NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]

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**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Kidney Cancer Support Network
   b. Kidney Cancer UK
   c. NCRI-ACP-RCP-RCR
   d. NHS England

4. **Expert personal perspectives** from:
   a. Ms Susanna Smith – patient expert nominated by Kidney Cancer UK
      Ms Smith indicated that she agreed with the statement submitted by Kidney Cancer UK
   b. Mr Colin Timney – patient expert nominated by the Kidney Cancer Support Network
      Mr Timney indicated that he agreed with the statement submitted by the Kidney Cancer Support Network
   c. Dr Paul Nathan – clinical expert nominated by the NCRI-ACP-RCP-RCR
      Dr Nathan indicated that he supported the statement submitted by the NCRI-ACP-RCP-RCR

5. **Evidence Review Group report** prepared by the **Liverpool Reviews and Implentation Group**
   The ERG report was amended after the factual accuracy check

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

7. **Technical engagement response** from **Merck**

8. **Technical engagement response from consultees and commentators:**
   a. Kidney Cancer Support Network
   b. NCRI-ACP-RCP-RCR

9. **Evidence Review Group critique of company response to technical engagement** prepared by the **Liverpool Reviews and Implentation Group**

10. **Final Technical Report**
the technical report was updated following the technical engagement stage

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

Document B

Company evidence submission

July 2019

File name	Version	Contains confidential information	Date
ID1547_avelumab-axitinib_Document_B_15Jul19_Redacted	1.0	No (Fully redacted)	15 July 2019

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Abbreviations

1L	first-line
2L	second-line
2L+	second- or later-line
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AIC	Akaike information criterion
ALT	alanine aminotransferase
aRCC	advanced renal cell carcinoma
ASCO	American Society of Clinical Oncology
ASR	age-standardised rate
AST	aspartate aminotransferase
AVE	avelumab
AXI	axitinib
BD	twice daily
BIC	Bayesian information criterion
BICR	blinded independent central review
BNF	British National Formulary
BOR	best overall response
BSC	best supportive care
CAB	cabozantinib
ccRCC	clear-cell renal cell carcinoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CrI	credible interval
CSR	clinical study report
CT	computerised tomography
CYP3A4	cytochrome P450 enzyme-3A4
CYP3A5	cytochrome P450 enzyme-3A5
DC	disease control
DCR	disease control rate
DOR	duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
EMA	European Medicines Agency
EOL	end of life
EudraCT	European Clinical Trials Database
EQ-5D	EuroQol 5-Dimension
EQ-5D-3L	EuroQol 5-Dimension 3-Level
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ESMO	European Society for Medical Oncology
Exp.	Exponential
FAS	full analysis set
FKSI-19	Functional Assessment of Cancer Therapy-Kidney Symptom Index-19
FKSI-DRS	Functional Assessment of Cancer Therapy-Disease Related Symptoms
G-CSF	granulocyte colony stimulating factor
Gen.	Generalised
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life

IA	interim analysis
IA1	first interim analysis
IA2	second interim analysis
IA3	third interim analysis
ICER	incremental cost-effectiveness ratio
IFN	interferon
IgG1	immunoglobulin G1
IL	interleukin
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	immune-oncology
irAE	immune-related adverse event
IRR	infusion-related reaction
ITC	indirect treatment comparison
ITT	intention to treat
IV	intravenous
kg	kilogram
KM	Kaplan–Meier
LCH	log-cumulative hazard
LY	Life year
MAA	marketing authorisation application
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MedDRA	medical dictionary for regulatory activities
mg	milligram
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
mTORI	mammalian target of rapamycin inhibitor
n	number of patients in the category
N	number of patients evaluable
N/A	not applicable
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	natural killer;
NMA	network meta-analysis
NR	not reported
OD	once daily
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PAZ	pazopanib
PD	progressive disease
PD-1	programmed death-1;
PD-L1	programmed death ligand-1
PFS	progression-free survival
PFS2	progression-free survival on next-line therapy
PH	proportional hazard
PLD	patient-level data
PO	orally
PP	per protocol
PPE	palmar-plantar erythrodysaesthesia
PPS	post-progression survival
PR	partial response

PRO	patient-reported outcome
PSM	parametric survival model
Q2W	every 2 weeks
Q3W	every 3 weeks
PS	performance status
PSS	personal social services
PSSRU	Personal Social Services Research Unit
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QoL	quality of life
RCC	renal cell carcinoma
RCT	randomised controlled trial
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RoW	rest of the world
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	summary of product characteristics
SOR	sorafenib
SUN	sunitinib
TA	technology appraisal
TEAE	treatment-emergent adverse event
TIV	tivozanib
TKI	tyrosine kinase inhibitor
TNM	Tumor-Node-Metastasis
ToT	time on treatment
TRAE	treatment-related adverse event
TTD	time to deterioration
TTR	Time to response
UK	United Kingdom
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WTP	willingness to pay

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

Executive summary

Renal cell carcinoma

- Kidney cancer is the seventh most common cancer in the UK, accounting for 3.1% of all cancer cases.[1]
- Renal cell carcinoma (RCC) is the most common form of kidney cancer, representing approximately 85–90% of all renal malignancies[2-4]
- As kidney cancers often remain asymptomatic until later stages,[5] cases are often diagnosed as advanced or metastatic disease (36.5% at stage III–IV in England in 2017)[6]
    - Although published incidence rates specific to RCC are lacking, it is estimated that 3,909–4,1393 cases of advanced RCC (aRCC) were diagnosed in England in 2018

Burden of disease

- Outcomes for advanced kidney cancer are poor, with prognosis significantly associated with the stage at diagnosis (five-year survival rates in England decrease from 76.7% at stage I–II to 10.7% at stage IV)[6]
- Due to the symptom burden and poor prognosis associated with advanced RCC (aRCC), there is a considerable negative impact on health-related quality of life (HRQoL), with baseline utility scores in clinical trials ranging from 0.69 to 0.76[7-10]

Clinical pathway of care

- As aRCC is currently incurable, the goal of treatment is to prevent disease progression, maintain HRQoL, provide relief from cancer symptoms and extend life[11]
- The National Institute for Health and Care Excellence (NICE) currently recommends the VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, tivozanib and cabozantinib (the latter in intermediate- and poor-risk only) as monotherapy options for the first-line treatment of aRCC. [12-15]

Unmet need

- Despite improvements in outcomes following the development of targeted therapies for aRCC, complete responses remain uncommon and almost all patients eventually progress.[16] As such, there is a clear unmet need for further first-line treatment options with greater and more durable responses and improved survival outcomes
    - Current NICE-recommended first-line treatments have demonstrated objective response rates (ORRs) of ≤33% and often fail to achieve sustained therapeutic responses, with median progression-free survival (PFS) below 13 months.[17-20]

Avelumab in combination with axitinib

- Avelumab is a human immunoglobulin G1 monoclonal antibody directed against the programmed cell death-ligand-1 (PD-L1) molecule expressed by tumour cells and a number of immune cells, while axitinib is potent and selective TKI of VEGFRs 1, 2 and

3

- Avelumab + axitinib represents a novel treatment approach in aRCC, and builds on the established efficacy of TKI monotherapy through the added benefit of an immunotherapy. Together, the combination has the potential for complimentary mechanisms of action,[21, 22] which may lead to more rapid and durable responses across all risk groups than is achieved with available therapies

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication (untreated advanced renal cell carcinoma [aRCC] – this includes both stage III and stage IV disease). A summary of the decision problem is provided in Table B.1.1.

Table B.1.1. The decision problem

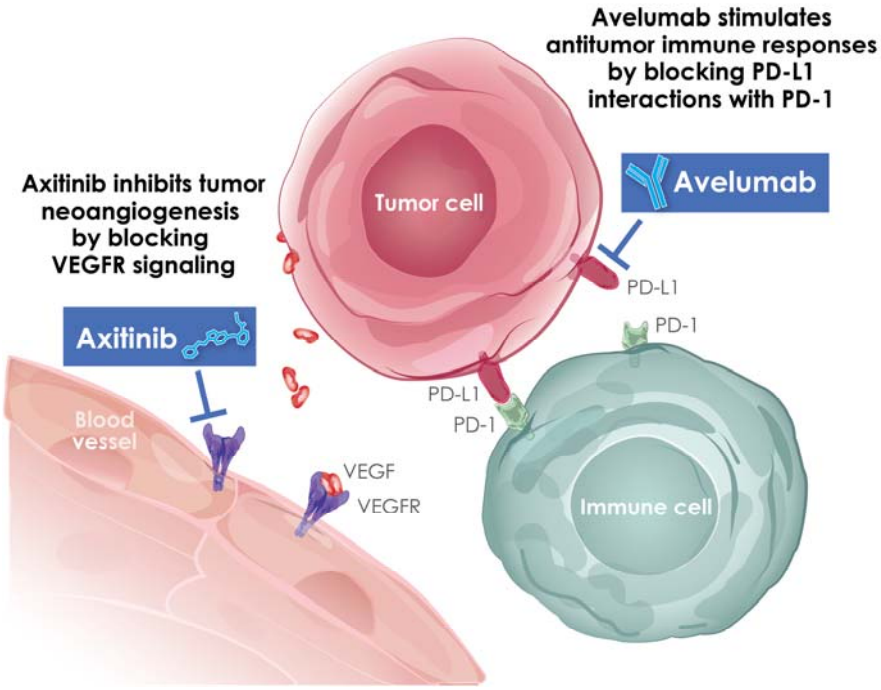
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated advanced or metastatic renal cell carcinoma	As per scope	N/A
Intervention	Avelumab with axitinib	As per scope	N/A
Comparator(s)	• Pazopanib • Sunitinib • Tivozanib • Cabozantinib (IMDC intermediate- or poor-risk only)	As per scope	N/A
Outcomes	• OS • PFS • Response rates • Adverse effects of treatment • HRQoL	As per scope	N/A

Abbreviations: HRQoL = health-related quality of life; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression free survival

B.1.2 Description of the technology being appraised

Avelumab is a human immunoglobulin G1 monoclonal antibody directed against the programmed cell death-ligand-1 (PD-L1) molecule expressed by tumour cells and a number of immune cells,[23] while axitinib is a potent and selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3.[24] The mechanisms of action of avelumab and axitinib are shown in Figure B.1.1 (see Section B.2.12 for further information on the rationale for combining avelumab and axitinib).

Figure B.1.1. Avelumab and axitinib mechanisms of action



Source: Motzer et al. 2018[25]

Summaries of avelumab and axitinib are provided in Table B.1.2 and the summary of product characteristics for each are included in Appendix C.

The anticipated licensed dose for avelumab is 800 mg every 2 weeks (Q2W). The avelumab dose evaluated in the pivotal Phase 3 study was 10 mg/kg Q2W (see Section B.2.3.3.2). Pharmacology data support a flat dosing regimen, and observed exposures to avelumab in the clinical trial generally correlate with simulations of 800 mg Q2W. A flat dosing regimen is expected to provide more consistent dosing across body weights, reduce drug wastage, facilitate preparation and administration, and reduce pharmacy errors (consistent with the NHS's recommended dose banding).[26]

Table B.1.2. Technology being appraised

UK approved name and brand name	Avelumab (Bavencio®) + axitinib (Inlyta®)
Mechanism of action	Avelumab is a human IgG1 mAb directed against the immune checkpoint protein PD-L1, which may be expressed on tumour cells and tumour-infiltrating immune cells and can contribute to the inhibition of the anti-tumour immune response in the tumour microenvironment.[23] Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the PD-1 and B7.1 receptors. This interaction suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production, leading to the restoration of immune responses, including anti-tumour immune responses. Avelumab has also been shown to induce NK cell-mediated direct tumour cell lysis via ADCC *in vitro*.[23] Axitinib is an oral, small molecule, second-generation TKI selective for VEGFR1, 2, and 3, which have been implicated in tumour angiogenesis, growth and metastasis. Axitinib inhibits VEGF-mediated endothelial cell proliferation and survival,[24] thereby preventing the formation of new blood vessels in tumours. Inhibition of VEFGF promotes an immune-stimulatory tumour microenvironment through increased T-cell infiltration, reduced accumulation and activity of immune suppressor cells, and a reduction in inflammatory signalling.[27-29]
Marketing authorisation	Avelumab as monotherapy is currently indicated for the treatment of adult patients with metastatic MCC.[23] Axitinib as monotherapy is currently indicated for the treatment of adult patients with aRCC after failure of prior treatment with sunitinib or a cytokine.[24] On 14 May 2019, the US Food and Drug Administration approved avelumab + axitinib for the first-line treatment of patients with aRCC.[30] Avelumab + axitinib is not currently approved in Europe: • MAA submitted to EMA on 7 February 2019 • CHMP opinion expected [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Proposed indication (as an extension of the marketing authorisation for avelumab): *Avelumab in combination with axitinib is indicated for the first-line treatment of adult patients with aRCC* (Note: aRCC comprises stage III–IV disease)
Method of administration and dosage	Avelumab: 800 mg IV Q2W Axitinib: 5 mg PO BD
Additional tests or investigations	None
List price and average cost of a course of treatment	The list price of avelumab will be £768.00 per 200 mg vial The list prices of axitinib will be £703.40 for the 1 mg strength, £2,110.20 for the 3 mg strength, £3,517.00 for the 5 mg strength and £4,923.80 for the 7 mg strength (all strengths will be provided in packs of 56 tablets)
[redacted]	[redacted]

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; aRCC = advanced renal cell carcinoma; BD = twice daily; CAA = commercial access agreement; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; IgG1 = immunoglobulin G1; IV = intravenous; mAb = monoclonal

antibody; MAA = marketing authorisation application; MCC = Merkel cell carcinoma; NK = natural killer; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PO = orally; Q2W = every 2 weeks; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor

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

B.1.3.1 Disease overview

Kidney cancer is the seventh most common cancer in the UK, accounting for 3.1% of all cancer cases.[1] Renal cell carcinoma (RCC) is a heterogeneous form of kidney cancer that arises from the renal tubule epithelium.[2] It is the most common kidney cancer, accounting for approximately 85–90% of all renal malignancies.[2-4]

