the company:** • Maintained that the constant HR approach used in the NMA are the most appropriate to inform the subgroup analysis of the intermediate/poor risk group in the economic model. **ERG critique:** • Clarified that the draft technical report required amendment, noting that the ERG did not disagree with the approach taken and that the time-varying hazards NMA approach produced unstable results. • The ERG agrees with the company (and the technical team) that despite the violation of the proportional hazards assumption in some instances, the use of a constant hazards NMA is more appropriate than time-varying fractional polynomials when length of follow-up is short, or sample size is small.
Technical team judgement after engagement	The technical team have amended the technical report in line with ERG comments (amended text underlined above). As the technical team, ERG and company are aligned in their viewpoint, and no further comments were made on this key issue, this issue is viewed to have been resolved at technical engagement.

Issue 7 – End of life

Questions for engagement	14. Do patients in the IMDC poor risk subgroup meet the end of life criteria? a. Under standard care/cabozantinib, is the life expectancy of people with poor risk RCC more than 24 months? b. Does pembrolizumab with axitinib extend life for more than 3 months for people with poor risk RCC compared with standard care/cabozantinib?
Background/description of issue	In its submission, **the company** does not consider pembrolizumab with axitinib to meet the NICE end of life criteria for the overall RCC patient population. The **technical team** and **ERG** note that estimates of OS for sunitinib in pivotal phase III RCTs are in excess of 24 months and therefore agree with the company that criterion 1 (which states that the treatment is indicated for patients with a short life expectancy, normally less than 24 months) would not be met for the overall RCC patient population. • A randomised, phase III trial of sunitinib compared with interferon alfa as first-line treatment for metastatic RCC reported median OS of 26.4 months in the sunitinib arm (Motzer et al 2009). • A randomised, open-label, phase III trial of pazopanib versus sunitinib reported median OS as 29.3 months in the sunitinib group and 28.4 months in the pazopanib group (Motzer et al 2013). However, **the company** considers that patients in the poor risk subgroup (as defined by the IMDC criterion) would meet end of life criteria with a life expectancy of less than 24 months, and an expected increase in life expectancy of greater than 3 months. The company cites the following evidence in support that patients in the poor risk subgroup (as defined by the IMDC criterion) would meet end of life criterion 1 (that the treatment is indicated for patients with a short life expectancy, normally less than 24 months): • A randomised, open label phase II trial comparing cabozantinib with standard-of-care sunitinib in IMDC intermediate and poor risk patients with advanced RCC in the first-line setting reported median OS of 21.8 months with sunitinib and 30.3 months with cabozantinib

	(Choueiri et al 2017). This patient population has inferior clinical outcomes compared to an all-comer population. • Final results from an extended follow-up of a global, expanded-access trial that, prior to regulatory approval, provided sunitinib to metastatic RCC patients, ineligible for registration-directed trials. Median OS was reported for the all-comer population of 18.7 months. The subpopulations stratified by risk group of favourable, intermediate and poor reported median OS of 56.5 months, 20.0 months and 9.1 months, respectively. The patient population included within this study had a proportion of patients that had received prior systemic therapy (Gore et al 2015). **The company** states that there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment: • Median OS does not accurately capture the OS benefit in patients treated with pembrolizumab in combination with axitinib; instead, the mean provides a more reliable statistical measure for estimated OS in patients treated with pembrolizumab in combination with axitinib, due to the longevity of the benefit observed in some patients. • Median OS was not reached in KEYNOTE426; however, there was an improvement in 12 months OS rate with pembrolizumab with axitinib versus sunitinib of 11.6% (89.9% vs 78.3%). • Based on economic modelling there is an estimated improvement in 2 years OS rate of 14.1% (78.0% vs 63.9%) and 3 years OS rate of 17.7% (68.8% vs 51.1%). In summary**, the company** claims that people with IMDC poor risk RCC would meet the end of life criteria as they have a life expectancy of less than 24 months, and would have an expected increase in life expectancy of greater than 3 months with pembrolizumab with axitinib. The company cites pivotal phase III trials of first line RCC treatments, including CABOSUN (median OS was 30.3 months for cabozantinib, and 21.8 months for sunitinib), which included intermediate/poor RCC risk patients. Other trial estimates of OS for sunitinib were in excess of 24 months (though not restricted to intermediate/poor risk patients). The company also notes final results from extended follow-up of a global, expanded-access trial of sunitinib treatment in 4543 patients with metastatic RCC ineligible for registration trials. Median OS stratified by risk group was 56.5 months (favourable risk), 20.0 months (intermediate risk), and 9.1 months (poor risk). The distribution of patients across