There are five major histological subtypes of RCC; of which clear-cell RCC (ccRCC) is the most common (approximately 75% of cases). Other subtypes include papillary (10%), chromophobe (5%), cystic-solid (1–4%), collecting duct (1%) and non-classified RCC (4–6%).[31]

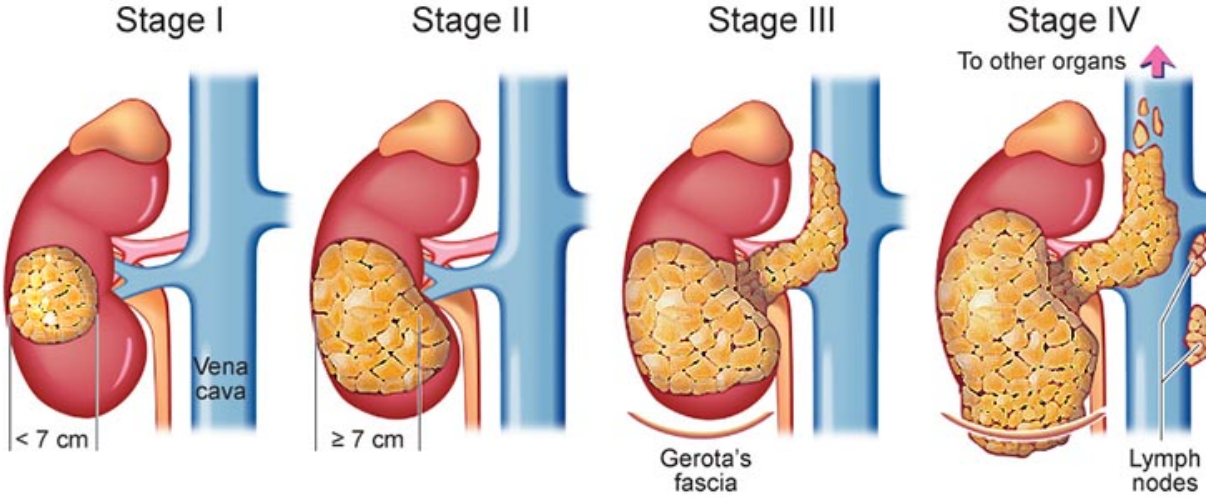
While the causes of RCC are not completely understood, a number of risk factors have been identified, including increasing age, male sex, obesity, hypertension and smoking.[2, 32, 33] In addition to these risk factors, four major, autosomal-dominant, heritable RCC syndromes have been identified (von Hippel-Lindau syndrome, hereditary leiomyomatosis and RCC, Birt-Hogg-Dubé syndrome and hereditary papillary renal carcinoma), which account for 5–8% of RCC cases.[3]

B.1.3.1.1 Staging and prognostic risk factors

RCC is generally staged using the Tumor-Node-Metastasis (TNM) system of the American Joint Committee on Cancer and the Union for International Cancer Control, which is based on local tumour growth (T), lymph node involvement (N) and the presence or absence of distant metastases (M).[34] The TNM system can be grouped into the following four stages (Figure B.1.2):

- Stage I: The tumour is ≤7 cm in the greatest dimension and confined to the kidney (T1, N0, M0)
- Stage II: The tumour is >7 cm in the greatest dimension and confined to the kidney (T2, N0, M0)
- Stage III: The tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia (T3, N0, M0), and/or has metastasised to a single regional lymph node (T1–3, N1, N0)
- Stage IV: The tumour extends beyond Gerota's fascia (T4, Any N, M0), or has metastasised to distant site(s) (Any T, Any N, M1)[34]

Figure B.1.2. Stages of RCC



Abbreviations: RCC = renal cell carcinoma
Source: Hamilton[35]

In England in 2017, 36.5% of all kidney cancer cases were diagnosed as advanced disease (stages III or IV).[6]

Multiple prognostic risk models have been developed to characterise prognosis in RCC, including the Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic RCC Database Consortium (IMDC) systems. Both are commonly used in clinical practice, and categorise patients into favourable-, intermediate- and poor-risk groups according to multiple prognostic factors, including Karnofsky performance status, time from diagnosis to treatment, haemoglobin level and corrected calcium concentration.[36, 37]

B.1.3.2 Epidemiology

The overall worldwide age-standardised rate (ASR) of kidney cancer is 4.5 cases per 100,000 population, with the highest incidence in North America (10.9 per 100,000) and Western Europe (9.7 per 100,000). In the UK, there were an estimated 13,683 cases of kidney cancer in 2018 (3.1% of all cancer cases), with an ASR of 10.2 cases per 100,000 population.[38] Kidney cancer is more common in males, with 63% and 37% of cases in the UK for males and females, respectively.[1] The incidence of kidney cancer is strongly associated with age, with incidence rates rising steeply from 65 to 69 years of age, and the highest rates observed among those aged between 85 and 89 years, for both men and women.[1]

Incidence rates specific to RCC are lacking. However, as RCC accounts for approximately 85–90% of kidney cancer cases,[2-4] estimates of the incidence of kidney cancer can be used to approximate the incidence of RCC (see Table B.1.3).

Table B.1.3. Estimated incidence of aRCC (stage III–IV) in England in 2018

	Parameter	Value	Source/calculation
A	England population	55,977,200	ONS[39]
B	Incidence rate stage I–II (per 100,000)	[redacted]	Public Health England[6]
C	Number diagnosed at stage I–II	[redacted]	A × B
D	Incidence rate stage III (per 100,000)	[redacted]	Public Health England[6]
E	Number diagnosed at stage III	[redacted]	A × D
F	Incidence rate stage IV (per 100,000)	[redacted]	Public Health England[6]
G	Number diagnosed at stage IV	[redacted]	A × E
H	Number diagnosed at stage III–IV	[redacted]	E + G
I	Proportion who progress from stage I–II to stage III–IV	22.6%	Dabestani et al. 2018[40]
J	Number who progress from stage I–II to stage III–IV	[redacted]	C × I
K	Total number of advanced (stage III–IV) kidney cancer	[redacted]	H + J
L	Percentage of stage III–IV RCC	85.0%	Nabi et al. 2018[2]
M	Total number of aRCC cases (85–90% of kidney cancer cases)[2-4]	[redacted]	K × L

Abbreviations: aRCC = advanced renal cell carcinoma; ONS = Office for National Statistics; RCC = renal cell carcinoma

B.1.3.3 Symptomatology and clinical presentation

Kidney cancers often remain asymptomatic until the advanced stage,[5] and the distinctive triad of flank pain, visible haematuria and palpable abdominal mass is rare (6–10% of cases).[34, 41] Paraneoplastic symptoms, such as hypercalcaemia, erythrocytosis, amyloidosis, hepatic dysfunction, unexplained fever and weight loss are found in approximately 30% of patients with symptomatic RCC.[34, 41, 42] Symptoms of metastatic disease may include bone pain and persistent cough.[34]

B.1.3.4 Burden to patients, carers and society

B.1.3.4.1 Mortality burden

There were 3,547 deaths due to RCC in England in 2017, equating to an ASR of 6.65 (95% confidence interval [CI]: 6.43, 6.88) per 100,000 population. Current one-, three- and five-year kidney cancer survival rates for England are 77.1% (95% CI: 76.7, 77.4), 63.5% (95% CI: 63.0, 64.1) and 55.2% (95% CI: 54.2, 56.2), respectively.[6]

Kidney cancer mortality is strongly related to age; with the ASR increasing from 1.2 deaths per 100,000 population among patients ages 40–49 years, to 30.4 per 100,000 for those aged ≥70 years.[38] The mortality burden is also significantly associated with stage at diagnosis; one- and five-year survival rates in England decrease from 93.4% and 76.7%, respectively, for patients diagnosed at stage I–II, to 90.0%/66.5% at stage III, and 37.2%/10.7 at stage IV.[6]

B.1.3.4.2 Humanistic burden

As well as high levels of mortality, aRCC is associated with a significant humanistic burden on patients and carers. Due to the symptom burden and poor prognosis associated with aRCC, there is a considerable negative impact on health-related quality of life (HRQoL).

Among patients with newly diagnosed aRCC with no prior chemotherapy, baseline EuroQol 5-Dimension (EQ-5D) utility scores in clinical trials range from 0.69 to 0.76.[7-10] Compared with the population normal utility score of 0.86, these scores represent a clinically meaningful decrease in HRQoL (≥0.05).[43] There is also a considerable psychosocial impact on patients with aRCC, as a result of being diagnosed with a cancer with a poor prognosis and a lack of curative treatments (see Section B.1.3.5.2).[44]

HRQoL continues to deteriorate as the disease progresses.[45] In a UK study, patients with aRCC who experienced disease progression had a greater reduction in HRQoL compared with those with stable disease.[46] Deterioration in HRQoL is largely driven by the symptoms of aRCC, which worsen with disease progression. As such, treatments which delay progression could in turn help to delay deterioration in HRQoL.[47]

B.1.3.4.3 Economic burden

The majority of costs associated with RCC are related to hospital care, accounting for approximately 70–80% of total costs.[48] While UK cost or healthcare resource utilisation data specific to RCC are not available, there were 20,654 finished consultant episodes, 17,520 admissions and 53,775 bed-days for malignant neoplasm of the kidney (excluding renal pelvis cancer) in England in 2017–2018.[49]

Kidney cancer is also associated with indirect costs, in part due to the time spent supporting patients by informal carers, which represents time not spent pursuing usual activities, including work. Although UK-specific data are not available, in a US study, carers spent an average of 11.4 months providing care to patients with kidney cancer. The average value of informal carer time over two years following diagnosis was $53,541 (2006 US$; equivalent to £29,051 [2006 UK£][50]).[51]

B.1.3.5 Clinical pathway of care

B.1.3.5.1 Diagnostic pathway

At present, there is no screening programme in place for detecting kidney cancer in the UK,[52] and there is no UK-specific diagnostic guidance, other than the National Institute for Health and Care Excellence (NICE) guidance on suspected cancer: recognition and referral (NICE guideline NG12). Due to the often asymptomatic nature of RCC, the majority of cases of RCC are identified incidentally.[41, 42]

While physical examination has a limited role in RCC diagnosis, the presence of a palpable abdominal mass, palpable cervical lymphadenopathy, and non-reducing varicocele and bilateral lower extremity oedema should prompt radiological examination. Common laboratory parameters assessed on suspicion of RCC include serum creatinine, glomerular filtration rate, complete cell blood count, lactate dehydrogenase, C-reactive protein and serum-corrected calcium.[34, 42]

The majority of cases of RCC are diagnosed by the use of diagnostic imaging tests, such as abdominal ultrasound, computer tomography (CT) and magnetic resonance imaging.[34, 42] According to European Society for Medical Oncology (ESMO) guidelines, contrast-enhanced chest, abdominal and pelvic CT is mandatory for accurate staging,[42] and a renal tumour biopsy may be used to determine the histological subtype.[34, 42]

B.1.3.5.2 Treatment pathway

As aRCC is currently incurable, the goal of treatment is to prevent disease progression, maintain HRQoL, provide relief from cancer symptoms and extend life.[11]

Prior to the relatively recent development of targeted therapies, immunotherapy with interleukins (ILs) and interferons (IFNs) was the only systemic therapy indicated for advanced kidney cancer. However, their use was limited by low response rates, modest survival gains and significant toxicity.[53] Targeted therapies were first approved in 2005, and act on two of the most commonly affected pathways in RCC, the VEGF and mammalian target of rapamycin pathways.[54, 55] More recently, the treatment landscape has changed further with the introduction of immune-oncology (IO) agents targeting the PD-1/PD-L1 checkpoint pathway, which have already demonstrated efficacy across a number of cancer types.[56]

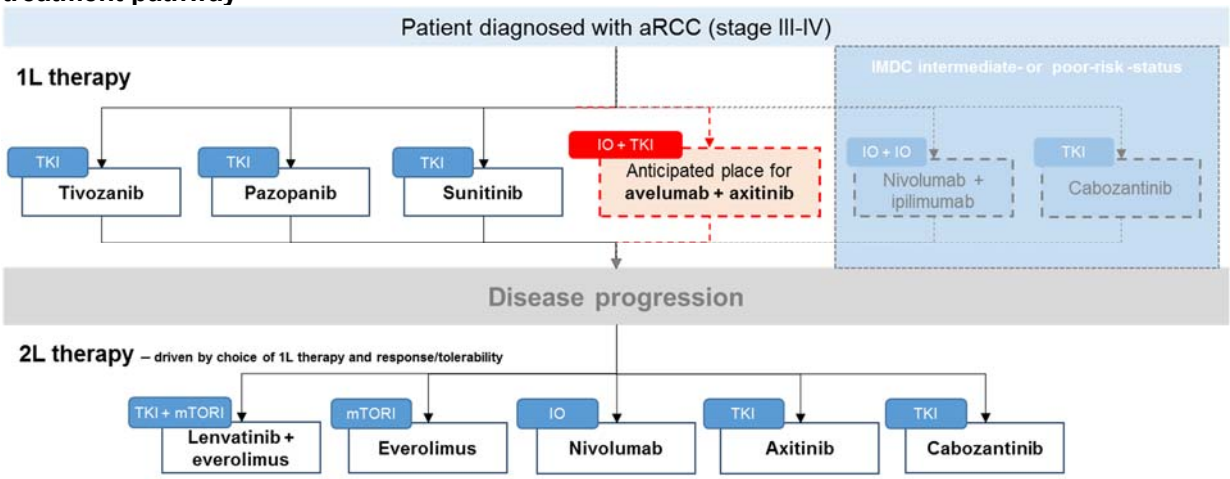
There are currently no UK-specific clinical guidelines for the treatment of RCC. Clinical practice in England and Wales therefore reflects guidelines from ESMO, the European Association of Urology and the US National Comprehensive Cancer Network,[4, 34, 42] along with NICE technology appraisal recommendations. For the first-line treatment of aRCC, NICE currently recommends the VEGFR TKIs sunitinib, pazopanib, tivozanib and cabozantinib (the latter in patients with intermediate- or poor-risk status only) as monotherapies.[12-15] A summary of current NICE guidance for first-line treatment is shown in Table B.1.4. The clinical pathway of care, including the proposed place of avelumab in combination with axitinib (avelumab + axitinib) in the treatment pathway is shown in Figure B.1.3.

Table B.1.4. Summary of NICE guidance for first-line treatment of aRCC (stage III–IV)

Treatment (TA)	Year	Guidance/population
Recommended		
Sunitinib (TA169)[14]	2009	Recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1 • The manufacturer has agreed a PAS, in which the first treatment cycle is free to the NHS
Pazopanib (TA215)[13]	2011	Recommended as a first-line treatment option for people with aRCC • Who have not received prior cytokine therapy and have an ECOG PS of 0 or 1, and • If the manufacturer provides a 12.5% discount on the list price as agreed in the PAS
Tivozanib (TA512)[12]	2018	Recommended as an option for treating aRCC in adults, only if: • They have had no previous treatment, and • The company provides the discount agreed in the PAS
Cabozantinib (TA542)[15]	2018	Recommended, within its marketing authorisation, for adults with untreated aRCC that is intermediate- or poor-risk as defined in the IMDC criteria. It is recommended only if the company provides cabozantinib according to the commercial arrangement
Cancer Drugs Fund		
Nivolumab with ipilimumab (TA581)[57]	2019	Recommended for use within the Cancer Drugs Fund as an option for adults with untreated aRCC that is intermediate- or poor-risk as defined in the IMDC criteria. It is recommended only if the conditions in the managed access agreement for nivolumab with ipilimumab are followed
Not-recommended		
Sorafenib (TA178)[58]	2009	Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma
Temsirolimus (TA178)[58]		
Bevacizumab (TA178)[58]		

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

Figure B.1.3. Clinical pathway of care and anticipated place of avelumab + axitinib in the treatment pathway



Abbreviations: 1L = first-line; 2L = second-line; aRCC = advanced renal cell carcinoma; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO= immuno-oncology; mTORI = mammalian target of rapamycin inhibitor; TKI= tyrosine kinase inhibitor
Sources: NICE TA169;[14] NICE TA215;[13] NICE TA333;[59] NICE TA417;[60] NICE TA432;[61] NICE TA463;[62] NICE TA498;[63] NICE TA512;[12] NICE TA542;[15] NICE TA581[57]

B.1.3.6 Unmet need

While survival rates for kidney cancer have improved over recent decades, five-year age-standardised survival rates in the UK remain below 60% (57% for men and 56% for women during 2010–2011, compared with 29% and 28% during 1971–1972 for men and women, respectively).[64] Historically, outcomes for patients with aRCC have been poor, with response rates of just 12–13% with IL or IFN therapy.[53] Despite recent progress following the development of targeted therapies, complete responses remain uncommon and almost all patients eventually progress.[16]

A summary of outcomes with the current NICE-recommended (or in development) first-line treatment options for aRCC is shown in Table B.1.5. In the pivotal trials of the TKIs sunitinib, pazopanib, tivozanib and cabozantinib, objective response rates (ORRs) ranged from 30% to 33%, with median progression-free survival (PFS) among treatment-naïve patients of less than 13 months for all four treatments.[17-20]

Table B.1.5. Summary of outcomes among treatment-naïve patients in pivotal trials of the current NICE-recommended 1L treatment options for aRRC (stage III–IV)

Experimental agent (study)	Control arm	ORR, % (95% CI)		Median PFS, months (95% CI)	
		Experimental arm	Control arm	Experimental arm	Control arm
Sunitinib (A6181034*)[17]	IFN-α	31 (26, 36)	6 (4, 9)†	11 (10, 12)	5 (4, 6)
Pazopanib (VEG105192*)[20]	Placebo	32 (24.3, 38.9)	4 (0.0, 8.1)	11.1 (NR, NR)	2.8 (NR, NR)
Tivozanib (TIVO-1*†)[18]	Sorafenib	33.1 (27.4, 39.2)	23.3 (18.3, 29.0)	12.7 (9.1, 15.0)	9.1 (7.3, 10.8)
Cabozantinib (CABOSUN‡)[19]	Sunitinib	33 (23, 44)	12 (5.4, 21)	8.2 (6.2, 8.8)	5.6 (3.4, 8.1)

Abbreviations: 1L = first-line; aRCC = advanced renal cell carcinoma; CI = confidence interval; IO = immune-oncology; NICE = National Institute for Health and Care Excellence; NR = not reported; ORR = objective response rate; PFS = progression-free survival

* Includes patients with ECOG PS 0–1; † includes patients who had received one prior systemic therapy; ‡ includes patients with ECOG PS 0–2

Despite the improvements seen since the introduction of targeted therapies for aRCC, patients treated with current first-line monotherapies often fail to achieve PFS of longer than 1 year and outcomes remain poor.[17-20] Given that only 50% of patients treated in the first-line setting go on to receive second-line therapies (typically due to a lack of fitness for treatment),[65, 66] it is important to ensure that patients are treated with the most effective first-line therapies. As such, there is a need for novel, innovative treatment approaches that increase patient and physician choice and offer greater durable responses and improved survival outcomes.

Avelumab + axitinib represents a novel treatment approach in RCC. It builds on the established efficacy of TKI monotherapy through the added benefit of an immunotherapy. Together, avelumab and axitinib have the potential for complimentary mechanisms of action (see Section B.2.12),[21, 22] which may lead to more rapid and durable responses, across all risk groups, than can be achieved with available therapies.

B.1.3.7 Place of avelumab + axitinib in the treatment pathway

It is anticipated that avelumab + axitinib will be used in accordance with its proposed marketing authorisation (first-line treatment of aRCC). It will therefore provide an additional first-line treatment option for aRCC (across all risk groups), alongside the TKIs sunitinib, pazopanib, tivozanib and cabozantinib, and the IO combination of nivolumab and ipilimumab (the latter recommended for use within the Cancer Drugs Fund; see Figure B.1.3).

If the combination is recommended by NICE for first-line treatment, it is anticipated that patients are likely to receive cabozantinib, lenvatinib plus everolimus or everolimus as subsequent therapy.

B.1.4 Equality considerations

There are no known equality issues relating to the use of avelumab + axitinib in patients with aRCC.

B.2. Clinical effectiveness

Executive summary

Javelin Renal 101

- The clinical effectiveness of avelumab + axitinib for the first-line treatment of advanced renal cell carcinoma (aRCC) has been established in the pivotal Phase 3 Study B9991003 (JAVELIN Renal 101; NCT02684006)
- There were six trial sites in the UK, and enrolled patients representative of those who would receive avelumab + axitinib in routine clinical practice in the UK
- JAVELIN Renal 101 is currently ongoing; results of the first and second pre-planned interim analyses (IAs) demonstrate that, compared with sunitinib, avelumab + axitinib provides a clinically meaningful benefit to patients with aRCC, irrespective of PD-L1 expression status.

Efficacy

- Compared with sunitinib, avelumab + axitinib demonstrated a clinically meaningful and statistically significant improvement in progression-free survival (PFS) in patients irrespective of PD-L1 expression status, with a median PFS of 13.8 months (95% confidence interval [CI]: 11.1, NE) in the combination arm, compared with 8.4 months (95% CI: 6.9, 11.1) in the sunitinib arm (hazard ratio [HR]: 0.69; 95% CI: 0.56, 0.84; one-sided p=0.0001)[67]
- Although overall survival data (OS) were immature at the time of the first interim analysis (IA1; [redacted] required for the final OS analyses), the results suggest an OS benefit for avelumab + axitinib (HR: 0.78 [95% CI: 0.55, 1.08])[67, 68]
  - OS data at the time of IA2 was also immature with the majority of patients alive at a minimum follow-up of 13 months[69]
  - In addition, with [redacted] follow-up in the Phase 1b JAVELIN Renal 100, median OS for patients treated with avelumab + axitinib was [redacted]. The majority of patients were still alive for up to 2 years of follow-up, with a probability of survival at 24 months of [redacted] (95% CI: [redacted], [redacted])[70]
  - Although OS data are still maturing, the potential for durable responses and long-term survival following treatment with IOs has previously been established,[71-74] and is supported by the immunogenic nature of RCC. Therefore, patients who achieve a durable response to avelumab + axitinib have the potential to achieve extended survival without the need for further systemic therapies, thereby avoiding adverse events (AEs) of further treatment and the associated impact on quality of life (QoL). This is particularly important given that only 50% of patients treated in the first-line setting go on to receive second-line therapies[65, 66]
- The objective response rate for avelumab + axitinib was doubled in the combination arm compared with the sunitinib arm (51.4% [95% CI: 46.6, 56.1] and 25.7% [95% CI: 21.7, 30.0], respectively; odds ratio [OR]: 3.10; 95% CI: 2.30, 4.15), representing a potentially significant benefit for patients over a current first-line therapy[67]
- Responses to avelumab + axitinib had an earlier onset compared with those to sunitinib (median TTR of 2.6 months [95% CI: 1.2, 13.8] and 3.2 months [95% CI: 1.2, 11.6],

respectively[67]

- Progression-free survival on next-line therapy (PFS2) appeared to be longer for patients in the combination arm compared with those in the sunitinib arm (NE [95% CI: 19.9, NE] and 18.4 months [95% CI: 15.7, 23.6]; HR: 0.56 [95% CI: 0.421, 0.735])[75]
- Patient-reported outcome analyses demonstrated that the combination was associated with similar QoL outcomes to sunitinib
- Where efficacy outcomes are available at the second IA, the results were consistent with those seen at IA1, alongside a tightening of the 95% CIs, which is expected to improve with time as data mature

Safety

- Treatment-emergent AEs (TEAEs), treatment-related adverse events (TRAEs) and Grade ≥3 AEs were reported at similar rates in both treatment arms
  - TEAEs: 432 (99.5%) and 436 (99.3%) in the avelumab + axitinib arm and sunitinib arms, respectively (309 [71.2%] and 315 [71.5%] Grade ≥3)[67]
  - TRAEs: 414 (95.4%) in the combination arm, compared with 423 (96.4%) in the sunitinib arm (246 [56.7%] and 243 [55.4%] Grade ≥3)[67]
- As would be expected, immune-related AEs were more frequent in the combination arm compared with the sunitinib arm (38.2% and 5.0%, respectively), and infusion-related reactions were reported only in the combination arm (12.0% [Preferred Term])[25, 68]
- AEs were typically manageable and were consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies
- Overall, avelumab + axitinib was generally well tolerated, and there appears to be no additional toxicity from the addition of an IO agent to a VEGFR TKI, compared with TKI monotherapy

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify and summarise the available randomised controlled trial (RCT) evidence for the current and future treatment options for previously untreated patients with advanced renal cell carcinoma (aRCC). Full details of the methodology and the results of the SLR are detailed in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

This submission is supported by efficacy data from the ongoing Phase 3 Study B9991003 (JAVELIN Renal 101; NCT02684006).[68] Data are presented for the first and second pre-planned interim analyses (IAs). Supplemental data are provided by the ongoing Phase 1b Study B9991002 (JAVELIN Renal 100 NCT02493751).[76] An overview of JAVELIN Renal 101 and JAVELIN Renal 100 is provided in Table B.2.1.

Table B.2.1. Clinical effectiveness evidence

Phase 3					
Study	Study B9991003 (JAVELIN Renal 101; NCT02684006)[25, 67, 75]				
Study design	Multicentre, randomised, open-label, parallel-arm Phase 3 trial				
Population	Treatment-naïve adult patients with histologically or cytologically confirmed aRCC with clear cell component, and an ECOG PS of 0 or 1				
Intervention(s)	Avelumab + axitinib				
Comparator(s)	Sunitinib				
Indicate if 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	Pivotal Phase 3 trial supporting this indication				
Reported outcomes specified in the decision problem	• **OS** • **PFS** • Response rates • **AEs of treatment** • **HRQoL**				
All other reported outcomes	• TTR • DOR • PFS2				
Phase 1b					
Study	Study B9991002 (JAVELIN Renal 100 NCT02493751)[77]				
Study design	Multicentre, open-label, dose-finding Phase 1b trial				
Population	Treatment-naïve adult patients with histologically or cytologically confirmed aRCC with clear cell component, and an ECOG PS of 0 or 1				
Intervention(s)	Avelumab + axitinib				
Comparator(s)	N/A				
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	Phase 1b trial supporting the evidence for the intervention within this indication				
Reported outcomes specified in the decision problem	• OS • AEs of treatment (pooled B9991002 + B9991003)				
All other reported outcomes	N/A				

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; HRQoL health-related quality of life; N/A = not applicable; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival on next-line therapy; PS = performance status; TTR = time to response

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

The primary source of clinical evidence for this submission is provided by the Phase 3 JAVELIN Renal 101, with supplemental OS and safety data provided by the Phase 1b JAVELIN Renal 100. A summary of methodology of JAVELIN Renal 101 is provided here, with methodology of JAVELIN Renal 100 summarised in Appendix M.

B.2.3.1 Study design and objectives

JAVELIN Renal 101 is an ongoing Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised (1:1) study, designed to assess the efficacy, safety and tolerability of avelumab + axitinib (also referred to as the 'combination arm' or 'combination treatment') versus sunitinib for the first-line treatment of aRCC (including metastatic disease).[68]

JAVELIN Renal 101 aims to demonstrate that avelumab + axitinib is superior to sunitinib monotherapy in prolonging PFS or OS in the first-line treatment of patients with aRCC, with hierarchical testing for patients with programmed death ligand-1 (PD-L1)-positive tumours.[68]

A summary of the methodology of JAVELIN Renal 101 is provided in Table B.2.2.