	IMDC risk categories was 22%, 48% and 20%, respectively. However, this study did not include cabozantinib. **The ERG** had concerns that the company appears to have used sunitinib as the standard of care arm instead of cabozantinib (which is currently recommended for this group, please see NICE TA542) in the end of life consideration in the poor RCC risk subgroup. The ERG noted that no rationale was provided by the company as to why the poor risk subgroup was chosen, when in their assessment of clinical and cost-effectiveness, the subgroup considered is intermediate/poor risk. The ERG was therefore unable to generate modelled estimates of OS for the poor risk subgroup patients to inform end of life assessment. The ERG disagreed with the company that pembrolizumab with axitinib meets the first end of life criterion (treatment is indicated in patients with a short life expectancy, normally less than 24 months) in the poor risk RCC subgroup. **The technical team** notes that the committee for TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma) considered that the end of life criteria in the intermediate-poor risk group had not been met because the median overall survival in the sunitinib arm of CheckMate 214 was 25.9 months.
Why this issue is important	The appraisal committee's judgements about the acceptability of the technology as an effective use of NHS resources will take into account whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'. A technology which meets the NICE end of life criteria has an increased maximum acceptable ICER.
Technical team preliminary judgement and rationale	It appears that pembrolizumab with axitinib meets the second end of life criterion (expected increase in life expectancy of greater than 3 months) for the poor/intermediate risk group. However, there is no supportive evidence presented that the first criterion is met in this subgroup for whom cabozantinib is the recommended first-line treatment. Based on evidence presented in TA581, the technical team considers it unlikely that end of life criteria is met for this indication. It is not clear if the end of life criteria are fully met for the poor risk subgroup and whether pembrolizumab with axitinib should be considered as a life-extending treatment for people with a short life expectancy in this subgroup in particular.

Summary of comments	**Comments received by the company:** • Patients in the IMDC poor risk subgroup meet the end of life criteria. The company reiterated the rationale provided within its submission. **ERG critique:** • Noted that the company reiterated arguments provided in the company submission and did not provide further data or justification for meeting the first or second end of life criterion • Disagreed with the company that pembrolizumab with axitinib meets the first end of life criterion in the poor risk subgroup, because the overall survival of 30.3 months for intermediate/poor risk patients in the CABOSUN trial of cabozantinib exceeds the end of life criterion of less than 24 months life expectancy. • Reiterated that the ERG could not generate modelled estimates of OS for poor risk subgroup because the company's assessment of clinical effectiveness and cost effectiveness is for the intermediate/poor risk subgroup combined. **A commentator** noted the lack of direct comparative data between pembrolizumab with axitinib and cabozantinib in the poor risk group. They also noted the limitations of using Gore et al (2015) to estimate survival in this group, and in particular noted issues in specification of baseline characteristics and applicability of findings to the present day. They noted that the CABOSUN trial was not powered for OS and included few poor-risk patients (15 cabozantinib, 15 sunitinib), which was noted by both the ERG and the committee during the appraisal of cabozantinib (TA542).
Technical team judgement after engagement	The technical team maintains that it is unlikely that end of life criteria is met for this indication in the poor risk subgroup, the intermediate/poor risk subgroup and in the general population of metastatic RCC.

Issue 8 – Cancer Drug Fund

Questions for engagement	13. Is there further data being collected that could reduce uncertainty surrounding longer-term effectiveness and health outcomes in this population? 14. When will these additional data become available? 15. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?