Table B.2.2. Summary of methodology of JAVELIN Renal 101 (Study B9991003; NCT02684006)

Trial design	Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised (1:1) study
Locations (number of patients recruited)	Australia (32), Austria (5), Belgium (9), Canada (74), Denmark (5), France (70), Germany (7), Hungary (2), Israel (41), Italy (15), Japan (67), Mexico (12); Netherlands (38), New Zealand (n=9); Republic of Korea (48), Romania (20); Russia (138), Spain (1), UK (32), US (261)

Study status	Ongoing
	• First subject first visit: 23 March 2016
	• Data cut-off date:
	  • IA1: 20 June 2018
	  • IA2: 28 January 2019
	  • [redacted]
	  • [redacted]

Key eligibility criteria	• Age ≥18 years (≥20 years in Japan) • Histologically or cytologically confirmed aRCC* with a clear cell component • At least one measureable lesion (as defined by RECIST version 1.1) that had not been previously irradiated • Estimated life expectancy of ≥3 months • ECOG PS 0 or 1 • Adequate bone marrow, renal and liver functions • No evidence of uncontrolled hypertension • No prior therapies, including systemic therapy for advanced or metastatic RCC, adjuvant or neoadjuvant therapy for RCC, immunotherapy and VEGF pathway inhibitors • No newly diagnosed brain metastases or known symptomatic brain metastases requiring steroids • No major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomisation
Study treatments	• Arm A: Avelumab + axitinib (n=442) • Arm B: Sunitinib (n=444)
Concomitant medication	**Permitted:** • Medications intended solely for supportive care • G-CSF • Local radiotherapy of isolated lesions with palliative intent • Systemic steroids (short-term administration) • Topical and inhaled steroids **Disallowed:** • Anti-cancer therapy (other than avelumab, axitinib or sunitinib) • Vaccine therapies ≤4 weeks prior to the start of study treatment (except inactive influenza vaccine) • Bisphosphonate or denosumab (unless initiated >14 days prior to the first dose of study treatment) • Other experimental pharmaceutical products • Herbal remedies with immune-stimulating properties or with the potential to interfere with major organ function
Primary outcomes	• PFS (according to RECIST version 1.1) by BICR assessment in patients with PD-L1-positive tumours (≥1% staining in tumour-associated immune cells) • OS in patients with PD-L1-positive tumours
Secondary outcomes	• PFS (according to RECIST version 1.1) by BICR assessment in patients unselected for PD-L1 expression • OS in patients unselected for PD-L1 expression • Objective response (BOR of CR or PR based on BICR assessment,

	according to RECIST version 1.1 • DC (BOR of CR, PR, non-CR/non-PD or stable disease based on BICR assessment, according to RECIST version 1.1) • TTR • DOR • PFS2
PROs	• TTD in FKSI-DRS • FKSI-19 • EQ-5D-5L
Safety outcomes	• AEs (including SAEs) • Vital signs • Physical examination • 12-lead ECG • Laboratory assessments • ECOG PS • Verification of concomitant medication use
Pre-planned subgroups	PFS, OS, ORR and DOR by: • PD-L1 status (positive, patients unselected for PD-L1 expression) • ECOG PS (0, 1) • Geographical region (US, Canada/Western Europe, RoW) • Pooled geographic region (North America, Europe, Asia, RoW) • Age (<65 years, ≥65 years) • Gender (male, female) • Race (Caucasian/White, Asian, Black/African American, other) • Ethnicity (Hispanic/Latino, Non-Hispanic/Latino) • Nephrectomy at baseline (yes, no) • MSKCC prognostic criteria at baseline (favourable, intermediate, poor) • IMDC prognostic criteria at baseline (favourable, intermediate, poor)

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; BICR = blinded independent central review; BOR = best overall response; CR = complete response; DOR = duration of response; ECG = electrocardiogram ; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony stimulating factor; EQ-5D-5L = EuroQol 5-Dimension 5-Level; FKSI-19 = Functional Assessment of Cancer Therapy-Kidney Symptom Index-19; FKSI-DRS = Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; IA1 = first interim analysis; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; ORR = objective response rate; PD = progressive disease; PD-L1 = programmed death ligand-1; PFS = progression-free survival; PFS2 = progression-free survival on next-line therapy; PR = partial response; PS = performance status; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RoW = rest of the world; SAE = serious adverse event; TTD = time to deterioration; TTR = time to response; US = United States; VEGF = vascular endothelial growth factor
* aRCC included unresectable locally advanced and metastatic disease
Source: Pfizer Inc., 2018;[78] Pfizer Inc., 2018;[68]

B.2.3.2 Eligibility criteria

JAVELIN Renal 101 included treatment-naïve, adult patients with aRCC (with a clear cell component), regardless of PD-L1 expression status.[68] Key inclusion and exclusion criteria are presented in Table B.2.3.

Table B.2.3. Key inclusion and exclusion criteria

Inclusion criteria	• Age ≥18 years (≥20 years in Japan) • Histologically or cytologically confirmed aRCC* with a clear cell component • At least one measureable lesion (as defined by RECIST version 1.1) that had not been previously irradiated • Estimated life expectancy of ≥3 months • ECOG PS 0 or 1 • No evidence of uncontrolled hypertension • Adequate bone marrow, renal and liver functions • Serum pregnancy test negative at screening (for females of childbearing potential) and the use of two highly effective methods of contraception throughout the study and for at least 90 days after the last dose (for male patients able to father children and female patients of childbearing potential)
Exclusion criteria	• Prior systemic therapy for advanced or metastatic RCC • Prior adjuvant or neoadjuvant therapy for RCC if disease progression or relapse has occurred during or within 12 months after the last dose of treatment • Prior immunotherapy with any antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways • Prior therapy with any VEGF pathway inhibitors • Newly diagnosed brain metastases or known symptomatic brain metastases requiring steroids (patients with previously diagnosed brain metastases who had completed their treatment and recovered from the acute effects of radiation therapy or surgery prior to randomisation, had discontinued corticosteroid treatment for these metastases for at least 4 weeks and were neurologically stable, were eligible) • Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomisation (prior palliative radiotherapy to metastatic lesion(s) was permitted, if completed ≥48 hours prior to randomisation)

Abbreviations: aRCC = advanced renal cell carcinoma; ECOG = Eastern Cooperative Oncology Group; PS = performance status; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; VEGF = vascular endothelial growth factor

* aRCC included unresectable locally advanced and metastatic disease

Source: Pfizer Inc., 2018[78]

B.2.3.3 Study treatments

B.2.3.3.1 Allocation to treatment

Patients were randomised in a 1:1 ratio to receive either avelumab + axitinib (Arm A) or sunitinib monotherapy (Arm B). Randomisation was stratified according to ECOG PS (0 or 1) and region (United States, Canada/Western Europe, or rest of the world). Crossover between treatment arms was not permitted.[78]

The study included the following periods:

- Screening (up to 28 days before randomisation)
- Study treatment
- Short-term follow-up for 90-days after the last dose of study treatment
- Long-term follow-up until death, end of study or withdrawal of consent, whichever occurred first.[68]

B.2.3.3.2 Treatments administered

All investigational products were administered on an outpatient basis. Patients in Arm A received avelumab 10 mg/kg as a 1-hour intravenous infusion Q2W in a 6-week cycle

(Days 1, 15 and 29 of each cycle). In order to mitigate infusion-related reactions (IRRs), premedication with an antihistamine and paracetamol administered approximately 30–60 minutes prior to each dose of avelumab was mandatory (modification based on local treatment standards and guidelines was permitted).[68, 78]

Patients in Arm A also received axitinib 5 mg twice daily (BD), administered orally on a continuous dosing schedule. Missed doses could be taken late, up to 3 hours before the next scheduled dose of that day, or otherwise skipped and dosing resumed with subsequent doses as prescribed.[68]

Patients in Arm B received sunitinib 50 mg once daily (OD), administered orally in 6-week cycles (4 consecutive weeks of treatment followed by a 2-week off-treatment period). Missed doses could be taken later the same day, or otherwise skipped and dosing resumed with subsequent doses as prescribed.[68]

Patients received study treatment until confirmed disease progression, global deterioration of health status requiring discontinuation or unacceptable toxicity. Treatment with single-agent avelumab, single-agent axitinib or avelumab + axitinib (in Arm A), or sunitinib monotherapy (in Arm B), could continue beyond confirmed disease progression if the patient was experiencing clinical benefit. Crossover between treatment arms was not permitted.[68, 78]

B.2.3.3.3 Dose modification

No avelumab dose modifications were permitted, but infusions could be omitted due to persisting toxicity. Infusion of avelumab was to be stopped in case of Grade ≥2 infusion-related, allergic or anaphylactic reactions, and the infusion rate reduced in case of Grade 1 reactions.[68, 78]

In the event of toxicity, axitinib dose modifications (including dosing interruption and/or dose reduction to 3 mg or 2 mg BD) were allowed. Dose modifications of axitinib and infusion omissions of avelumab could occur independently, and patients who stopped either avelumab or axitinib for reasons other than confirmed disease progression could continue on single-agent treatment until disease progression. Axitinib dose escalation to 7 mg BD and 10 mg BD was allowed if patients tolerated the current dose without axitinib-related Grade 3 or higher adverse events (AEs) for two consecutive weeks. [68, 78] A summary of axitinib dose levels is shown in Table B.2.4.

As with axitinib, sunitinib treatment could be adjusted by dosing interruption and/or dose reduction to 37.5 mg or 25 mg OD for the management of toxicities (Table B.2.4).[78]

Table B.2.4. Permitted axitinib and sunitinib dose levels

Dose level	Dose	
	Axitinib	**Sunitinib**
+2	10 mg BD	N/A
+1	7 mg BD	N/A
Starting dose	5 mg BD	50 mg OD
-1	3 mg BD	37.5 mg OD
-2	2 mg BD	25 mg OD

Abbreviations: BD = twice daily; OD = once daily; mg = milligram; N/A = not applicable
Source: Pfizer Inc., 2018[68]

B.2.3.3.4 Concomitant therapies

A summary of allowed and disallowed concomitant therapies is shown in Table B.2.5. In addition, the use of concomitant use of strong cytochrome P450 enzyme-3A4/5 (CYP3A4/5) inhibitors or inducers was to be avoided and selection of alternative concomitant medication with no or minimal CYP3A4/5 inhibition/induction potential was recommended. Moderate CYP3A4/5 inducers were also to be avoided, if possible.[68]

Table B.2.5. Allowed and disallowed concomitant therapies

Allowed	• Medications intended solely for supportive care (e.g., antiemetics, analgesics) • G-CSF (in agreement with ASCO guidelines) • Local radiotherapy of isolated lesions with palliative intent • Short-term administration of systemic steroids (e.g. for allergic reactions or the management of irAEs) • Topical and inhaled steroids
Disallowed	• Anti-cancer therapy with agents other than avelumab and axitinib in Arm A or sunitinib in Arm B • Any vaccine therapies for the prevention of infectious disease within 4 weeks of the start of study treatment (except inactive influenza vaccine) • Bisphosphonate or denosumab (unless initiated >14 days prior to the first dose of study treatment) • Other experimental pharmaceutical products • Herbal remedies with immune-stimulating properties or with the potential to interfere with major organ function

Abbreviations: ASCO = American Society of Clinical Oncology; G-CSF = granulocyte colony stimulating factor; irAE = immune-related adverse event
Source: Pfizer Inc., 2018[68]

B.2.3.4 Assessments and outcomes

B.2.3.4.1 Survival status

The survival status of each patient was monitored during study treatment and the safety follow-up period. Subsequently survival information was collected every 3 months (±14 days).[68]

B.2.3.4.2 Tumour assessments

Anti-tumour activity was assessed by radiological tumour assessments conducted at screening, at 6 weeks from randomisation, then every 6 weeks up to 18 months from randomisation, and every 12 weeks thereafter until confirmed disease progression. Tumour

assessments were conducted by the investigator, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and blinded independent reviewers provided central assessment of study imaging and relevant clinical data to determine overall tumour assessment (also based on RECIST version 1.1). The review process included primary radiology review, global radiology review, and as required, adjudication radiology review.[68]

Computerised tomography (CT) or magnetic resonance imaging (MRI) included the chest, abdomen and pelvis at all time points, and were performed with contrast agents unless contraindicated. Bone scintigraphy was required at screening and repeated as clinically indicated or at the time of confirmed complete response (CR). Bone lesions identified at screening by bone scintigraphy could be re-assessed by CT or MRI according to the tumour assessment schedule, or by bone scintigraphy every 12 weeks after randomisation. Head CT/MRI was also required at screening, and repeated at subsequent tumour assessments only for patients with brain metastases at screening, or as clinically indicated.[68]

B.2.3.4.3 Efficacy outcomes

The primary efficacy endpoints were:

- PFS, defined as the time from randomisation to the date of the first documentation of objective disease progression (according to RECIST version 1.1 and based on blinded independent central review [BICR]) or death due to any cause, whichever occurred first, in patients with PD-L1-positive tumours, defined as those with PD-L1 staining of any intensity in tumour-associated immune cells covering ≥1% of tumour area
- OS, defined as the time from date of randomisation to the date of death due to any cause, in patients with PD-L1-positive tumours[68, 78]

Secondary efficacy endpoints included:

- PFS (according to RECIST version 1.1) by BICR in patients unselected for PD-L1 expression
- OS in patients unselected for PD-L1 expression
- Objective response, defined as a best overall response (BOR) of CR or partial response (PR) according to RECIST version 1.1, from randomisation until disease progression assessed by BICR or death due to any cause
- Disease control (DC), defined as a BOR of CR, PR, non-CR/non-progressive disease (PD) or stable disease according to RECIST version 1.1, from randomisation until disease progression assessed by BICR or death due to any cause
- Time to response (TTR), defined as the time from randomisation to first documentation of objective response (CR or PR)
- Duration of response (DOR), defined as the time from the first documentation of objective response (CR or PR) to the first documentation of PD or death due to any cause, whichever occurs first
- PFS on next-line therapy (PFS2), defined as the time from randomisation to discontinuation of next-line treatment after first objective disease progression (by investigator assessment), second objective disease progression (by investigator assessment) after initiation of next-line treatment, or death due to any cause, whichever occurs first[68, 78]

B.2.3.4.4 Safety outcomes

Safety assessments consisted of the collection of AEs, serious AEs (SAEs), vital signs, physical examination, 12-lead electrocardiogram, laboratory assessments (including pregnancy tests), ECOG PS, and verification of concomitant medication use.[68]

AEs were classified using the medical dictionary for regulatory activities (MedDRA) classification system, and the severity of the toxicities was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[68]

B.2.3.4.5 Patient-reported outcomes

Patient-reported outcomes (PROs) were assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 (FKSI-19) and EuroQol 5-Dimension 5-Level (EQ-5D-5L) instruments. The FKSI-19 and EQ-5D-5L questionnaires were administered at the time of tumour assessments.[68]

The primary PRO endpoint was the time to deterioration (TTD) in the FKSI-Disease Related Symptoms (FKSI-DRS) subscale, defined as the time from date of randomisation to the first ≥3-point decrease from baseline.[68]

B.2.3.5 Study population

B.2.3.5.1 Disposition

As of the data cut-off date for the first pre-planned IA (IA1; 20 June 2018), 886 patients from 20 countries were randomised to receive either avelumab + axitinib (N=442) or sunitinib (N=444).[67]

Of the 886 randomised patients, 873 received at least one dose of study treatment (434 patients in the combination arm and 439 patients in the sunitinib arm). As of the data cut-off date (20 June 2018), 212 (48.0%) patients had discontinued avelumab, 196 (44.3%) had discontinued axitinib, and 277 (62.4%) patients had discontinued sunitinib. Disease progression was the primary reason for discontinuation of avelumab and axitinib (19.5% and 20.8%, respectively) and sunitinib (35.4%).[67] A summary of patient disposition is shown in Table B.2.6.

Table B.2.6. Patient disposition at end of treatment (FAS)

Disposition	Avelumab + axitinib (N=442)		Sunitinib (N=444)
	Avelumab	Axitinib	
Discontinued, n (%)	212 (48.0)	196 (44.3)	277 (62.4)
Death	[redacted]	[redacted]	[redacted]
Progressive disease	86 (19.5)	92 (20.8)	157 (35.4)
AE	71 (16.1)	43 (9.7)	49 (11.0)
Non-compliance	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]
No longer meets eligibility criteria	[redacted]	[redacted]	[redacted]
Global deterioration of health status	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ongoing, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; FAS = full analysis set; n = number of patients in the category; N = number of patients evaluable
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[68]

Patients who discontinued treatment and continued in the study could proceed into the follow-up phase or directly into long-term follow-up phase (if the patient initiated subsequent anti-cancer therapy at the end of treatment or by patient request). As of the data cut-off date (20 June 2018), there were [redacted] ([redacted]) and [redacted] ([redacted]) patients in the combination arm, and [redacted] ([redacted]) and [redacted] ([redacted]) patients in the sunitinib arm, ongoing in the follow-up and long-term follow-up phases, respectively.[68]

B.2.3.5.2 Data sets analysed

The number and percentage of patients included in each analysis data set are summarised in Table B.2.7.

Table B.2.7. Analysis data sets

Analysis set	Avelumab + axitinib	Sunitinib	Total
FAS, n	442	444	886
SAS, n (%)	[redacted]	439 (98.9)	873 (98.5)
PP analysis set for OS, n (%)	[redacted]	[redacted]	[redacted]
PP analysis set for PFS, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: FAS = full analysis set; n = number of patients in the category; OS = overall survival; PFS = progression-free survival; PP= per protocol; SAS = safety analysis set
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[68]

B.2.3.5.3 Demographics and baseline characteristics

Of the 886 enrolled patients, 560 (63.2%) had a tumour sample which scored positive for PD-L1 expression (270 [61.1%] patients in the avelumab + axitinib arm and 290 [65.3%] patients in the sunitinib arm); 252 (28.4%) patients (132 [29.9%] in the combination arm and 120 [27.0%] in the sunitinib arm) had a tumour sample which scored negative for PD-L1 expression.[67]

Demographics and baseline characteristics were similar across treatment arms, both among patients with PD-L1-positive tumours and patients irrespective of PD-L1 status.[68] A summary of demographics and baseline characteristics is shown in Table B.2.8.

Table B.2.8. Demographics and baseline characteristics (FAS)

Demographic/baseline characteristic	Avelumab + axitinib (n=442)	Sunitinib (n=444)	Total (n=886)
Mean age (SD), years	[redacted]	[redacted]	[redacted]
≥65 years, n (%)	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Female	126 (28.5)	100 (22.5)	226 (25.5)
Male	316 (71.5)	344 (77.5)	660 (74.5)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian/Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian/other Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Geographic Region, n (%)			
North America	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]
RoW	[redacted]	[redacted]	[redacted]
Histopathology			
Clear cell only	[redacted]	[redacted]	[redacted]
Clear cell plus other	[redacted]	[redacted]	[redacted]
Other only	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]
ECOG PS			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]
Prior nephrectomy, n (%)	352 (79.6)	355 (80.0)	707 (79.8)
MSKCC prognostic criteria			
Favourable	96 (21.7)	100 (22.5)	196 (22.1)
Intermediate	283 (64.0)	293 (66.0)	576 (65.0)
Poor	51 (11.5)	45 (10.1)	96 (10.8)
NR	12 (2.7)	6 (1.4)	18 (2.0)
IMDC prognostic criteria			
Favourable	94 (21.3)	96 (21.6)	190 (21.4)
Intermediate	271 (61.3)	276 (62.2)	547 (61.7)
Poor	72 (16.3)	71 (16.0)	143 (16.1)
NR	5 (1.1)	1 (0.2)	6 (0.7)
PD-L1 status			
Positive	270 (61.1)	290 (65.3)	560 (63.2)
Negative	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Mean time (SD) since initial diagnosis, months	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; n = number of patients in the category; N = number of patients evaluable; NR = not reported; PD-L1 = programmed death-ligand 1; PS = performance status; RoW = rest of the world; SD = standard deviation
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[68]

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

B.2.4.1 Statistical hypotheses

The following statistical hypotheses were tested to address the primary objectives:

H_{01}: $HR_{PFS+} \geq 1$ vs H_{11}: $HR_{PFS+} < 1$

H_{02}: $HR_{OS+} \geq 1$ vs H_{12}: $HR_{OS+} < 1$

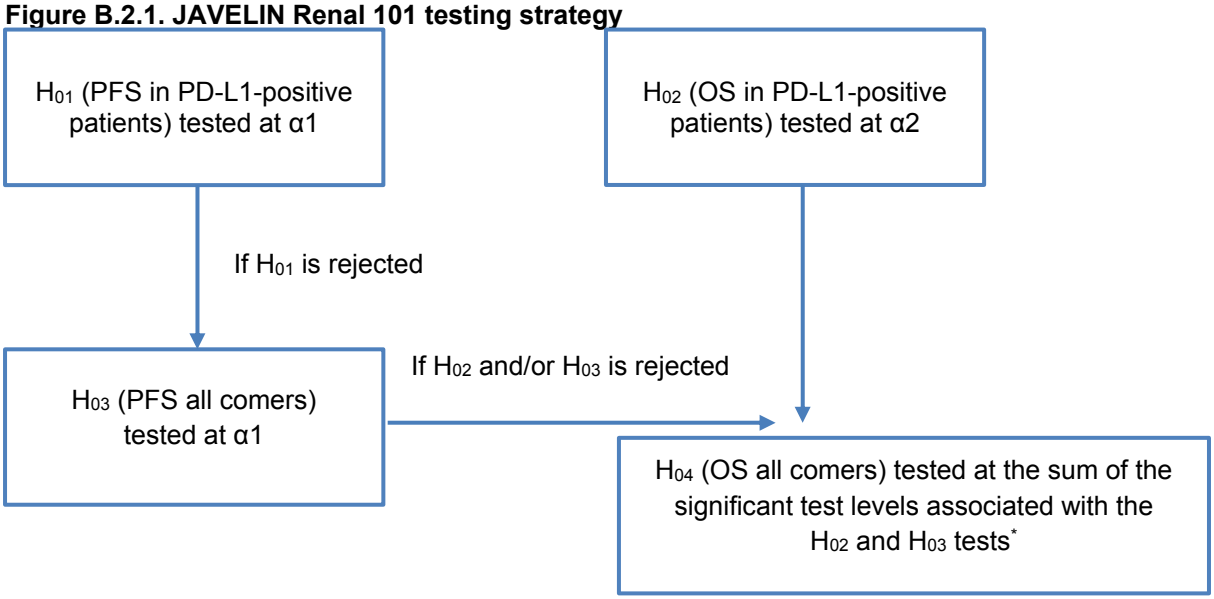
where HR_{PFS+} and HROS+ are the hazard ratios (HRs; Arm A versus Arm B) of PFS and OS, respectively, in patients with PD-L1-positive tumours. In addition, the following statistical hypotheses were to be tested to address secondary objectives:

H_{03}: $HR_{PFS} \geq 1$ vs H_{13}: $HR_{PFS} < 1$

H_{04}: $HR_{OS} \geq 1$ vs H_{14}: $HR_{OS} < 1$

where HR_{PFS} and HR_{OS} are the HRs (Arm A versus Arm B) of PFS and OS, respectively, for patients unselected for PD-L1 expression (all comers). Overall type I-error was maintained at or below one-sided 0.025 by allocating $\alpha=0.004$ (α_1) to the PFS comparison in the PD-L1-positive population and by allocating $\alpha=0.021$ (α_2) to the OS comparison in the PD-L1-positive populations. A gatekeeping procedure was used to allow further testing of PFS and OS in patients irrespective of PD-L1 expression (Figure B.2.1). The significance levels for each test also took into account the group sequential nature of the design.[68]

Figure B.2.1. JAVELIN Renal 101 testing strategy



Abbreviations: H = hypothesis; OS = overall survival; PFS = progression-free survival
* α level for H_{04} will be $\alpha_1 + \alpha_2$ if both H_{02} and H_{03} are rejected; α_2 if H_{02} is rejected and H_{03} is not rejected; α1 if H_{02} is not rejected and H_{03} is rejected
Source: Pfizer Inc., 2018[68]

B.2.4.2 Determination of sample size

JAVELIN Renal 101 was to randomise approximately 830 patients, including a minimum of 580 patients (70%) with PD-L1-positive tumours.[68]

For the primary analysis of PFS in patients with PD-L1-positive tumours, 336 events would provide 90% power to detect a HR of 0.65 using a one-sided log-rank test at a significance level of 0.004, with a two-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. For the primary analysis of OS in patients with PD-L1-positive tumours, 368 events would provide 90% power to detect a HR of 0.70 using a 1-sided log-rank test at a significance level of 0.021, with a 4-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.[68]

The sample size of approximately 830 patients would also allow assessment of PFS and OS in patients unselected for PD-L1 expression. If H_{01} was rejected, PFS in patients unselected for PD-L1 expression could be tested, and 490 PFS events were required to provide ≥90% power to detect a HR of 0.70 using a one-sided log rank test at a significance level of 0.004, and a two-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. If either H_{02} or H_{03} was rejected, OS in patients unselected for PD-L1 expression could be tested at the sum of the significance levels associated with the significant H_{02} and H_{03} tests. With 534 OS events, the power was 91% (if both H_{02} and H_{03} were rejected), 90% (if H_{02} was rejected and H_{03} was not rejected) or 74% (if H_{02} was not rejected and H_{03} was rejected) to detect a HR of 0.75 using a one-sided log rank test at a significance level of 0.025, 0.021 or 0.004, respectively, and a four-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.[68]

The data cut-off for the first pre-planned IA (IA1) was at the time when approximately 235 events for PFS (70% information fraction) had occurred in patients with PD-L1-positive tumours.[68]

B.2.4.3 Efficacy analyses

The primary analysis set for all efficacy endpoints was the full analysis set (FAS), which included all randomised patients. Patients were classified according to the study treatment assigned at randomisation.[68]

B.2.4.3.1 Primary efficacy analyses

The primary endpoints were PFS based on BICR assessment (according to RECIST version 1.1) and OS, in patients with PD-L1-positive tumours. The study was considered positive if the stratified log-rank test was significant at the respective α levels for either of these two endpoints.[68]

One-sided stratified log rank tests, stratified by randomisation stratification factors, were performed for both endpoints. Duration of PFS and OS were summarised by treatment arm using the Kaplan-Meier (KM) method. The treatment effect was estimated using a Cox's

proportional hazard model stratified by the randomisation stratification factors to calculate the HR. In order to account for the group sequential design in this study, the repeated CI (RCI) method was used to construct the two-sided RCI for the HR.[68, 79]

B.2.4.3.2 Secondary efficacy analyses

B.2.4.3.2.1 Progression-free survival and overall survival for patients unselected for PD-L1 expression

The methodology used for the primary analyses of PFS and OS in patients with PD-L1-positive tumours was followed for the analyses of PFS and OS in patients unselected for PD-L1 expression. One-sided stratified log-rank tests, stratified by randomisation stratification factors, were performed at the significance levels associated with the testing strategy shown in Figure B.2.1 for the testing of H_{03} and H_{04}.[68]

B.2.4.3.2.2 Objective response

BOR was derived according to the following rules:

- CR: ≥2 determinations of CR ≥4 weeks apart and before first documentation of PD
- PR: ≥2 determinations of PR or better ≥4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- Stable disease: ≥1 stable disease assessment (or better) ≥6 weeks after the date of randomisation and before first documentation of PD (and not qualifying for CR or PR)
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline): ≥1 non-CR/non-PD assessment (or better) ≥6 weeks after the date of randomisation and before first documentation of PD (and not qualifying for CR or PR)
- PD: progression ≤12 weeks after the date of randomisation (and not qualifying for CR, PR, SD or non-CR/non-PD)
- Not evaluable: all other cases.[68]