Background/description of issue	The overall survival data is immature. Overall, there is no long-term data available to understand duration of treatment effect. Longer term follow-up data may provide greater certainty regarding the duration of sustained effect of pembrolizumab with axitinib (taking into account the 35-dose stopping rule of pembrolizumab), as well as, the overall survival of people with untreated metastatic RCC who have pembrolizumab with axitinib. The KEYNOTE-426 trial is currently ongoing, with an estimated end date of January 2020. **The company** has noted a preference for routine commissioning in the NHS in England and did not comment on the suitability of pembrolizumab with axitinib for the CDF within the main submission. **The ERG** has made no comment on the suitability of pembrolizumab with axitinib for funding through the CDF as the company have not expressed any intention to pursue it in its submission. **The technical team** notes that the available KEYNOTE-426 OS data is immature. If there was a plausible potential for the technology to be cost-effective, further data from KEYNOTE-426 trial may help to reduce uncertainty regarding overall survival extrapolation (issue 1), treatment effect of pembrolizumab with axitinib (issue 2) and the most appropriate time horizon to use in the economic model (issue 3).
Why this issue is important	The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid delaying patient access, but would require further information on its effectiveness before it can be considered for routine commissioning when the guidance is reviewed.
Technical team preliminary judgement and rationale	The technical team is aware of the high level of uncertainty resulting from the immature data presented from the KEYNOTE-426 trial and that overall survival estimates impact substantially on cost-effectiveness estimates. Additionally, it is unclear whether pembrolizumab with axitinib has a sustained treatment effect (taking into account the potential impact of stopping pembrolizumab after 2 years). Duration of treatment effect also has a large impact on the expected cost effectiveness of the intervention.

	The technical team would like input from the company regarding the timescale of when further data from KEYNOTE-426 is likely to become available, what this additional data will be, and whether any uncertainty around the company's assumed lifetime treatment effect and duration of response can be resolved. Therefore, the drug may be a candidate for the CDF, but there is uncertainty regarding its suitability.
Summary of comments	**Comments received by the company:** • The combination of pembrolizumab and axitinib for treating RCC is a suitable candidate for the Cancer Drug Fund. The completion of KEYNOTE-426 has been postponed to [redacted] and a Clinical Study Report for KEYNOTE-426 is expected in [redacted] **ERG critique:** • **The ERG** had no additional comments to those stated in this report in relation to uncertainties around clinical effectiveness and cost-effectiveness **A patient representative** commented that the Cancer Drug Fund would be a good choice for this technology while the clinical trial data matures.
Technical team judgement after engagement	At the current value proposition and using the technical team's preferred assumptions, pembrolizumab with axitinib does not appear to have plausible potential for cost-effectiveness with ICERs all above the £20,000–£30,000 per QALY gained range (when commercial arrangements are considered). It is therefore unlikely to meet the criteria for inclusion in the Cancer Drugs Fund. The available KEYNOTE-426 data are immature. If there was a plausible potential for the technology to be cost-effective, further data collection in the Cancer Drugs Fund may help to reduce uncertainty; however, it is uncertain whether the data will become sufficiently mature within the proposed timeframe to resolve uncertainties in the evidence base.

Issue 9 – Stopping rule in the treatment of pembrolizumab at 2 years

Questions for engagement	16. Are treatment stopping rules appropriate in the treatment of RCC? 17. Would the 2-year stopping rule for pembrolizumab be implemented in clinical practice for RCC?
Background/description of issue	The KEYNOTE 426 trial protocol states that patients in the combination arm must discontinue pembrolizumab after receiving 35 doses but may continue receiving axitinib until disease progression. 35 doses equate to approximately 2 years of treatment. **The company** comment that, as per the anticipated licensed indication, patients treated with pembrolizumab with axitinib were expected to be treated until disease progression or unacceptable toxicity. In line with the KEYNOTE-426 protocol, a stopping rule was implemented in the economic model whereby patients did not receive pembrolizumab therapy beyond 2 years (and no costs for pembrolizumab were applied beyond 2 years). Patients discontinuing pembrolizumab after 24 months could continue treatment with axitinib, as per KEYNOTE-426 protocol, until disease progression or unacceptable toxicity. In the company scenario analysis 13, patients also discontinued treatment with axitinib after a maximum of 2 year, resulting in an ICER of £50,436. **One clinical expert** commented that stopping rules for the combination therapy would be according to patient tolerance. Following a very good response then pembrolizumab and axitinib could be stopped after 2 years of therapy with the expectation of continued treatment effect. Another **clinical expert** commented that the company had set a stopping rule of a maximum of 35 infusions for pembrolizumab, which would be followed in clinical practice. During the process of technical engagement, **the technical team** questioned whether a 2-year stopping rule for pembrolizumab would be clinically appropriate for untreated metastatic RCC. A stopping rule (to stop treatment after 5 years) was not accepted in TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma); however, the pivotal trial supporting this appraisal did not have a specified stopping rule (in contrast to KEYNOTE-426).
Why this issue is important	In the economic model, the stopping rule stops the accrual of treatment costs of pembrolizumab for all patients after 2 years. However, it is assumed in the company base case that there is a continued lifetime treatment effect. If the stopping rule in the model was removed, it is likely that the ICER would increase.