The objective response rate (ORR) was defined as the proportion of patients with an objective response (BOR of CR or PR), and was calculated, for each treatment arm, along with the two-sided 95% CI using the Clopper-Pearson method.[68]

The DC rate (DCR) was defined as the proportion of patients with DC, and was summarised by frequency counts and percentages.[68]

B.2.4.3.2.3 Time to response and duration of response

TTR was summarised using simple descriptive statistics and DOR was analysed using KM methodology. KM estimates were presented by treatment arm together with a summary of associated statistics, including the median DOR time with two-sided 95% CI calculated according to the Brookmeyer and Crowley method.[68]

B.2.4.3.2.4 Progression-free survival on next-line therapy

PFS2 was summarised by treatment arm using KM methodology. KM estimates were presented by treatment arm together with a summary of associated statistics, including the median PFS2 time with two-sided 95% CIs calculated according to the Brookmeyer and Crowley method.[68, 79]

B.2.4.4 Safety analyses

Safety analyses were performed using the safety analysis set, which included all patients who received at least one dose of study treatment (avelumab, axitinib or sunitinib). Patients were classified according to the study treatment assigned at randomisation unless the incorrect treatment(s) was/were received throughout the dosing period, in which case patients were classified according to the first study treatment received.[68]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table B.2.9. Quality assessment of JAVELIN Renal 101

Was randomisation carried out appropriately?	Yes. A total of 886 patients were randomised in a 1:1 ratio to treatment with avelumab + axitinib, or placebo, via an interactive response technology system (interactive web-based response or interactive voice response).
Was the concealment of treatment allocation adequate	Due to the different routes of administration (IV for avelumab; orally for axitinib and sunitinib), concealment of treatment allocation was not possible. The unblinded nature of the trial lead to differential use of second-line therapies, with the potential for bias analogous to cross-over bias seen in other unblinded studies. For PFS, BICR was used to minimise bias (see below).
Were the groups similar at the outset of the study in terms of prognostic factors?	In patients irrespective of PD-L1 expression as well as in patients with PD-L1 positive tumours, similar distributions of ECOG PS, MSKCC and IMDC prognostic criteria at baseline were observed in both treatment arms.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although JAVELIN Renal 101 was an open-label study, BICR was used to minimise bias that could be introduced into the assessment by the investigator, based on the knowledge of treatment assignment at randomisation. To mitigate the potential for bias in determining disease progression, expedited BICR review was performed for investigator-assessed disease progression. All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory. All patients' files and radiologic images must be available for source verification and peer review.
Were there any unexpected imbalances in drop-outs between groups?	No. A larger proportion of patients discontinued sunitinib treatment (62.4%), compared with avelumab (48.0%) or axitinib (44.3%). However, this reflected the higher rate of discontinuation due to disease progression in the sunitinib arm (19.5%, 20.8% and 35.4% for avelumab, axitinib and sunitinib, respectively).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the CSR. Pfizer fulfils its commitment to publicly disclose clinical trial results through posting the results of studies on ClinicalTrials.gov, EudraCT and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner, and are reported regardless of the outcome of the study or the country in which the study was conducted. In addition, Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favourable to the Pfizer product.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed using the FAS, defined as all randomised patients. Unless otherwise specified, all data were evaluated as observed, and no imputation method for missing values was used.

Abbreviations: BICR = blinded independent central review; CSR = clinical study report; EudraCT = European Clinical Trials Database; FAS = full analysis set; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenous; MSKCC = Memorial Sloan–Kettering Cancer Center

Sources: Pfizer Inc., 2018;[78]; Pfizer Inc., 2018;[79] Pfizer Inc., 2018[68]

B.2.6 Clinical effectiveness results of the relevant trials

Efficacy data from JAVELIN Renal 101 are presented for the FAS (patients irrespective of PD-L1 expression status), representing the proposed licensed indication. Data for patients with PD-L1-positive tumours (including the primary efficacy analyses) are provided in Appendix M. In addition, supplemental OS data (with longer follow-up) from JAVELIN Renal 100 are provided in Section B.2.6.2.

This submission is primarily based on the results of IA1 (data cut-off date: 20 June 2018). A summary of the results of the second interim analysis (IA2) (data cut-off date: 28 January 2019) are also presented, where available at the time of submission.

B.2.6.1 JAVELIN Renal 101

B.2.6.1.1 Duration of follow-up

A summary of the median duration of follow-up for PFS and OS analyses at IA1 is shown in Table B.2.10. The duration of follow-up was similar between treatment arms.[68]

Table B.2.10. Duration of follow-up (IA1)

Analysis	Avelumab + axitinib (N=270)	Sunitinib (N=290)
Median follow-up time (95% CI) for PFS, months		
Patients with PD-L1-positive tumours	9.9 ( )	8.4 ( )
Patients irrespective of PD-L1 status	10.8 ( )	8.6 ( )
Median follow-up time (95% CI) for OS, months		
Patients with PD-L1-positive tumours	11.6 ( )	10.7 ( )
Patients irrespective of PD-L1 status	12.0 ( )	11.5 ( )

Abbreviations: CI = confidence interval; IA1 = first interim analysis; N = number of patients evaluable; PD-L1 = programmed death-ligand 1; OS = overall survival; PFS = progression-free survival
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[68]

B.2.6.1.2 Progression-free survival

According to the pre-specified gatekeeping testing strategy, PFS in the entire study population was analysed, given the statistically significant effect observed in patients with PD-L1-positive tumours (see Appendix M).[79]

At the time of IA1, treatment with avelumab + axitinib significantly prolonged PFS (as assessed by BICR) in patients irrespective of PD-L1 status (Table B.2.11).The median PFS was 13.8 months (95% CI: 11.1, NE) and 8.4 months (95% CI: 6.9, 11.1) in the combination and sunitinib arms, respectively. Therefore, patients who received the combination had a clinically meaningful 31% reduction in the risk of progression or death, compared with those who received sunitinib (HR=0.69; 95% CI: 0.56, 0.84; one-sided p=0.0001).[67] The probability of being event-free was higher for avelumab + axitinib than sunitinib at 6, 12 and 18 months, with the probabilities diverging at each time point.[68]

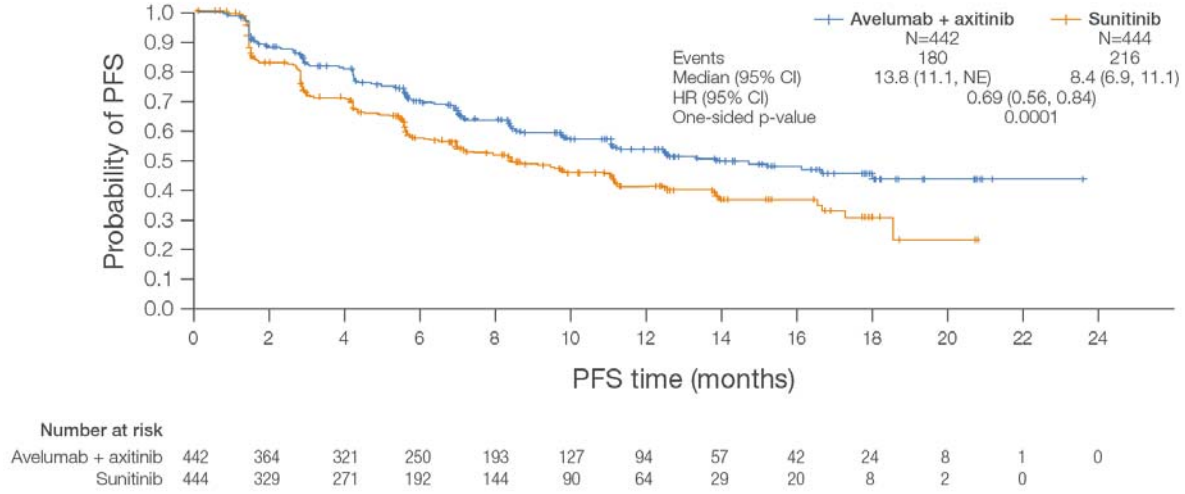
Table B.2.11. Summary of PFS by BICR assessment (FAS; IA1)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI), months	10.8 ( )	8.6 ( )
Events, n (%)	180 (40.7)	216 (48.6)
PD		
Death		
Censored, n (%)		
Ongoing without event, n (%)		
Median PFS (95% CI), months	13.8 (11.1, NE)	8.4 (6.9, 11.1)
HR (95% CI)	0.69 (0.56, 0.84)	
One-sided p-value	0.0001	
Two-sided p-value		
Probability (95% CI) of being event-free at:		
6 months		
12 months		
18 months		
24 months		

Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA1 = first interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; PD = progressive disease; PFS = progression-free survival
Source: Motzer et al. 2019;[67] Motzer et al. 2018;[25] Pfizer Inc., 2018[68]

A KM plot of PFS in patients irrespective of PD-L1 status is shown in Figure B.2.2. The effect of avelumab + axitinib compared with sunitinib was apparent at the time of the first tumour assessment and remained throughout the follow-up period.[67]

Figure B.2.2. KM plot of PFS by BICR assessment (FAS; IA1)



Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA1 = first interim analysis; KM = Kaplan-Meier; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; PFS = progression-free survival
Source: Motzer et al. 2019;[67] Motzer et al. 2018[25]

PFS was also analysed by investigator assessment and sensitivity analyses were performed to explore the robustness of the BICR analysis. These analyses used a similar methodology to those for patients the BICR analysis, and were consistent with the analyses of PFS in patients irrespective of PD-L1 status reported above (see Appendix D).[68]

A summary of PFS at the second pre-planned IA (IA2) is shown in Table B.2.12, and a KM plot in Figure B.2.3. The updated results reinforce the PFS benefit of avelumab + axitinib compared with sunitinib, with a clinically meaningful reduction in the risk of progression or

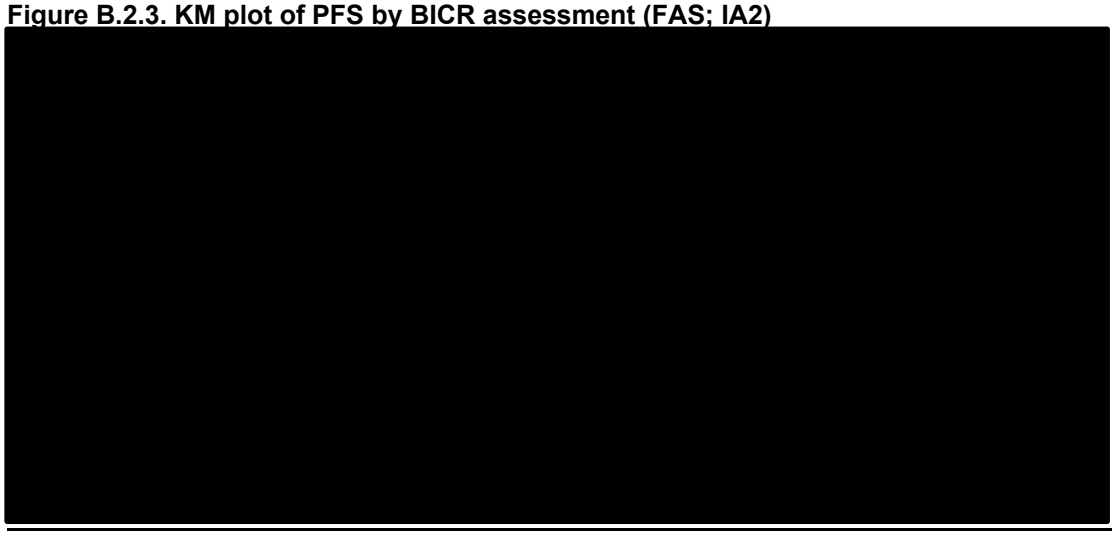
death, compared with those who received sunitinib (HR=[redacted]; 95% CI: [redacted], [redacted]; one-sided p[redacted]). The probability of being event-free was again higher for avelumab + axitinib, having reached [redacted] (95% CI: [redacted], [redacted]) at 24 months, compared with [redacted] ([redacted],[redacted]) for sunitinib.[69]

Table B.2.12. Summary of PFS by BICR assessment (FAS; IA2)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
Events, n (%)	[redacted]	[redacted]
PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]
Median PFS (95% CI), months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
One-sided p-value	[redacted]	
Two-sided p-value	[redacted]	
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA2 = second interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; PD = progressive disease; PFS = progression-free survival
Source: Pfizer Inc., 2018[68]

Figure B.2.3. KM plot of PFS by BICR assessment (FAS; IA2)



Abbreviations: BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA2 = second interim analysis; KM = Kaplan-Meier; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; PFS = progression-free survival
Source: Pfizer Inc., 2019[69]

B.2.6.1.3 Objective response

A summary of BOR, objective response and DC is shown in Table B.2.13. The ORR for avelumab + axitinib was double that for sunitinib (51.4% and 25.7%, respectively). The proportion of patients with a CR was also higher in the combination arm compared with the

sunitinib arm (3.4% and 1.8%, respectively), while the proportion of patients with PD was lower in the combination arm (11.5%) compared with the sunitinib arm (18.7%). In addition, a larger proportion of patients in the avelumab + axitinib arm had at least some degree of tumour shrinkage, compared with those in the sunitinib arm (Figure B.2.4).[67]

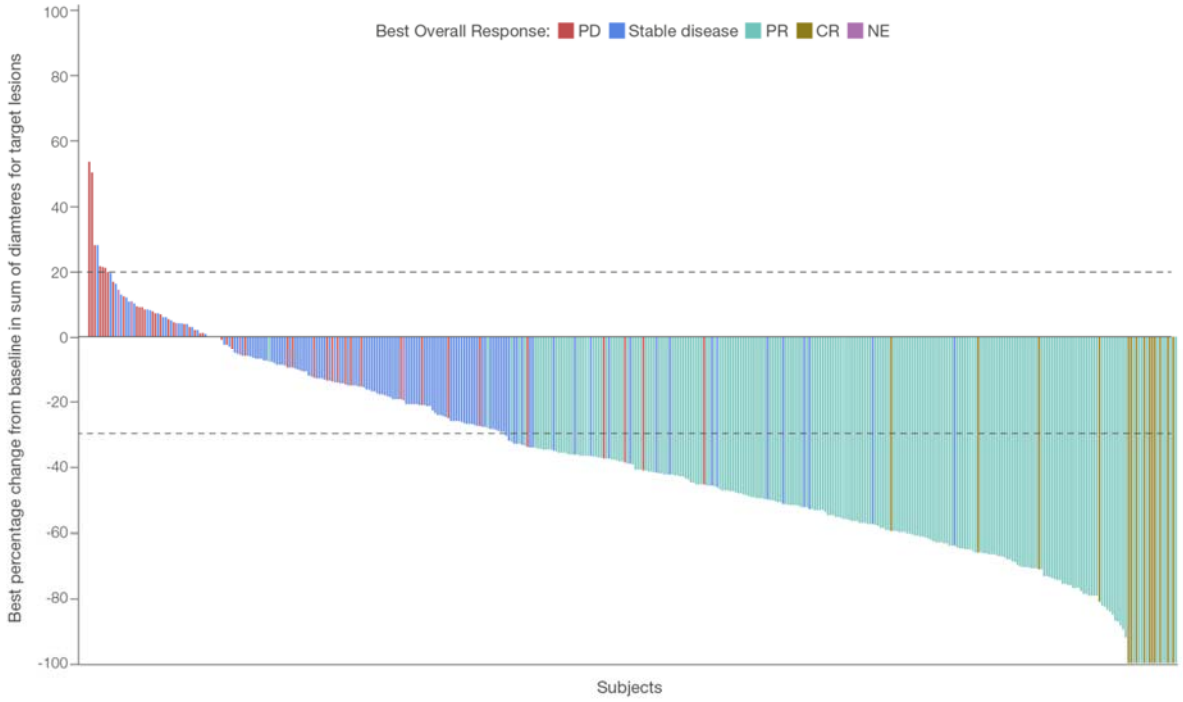
Table B.2.13. Summary of objective response by BICR assessment (FAS; IA1)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
BOR		
CR	15 (3.4)	8 (1.8)
PR	212 (48.0)	106 (23.9)
Stable disease	131 (29.6)	202 (45.5)
Non-CR/Non-PD	8 (1.8)	10 (2.3)
PD	51 (11.5)	83 (18.7)
Not evaluable	25 (5.7)	35 (7.9)
Objective response, n (%)	227 (51.4)	114 (25.7)
95% CI	46.6, 56.1	21.7, 30.0
OR (95% CI)	3.10 (2.30, 4.15)	
DC, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

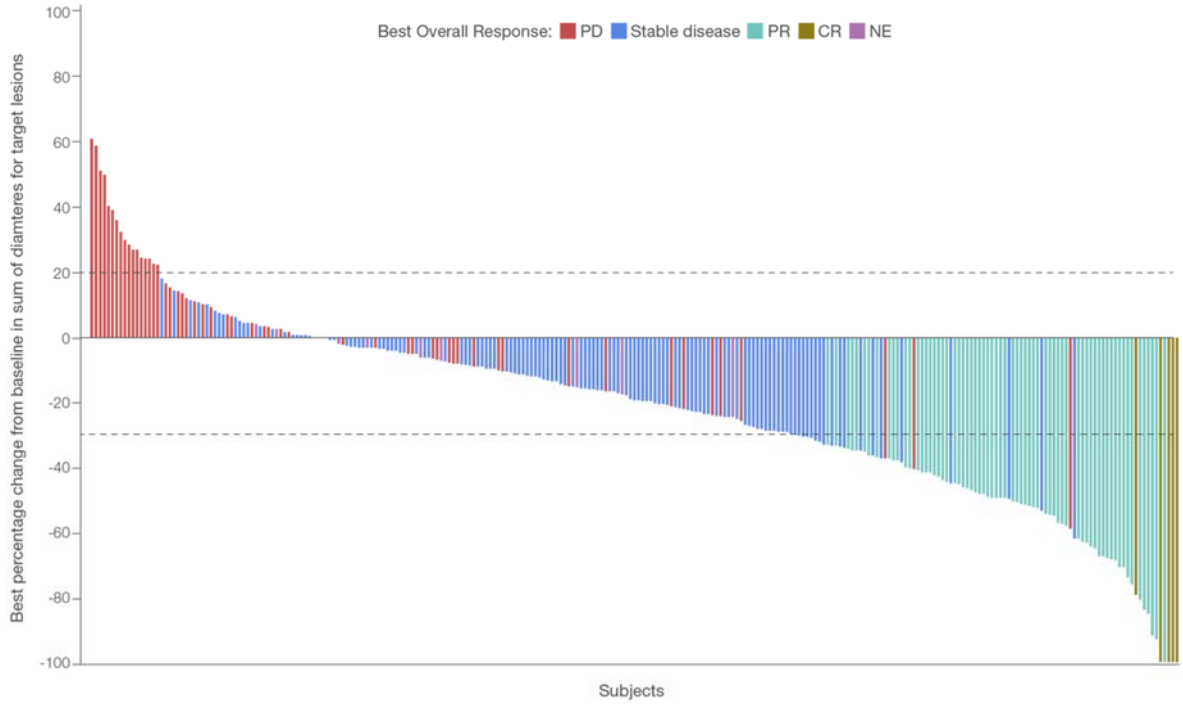
Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DC = disease control; FAS = full analysis set; IA1 = first interim analysis; n = number of patients in the category; N = number of patients evaluable; OR = odds ratio; PD = progressive disease; PR = partial response
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[68]

Figure B.2.4. Change from baseline in sum of tumour diameters by BICR assessment (FAS; IA1)

Avelumab + axitinib (N=412):



Sunitinib (N=408):



Abbreviations: BICR = blinded independent central review; BOR = best overall response; CR = complete response; FAS = full analysis set; IA1 = first interim analysis; N = number of patients evaluable; NE = not estimable; PD = progressive disease; PR = partial response

Source: Motzer et al. 2019;[67]

The results of IA2 continue to demonstrate the benefit of avelumab + axitinib, compared with sunitinib, with ORRs of [redacted] and [redacted] respectively (Table B.2.14). As with IA1, the proportion

of patients with a CR was also higher in the combination arm compared with the sunitinib arm ([redacted] and [redacted], respectively), while the proportion of patients with PD was lower in the combination arm ([redacted]) compared with the sunitinib arm ([redacted]).

Table B.2.14. Summary of objective response by BICR assessment (FAS; IA2)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
BOR		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/Non-PD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
Objective response, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
OR (95% CI)	[redacted]	

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DC = disease control; FAS = full analysis set; IA2 = second interim analysis; n = number of patients in the category; N = number of patients evaluable; OR = odds ratio; PD = progressive disease; PR = partial response
Source: Pfizer Inc., 2019[69]

B.2.6.1.4 Time to response and duration of response

A summary of TTR and DOR is shown in Table B.2.15. Responses to avelumab + axitinib had an earlier onset (2.6 months and 3.2 months in the combination and sunitinib arms, respectively). While the median DOR was not reached for either treatment arm, responses to avelumab + axitinib were more durable than those to sunitinib ([redacted] and [redacted] probabilities of being event-free at 12 months, respectively).[67, 68]

Table B.2.15. Summary of TTR and DOR for patients with a CR or PR by BICR assessment (FAS; IA1)

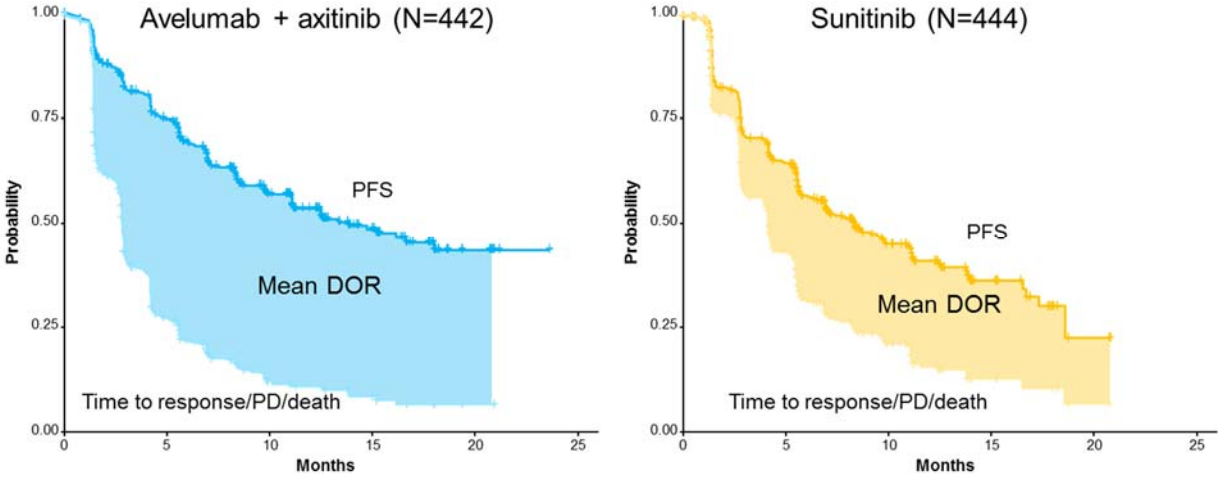
Endpoint	Avelumab + axitinib (N=227)	Sunitinib (N=114)
Median TTR (range), months	2.6 (1.2, 13.8)	3.2 (1.2, 11.6)
Median DOR (95% CI), months	NE (NE, NE)	NE (11.2, NE)
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; FAS = full analysis set; n = number of patients in the category; IA1 = first interim analysis; N = number of patients evaluable; NE = not estimable; TTR = time to tumour response
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[68]

Ad-hoc analyses of DOR including all randomised patients (irrespective of whether the patient had an OR) were performed to compare the mean DOR between the two treatment arms.[80] For each randomised patient, DOR was defined as PFS time minus event-free time, where an event was a confirmed OR, PD or death. For patients with a confirmed OR, this corresponds to the time from OR to the earliest of PD or death, as in the DOR definition used in responder analyses.

KM plots of PFS and time to response, PD or death are shown in Figure B.2.5. The mean DOR up to a cut-off follow-up time is equal to the area between the KM curves within the follow-up window. The mean DOR can then be interpreted as the expected DOR for a randomised patient. Compared with sunitinib, avelumab + axitinib had a higher mean DOR, with a difference of >4.22 months (95% CI: 2.88, 5.56).[75] This benefit favouring avelumab + axitinib continued in IA2, with a mean DOR of [redacted] (95% CI: [redacted], [redacted]).[69]

Figure B.2.5. Mean DOR by BICR Assessment (FAS; IA1)



Abbreviations: BICR = blinded independent central review; DOR = duration of response; FAS = full analysis set; IA2 = second interim analysis; N = number of patients evaluable; PD = progressive disease; PFS = progression-free survival
Source: Choueiri et al. 2019[75]

B.2.6.1.5 Overall survival

OS in the entire study population was analysed in accordance with the pre-specified gatekeeping testing strategy, given the statistically significant effect on PFS observed in patients irrespective of PD-L1 status.[79]

OS data in patients irrespective of PD-L1 status were immature at the time of IA1, with 138 deaths observed (63 [14.3%] in the combination arm and 75 [16.9%] in the sunitinib arm; 25.8% of the 535 deaths required for the final OS analyses). While the median OS was not reached in either treatment arm (Table B.2.16), the results suggest an OS benefit in favour of avelumab + axitinib (HR=0.78 [95% CI: 0.55, 1.08]).[67]

Table B.2.16. Summary of OS (FAS; IA1)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI), months	12.0 ( )	11.5 ( )
Events, n (%)	63 (14.3)	75 (16.9)
Censored, n (%)		
Ongoing without event, n (%)		
Median OS (95% CI), months	NE ( )	NE ( )
HR (95% CI)	0.78 (0.55, 1.08)	
One-sided p-value	0.0679	
Two-sided p-value		
Probability (95% CI) of being event-free at:		
6 months		
12 months		
18 months		
24 months		

Abbreviations: CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA1 = first interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; OS = overall survival
Source: Motzer et al. 2019;[67] Motzer et al. 2018;[25] Pfizer Inc., 2018[68]

Sensitivity analyses were performed to explore the robustness of the analysis of OS in patients irrespective of PD-L1 status. These analyses used a similar methodology, and were consistent with the main analysis of OS in patients irrespective of PD-L1 status reported above. Data for OS are immature and definitive conclusions cannot yet be drawn based on the results of these analyses.[68]

As with IA1, OS data were immature at the time of IA2. However, results continue to suggest a benefit for avelumab + axitinib compared with sunitinib in prolonging OS (Table B.2.17; HR= ; [95% CI: ,]).[69]

Table B.2.17. Summary of OS (FAS; IA2)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI), months		
Events, n (%)		
Censored, n (%)		
Ongoing without event, n (%)		
Median OS (95% CI), months		
HR (95% CI)		
One-sided p-value		
Probability (95% CI) of being event-free at:		
6 months		
12 months		
18 months		
24 months		
30 months		

Abbreviations: CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA2 = second interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; OS = overall survival
Source: Pfizer Inc., 2019[69]

B.2.6.1.6 Progression-free survival on next-line therapy

A summary of PFS2 (defined as time to discontinuation of next-line therapy after first objective disease progression, second objective disease progression after initiation of next-

line therapy, or death due to any cause) at the time of IA1 is shown in Table B.2.18. Although a formal comparison of PFS2 was not planned, outcomes on further treatments can support the relevance of meaningful improvements in PFS when OS is not available,[81] and may be a prognostic-factor of long-term survival.[82] PFS2 for patients in the combination arm appeared to be longer than for the patients in the sunitinib arm (NE [95% CI: 19.9, NE] and 18.4 months [95% CI: 15.7, 23.6]; HR: 0.56 [95% CI: 0.421, 0.735]) at the time of IA1.[75]