Technical team preliminary judgement and rationale	The application of a stopping rule for pembrolizumab, in the combination treatment of pembrolizumab with axitinib for untreated metastatic RCC, is appropriately applied within the company economic model given that a stopping rule was implemented within the pivotal trial informing the economic model. As such, no cost-effectiveness evidence was submitted for this appraisal without the stopping rule for pembrolizumab applied; therefore, the cost-effectiveness for this scenario cannot be determined. Further clinical expert input would be required to determine whether the 2-year stopping rule for pembrolizumab would be clinically appropriate in the treatment of RCC.

4. Issues for information

Tables 1 to 5 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab with axitinib versus sunitinib for untreated metastatic renal cell carcinoma (estimates are based on list price of all treatments and apply to the overall RCC population).

Alteration	Technical team rationale	ICER	Change from base case
Company base case		£59,292	
1. Extrapolation of overall survival to use the Weibull distribution for both intervention and comparator	The technical team agree with the ERG that the Weibull distribution is the best fit (see issue 1).	£118,931	£59,639
2. A treatment waning effect of 5 years is used.	The technical team questioned if treatment effect was likely to extend beyond 5 years (see issue 2).	£133,900	£74,608
3. Likelihood of subsequent treatment is in line with the ERG preferred assumption and includes cabozantinib as a valid second line treatment for the intervention.	The technical team believe the ERG preferred assumptions regarding likelihood of subsequent treatment are preferable given clinical opinion and the distribution of people	£62,678	£3,385

Alteration	Technical team rationale	ICER	Change from base case
	taking subsequent therapy in the pivotal trial (see issue 4).		
4. Pooled health state utilities are used instead of time to death estimated utilities with an age-related decrement (i.e. company submission scenario 7).	The technical team notes that the ERG believe both methods of utility estimation are acceptable, however, the technical team believe that using time to death utilities may overestimate the benefit of OS (which is uncertain and possibly overestimated in the model due to immature data) and underestimate the difference in benefit observed with PFS. The technical team agree with the company and ERG that the same utilities can be used for the different treatment arms. In line with methodological guidance and due to health state utilities employed, an age-related decrement is used (see issue 5).	£63,400	£4,107
5. Estimation of time on treatment (ToT) to be estimated using a Weibull distribution.	The technical team agreed with the ERG that the Weibull distribution should be used to extrapolate treatment for pembrolizumab, axitinib and sunitinib because there is not substantial justification presented for a different distribution (exponential) to be used for axitinib and sunitinib. The Weibull gives estimates which are similar to the company's clinical experts and in line with methodological advice in DSU 14.	£58,671	-£621
6. Cost of terminal care to £8,073 (the company model cost was £6,789.76)	The technical team considers the ERG estimate to be more comprehensive and in line with TA542.	£59,235	-£58

Alteration	Technical team rationale	ICER	Change from base case
7. Administration costs of oral treatment set to £0 (The company includes a £174.40 administration cost for IV and oral treatments in the model.)	The technical team recognises that the company may have double counted the cost of oral drug administration given a follow-up outpatient consultation is included (equating to approximately 1 consultation every 4 weeks). The technical team therefore agrees with the ERG base case assumption of zero cost for the administration of oral drugs.	£59,488	£196
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate		£175,316[a]	£116,024[b]

a) Updated from previously reported ICER of £150,257; b) Updated from previously reported change of base-case of £90,064

Table 2: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab with axitinib versus the comparator in the main general RCC population analysis (estimates are based on list price for all treatments)[a]

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
Company base case	£59,292	£56,648	£57,540	Not applicable				Not applicable
1. Weibull distribution to model OS	£118,931	£113,472	£115,314		£59,639	£56,824	£57,774	
2. A treatment waning effect of 5 years	£133,900	£127,687	£129,783		£74,608	£71,039	£72,243	
3. Likelihood of subsequent treatment is in line with the ERG assumption	£62,678	£60,033	£60,925		£3,385	£3,385	£3,385	

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
4. Pooled health state utilities with an age-related decrement	£63,400	£60,572	£61,526		£4,107	£3,924	£3,986	
5. Weibull distribution to model ToT	£58,671	£55,895	£56,829		-£621	-£753	-£711	
6. Cost of terminal care: £8073	£59,235	£56,590	£57,483		-£58	-£58	-£58	
7. Administration costs of oral treatment set to £0	£59,488	£57,136	£58,029		£196	£489	£489	
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate [a]	£175,316	£168,173	£170,877		£116,024	£111,525	£113,337	

a) Table correction: Respectively for sunitinib, tivozanib and pazopanib, previous ICERs were £150,257, £144,425 and £146.638; previous changes from ICER were £90,064, £87,777 and £89,098.

Table 3: Technical team preferred assumptions and impact on the cost-effectiveness estimate for pembrolizumab with axitinib versus the comparator for the intermediate/poor risk subgroup analysis (estimates are based on list price of all treatments)[a]

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
Company base case	£59,766	£57,611	£58,350	£21,452				
1. Weibull distribution to model OS	£134,527	£129,524	£131,241	£35,338	£74,761	£71,913	£72,890	£13,886
2. A treatment waning effect of 5 years	£125,775	£121,043	£122,667	£54,108	£66,009	£63,432	£64,316	£32,657

	ICER				Change from base case			
Alteration	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
3. Likelihood of subsequent treatment is in line with the ERG assumption	£63,244	£61,089	£61,829	£26,931	£3,478	£3,478	£3,478	£5,479
4. Pooled health state utilities with an age-related decrement	£63,837	£61,535	£62,325	£23,351	£4,071	£3,924	£3,975	£1,899
5. Weibull distribution to model ToT	£60,513	£58,305	£59,061	£22,874	£747	£694	£711	£1,422
6. Cost of terminal care: £8073	£59,709	£57,554	£58,293	£21,395	-£57	-£57	-£57	-£57
7. Administration costs of oral treatment set to £0	£59,902	£57,988	£58,727	£23,176	£136	£377	£377	£1,724
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate[a]	£179,701	£173,921	£176,150	£82,488	£119,935	£116,310	£117,800	£61,036

a) Table correction: Respectively for sunitinib, tivozanib, pazopanib and cabozantinib, previous ICERs were £141,025, £136,590, £138,304 and £75,589; previous changes from ICER were £81,259; £78,979; £79,953 and £54,137.

Table 4: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
There is an immature evidence base to inform overall survival.	The KEYNOTE-426 trial showed statistically significant improvement in both co-primary endpoints and key secondary endpoint. Efficacy testing was therefore stopped at an interim time point. The median duration of follow-up at this time was 13.2 months	It is unknown what impact this could have on the cost-effectiveness results as survival estimates may be overestimated for both intervention and comparator.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	(pembrolizumab with axitinib) and 12.1 months (sunitinib). The early stopping of trials can lead to overestimation of treatment effect. Median overall survival in the trial had not yet been reached and analyses are based on extrapolated mean values.	

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Demographics and clinical characteristics of the KEYNOTE 426 trial population. The pivotal trial population may not be representative of the people with untreated metastatic renal cancer in the UK. The trial population may be younger and fitter than people in the UK with untreated metastatic RCC.	Findings of the trial and economic model may have limited applicability to the UK NHS. 63% of trial participants were from outside of Europe, and the number of participants randomised in the UK was unclear. The median age of the trial population was 62 years (range 26 to 90 years), with 38% of the trial population greater than 65 years of age, and 73% were men. In the UK, estimates suggest 65% of new cases of kidney cancer are in people greater than 65 years of age (data from years 2014 to 2016). The trial population had locally advanced or metastatic RCC with clear cell component ± sarcomatoid features. The population may therefore not be generalisable to the wider RCC population. Additionally, there were some participants who had recurrent disease which may have been treated at the advanced stage.	Younger people are likely to have better outcomes so if the trial population is younger than the people whom will be seen in clinical practice in the UK, then the survival estimates from the trial could be overestimated. The impact of this area of uncertainty on cost effectiveness is not clear.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Demographics and clinical characteristics of the populations within the studies informing the NMA.	The populations of the studies included within the NMA may not be representative of the people with untreated metastatic renal cancer in the UK and therefore findings of NMA may have limited applicability to the UK NHS. The evidence used in the NMA reflects the decision problem with the exception of the population having a more precise definition for clear cell (± sarcomatoid features) and some participants may have been treated at an advanced stage previously.	In the economic model, only the subgroup analysis for intermediate/poor risk subgroup was informed by the NMA. The impact of this area of uncertainty on cost effectiveness is not clear.
Small datasets and potential heterogeneity in studies used in NMA	The subgroup NMA analyses are based on subsets of randomised patients in the KEYNOTE 426 trial. The use of subsets and smaller samples of patients within the analysis can increase uncertainty about the precision of treatment effects.	The impact of this area of uncertainty on cost effectiveness is not clear.
Adverse events in second-line treatment were not explicitly modelled.	This assumption will have more importance if the it is assumed a higher proportion of patients have active second-line treatment and/or the safety profile of those treatments result in high cost or HRQoL reducing adverse events.	The impact of this area of uncertainty on cost effectiveness is not clear.

Table 5: Other issues for information

Issue	Comments
A separate subgroup analysis was performed for the IMDC poor/intermediate risk subgroup	The NICE scope for this appraisal did not specify any subgroups of relevance. However, the company conducted separate NMAs for the RCC risk subgroups: intermediate/poor and favourable. The company also performed a separate subgroup analysis in the economic model for the IMDC poor/intermediate risk subgroup using the findings of the associated NMA. The company and ERG agree that the RCC risk score is an effect modifier in the treatment of RCC. Further, cabozantinib is only indicated in the intermediate/poor risk subgroup of patients. Therefore, the technical team agree that it is appropriate to undertake a subgroup analysis in the intermediate/poor risk group.
Use of fully parametric modelling instead of the NMA to inform the economic model	The company, ERG and technical team agree that the use of parametric modelling using data from the KEYNOTE-426 trial in the main base case analysis is appropriate. This assumes that pazopanib and tivozanib are clinically equivalent to sunitinib. In previous NICE appraisals of first-line treatments for advanced RCC, the appraisal committees have agreed, based on expert clinical opinion, that sunitinib, pazopanib and tivozanib are broadly similar to each other in efficacy and safety, and therefore have not considered indirect comparisons as a key factor in their decision making. However, the current appraisal includes cabozantinib as a comparator, and it cannot be assumed that it is similar in efficacy and safety to the existing comparators. It is therefore appropriate that indirect comparison methods, in the absence of head to head trials, were used to inform the economic subgroup analysis of the intermediate/poor risk subgroup of people with untreated RCC.
Innovation	The company considers the drug to be innovative. One clinical expert, in support that the intervention was innovative, commented on the proportion of patients that may achieve a durable response without the significant adverse events noticed with ipilimumab or nivolumab. They also stated this technology would be first of its kind to combine immune checkpoint inhibitor and VEGF TKI. Another clinical expert supported the notion that the intervention was innovative due to the potential durability of response and improved survival. However, the technical team believes that all relevant benefits associated with the drug are adequately captured in the model and the QALY calculation.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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