Table B.2.18. Summary of PFS2 by BICR assessment (FAS; IA1)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
Events, n (%)	[redacted]	[redacted]
Discontinuation of next-line treatment after first PD		
Second PD after next-line treatment		
Death		
Censored, n (%)		
Ongoing without event, n (%)		
Median PFS2 (95% CI), months	NE (19.9, NE)	18.4 (15.7, 23.6)
HR (95% CI)	0.56 (0.42, 0.74)	
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months		
18 months		
24 months		

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; FAS = full analysis set; IA1 = first interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; PD= progressive disease
Source: Choueiri et al. 2019;[75] Pfizer Inc., 2018[68]

A summary of PFS2 at the time of IA2 is shown in Table B.2.19. Results reinforce those of IA1, demonstrating that avelumab + axitinib substantially prolongs PFS2 (HR=[redacted]; 95% CI: [redacted], [redacted]) and that there is no negative impact of first-line treatment with the combination on subsequent benefit from second-line treatment.[69]

Table B.2.19. Summary of PFS2 by BICR assessment (FAS; IA2)

Endpoint	Avelumab + axitinib (N=442)	Sunitinib (N=444)
Events, n (%)	[redacted]	[redacted]
Discontinuation of next-line treatment after first PD	[redacted]	[redacted]
Second PD after next-line treatment	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]
Median PFS2 (95% CI), months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; FAS = full analysis set; IA2 = second interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; PD= progressive disease
Source: Pfizer Inc., 2019[69]

B.2.6.1.7 Patient-reported outcomes

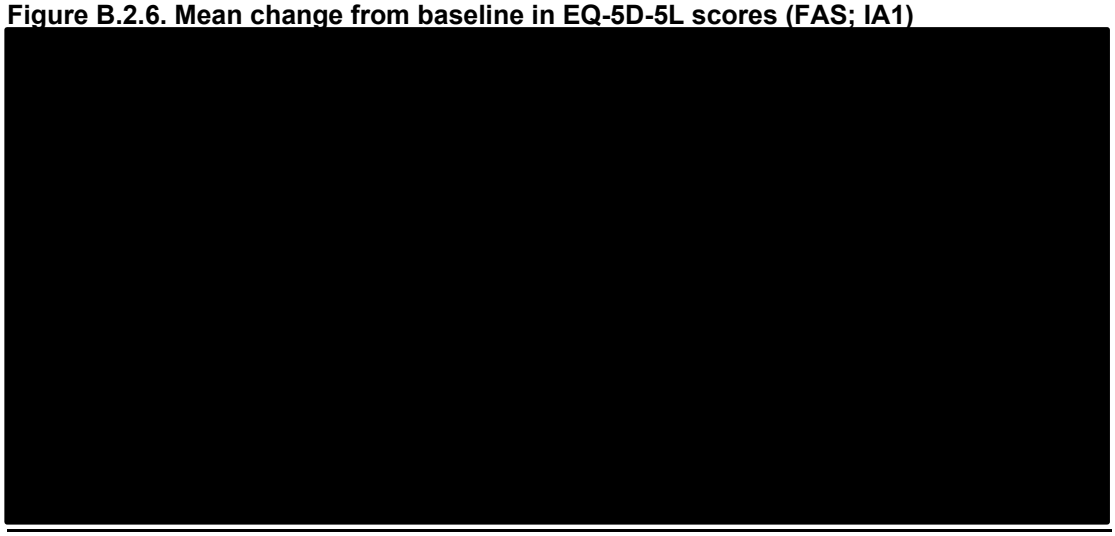
PROs were assessed using the disease-specific FKSI-19 and FKSI-DRS, along with the generic EQ-5D. It should be noted that the scheduling of PRO assessments occurred at the end of the 2‑week off period for sunitinib, which would be the time point at which sunitinib patients typically report the most favourable outcomes.[68]

PRO data are presented for IA1; no PRO data were available for IA2 at the time of submission.

B.2.6.1.7.1 EQ-5D-5L

In both treatment arms, the EQ-5D-5L completion rate was ≥90% while on treatment. A summary of the mean change from baseline in EQ-5D-5L scores is shown in Figure B.2.6. Linear mixed model analysis of EQ-5D-5L scores showed similar results between the two treatment arms.[68]

Figure B.2.6. Mean change from baseline in EQ-5D-5L scores (FAS; IA1)

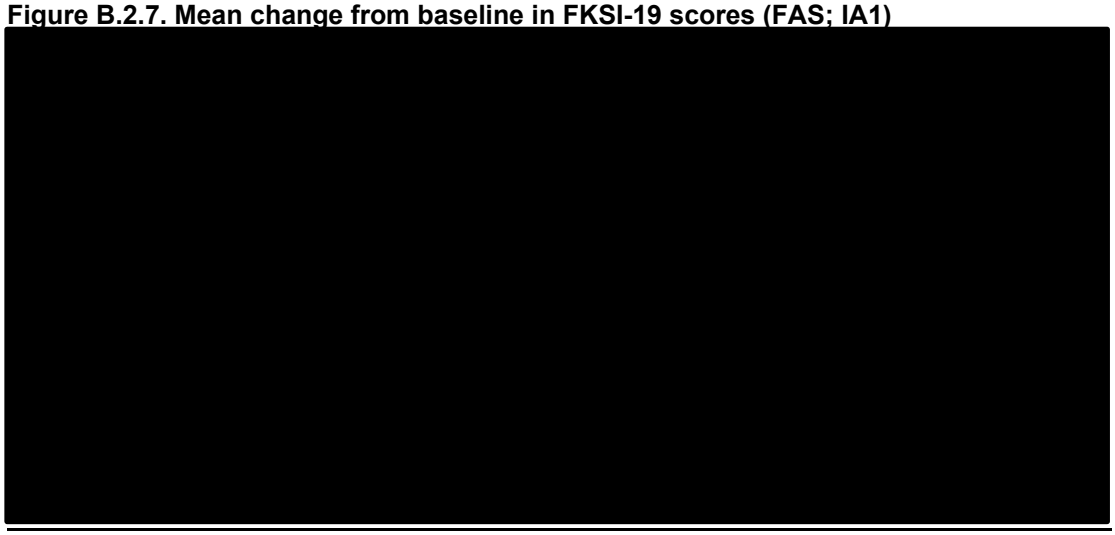


Abbreviations: BL = baseline; C = cycle; D = day; EOT = end-of-treatment; EQ-5D-5L = EuroQol 5-Dimension 5-Level; FAS = full analysis set; FUP = follow-up; HRQoL = health-related quality of life; IA1 = first interim analysis; LFUP = long-term follow-up; N = number of patients evaluable; SE = standard error
Note: lower scores indicate worsening HRQoL
Source: Pfizer Inc., 2018[68]

B.2.6.1.7.2 FKSI-19

In both treatment arms, the FKSI-19 completion rate was ≥90% while on treatment. A summary of the mean change from baseline in EQ-5D-5L scores is shown in Figure B.2.7. Linear mixed model analysis of FKSI-19 scores showed similar results between the two treatment arms, numerically favouring avelumab + axitinib. Within the combination arm, there was also no observed worsening in estimated mean FKSI-19 scores compared with baseline.[68]

Figure B.2.7. Mean change from baseline in FKSI-19 scores (FAS; IA1)

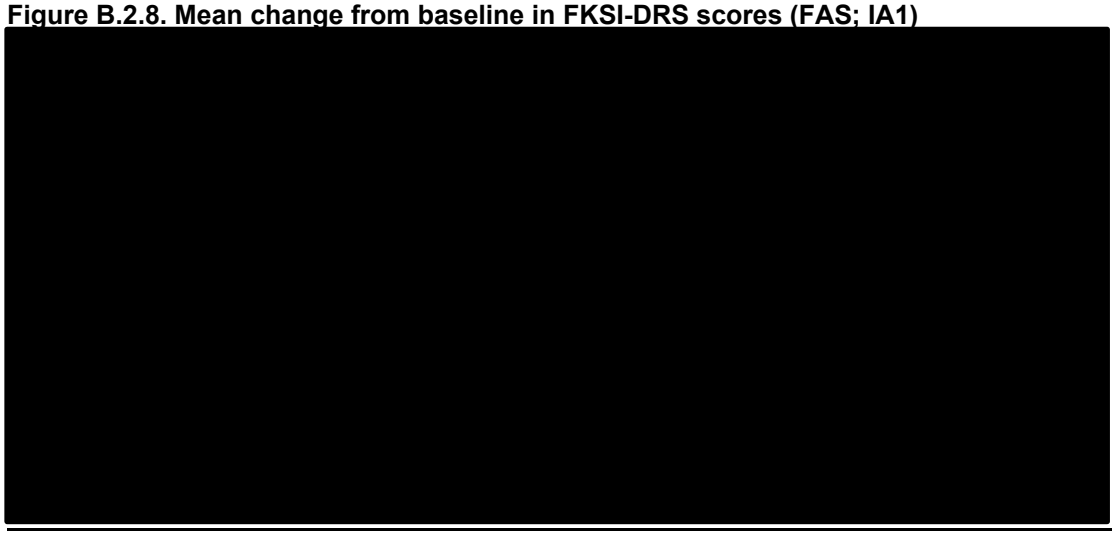


Abbreviations: BL = baseline; C = cycle; D = day; EOT = end-of-treatment; FAS = full analysis set; FKSI-19 = Functional Assessment of Cancer Therapy-Kidney Symptom Index-19; FUP = follow-up; HRQoL = health-related quality of life; IA1 = first interim analysis; LFUP = long-term follow-up; N = number of patients evaluable; SE = standard error
Note: lower scores indicate worsening HRQoL
Source: Pfizer Inc., 2018[68]

B.2.6.1.7.3 FKSI-DRS

As with the FKSI-19, linear mixed model analysis of FKSI-DRS scores showed similar results between the two treatment arms. A summary of the mean change from baseline in FKSI-DRS scores is shown in Figure B.2.8. While there was a slight difference in scores for the first cycle (favouring sunitinib) all other cycles showed no difference between treatment arms. The greatest decrease in FKSI-DRS scores occurred at the end of treatment, when disease progression may have occurred or patients had discontinued study treatment.[68]

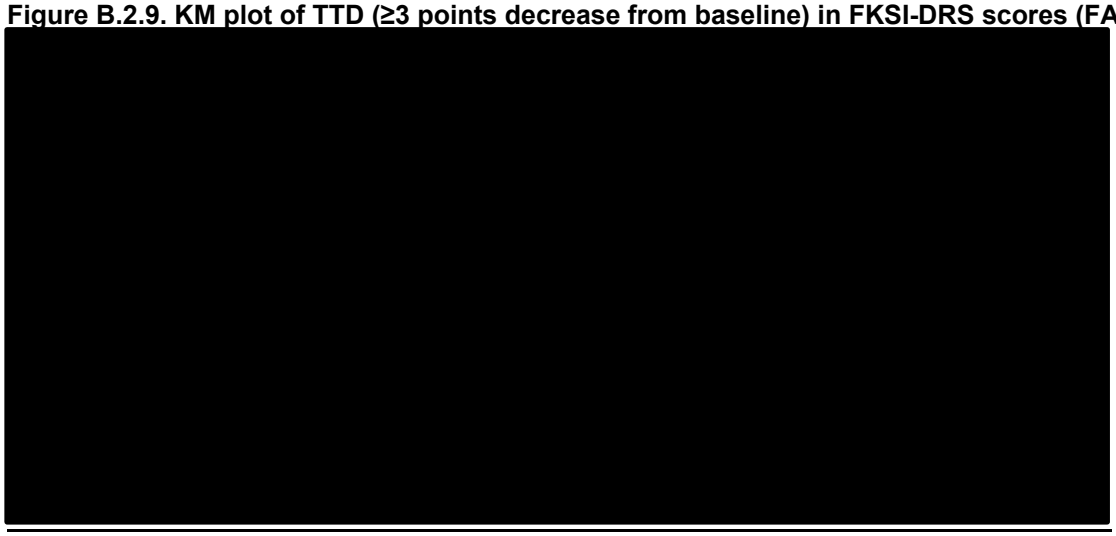
Figure B.2.8. Mean change from baseline in FKSI-DRS scores (FAS; IA1)



Abbreviations: BL = baseline; C = cycle; D = day; EOT = end-of-treatment; FAS = full analysis set; FKSI-DRS = Functional Assessment of Cancer Therapy-Disease Related Symptoms; FUP = follow-up; HRQoL = health-related quality of life; IA1 = first interim analysis; LFUP = long-term follow-up; N = number of patients evaluable; SE = standard error
Note: lower scores indicate worsening HRQoL
Source: Pfizer Inc., 2018[68]

A KM plot of TTD (≥3 points decrease from baseline) in FKSI-DRS is shown in Figure B.2.9. While the HR for TTD in FKSI-DRS favoured the sunitinib arm, it should be noted that the schedule of PRO assessments coincided with the schedule of tumour assessments, with the first assessment 6 weeks after randomisation, subsequent assessments every 6 weeks thereafter until the end of treatment (or every 12 weeks after 18 months from randomisation), then at the time of any tumour assessments in the long-term follow-up period. Given the sunitinib treatment schedule of 4 weeks on and 2 weeks off treatment, PRO assessments occurred at the end of the 2-week off-treatment period for sunitinib, which would be the time point where sunitinib patients typically report the most favourable outcomes.[68] PRO analyses using the FKSI-DRS and EQ-5D during the 4 week sunitinib on-treatment period have previously been shown to be significantly worse than observations during the 2 week off-treatment period.[83] Therefore, the schedule of PRO assessments may have resulted in a significant impact favouring the sunitinib arm in the time-to-event analyses, since these analyses measure how quickly the patients deteriorate and are sensitive to the schedule of assessments relative to the dosing period.[68]

Figure B.2.9. KM plot of TTD (≥3 points decrease from baseline) in FKSI-DRS scores (FAS; IA1)



Abbreviations: FAS = full analysis set; FKSI-DRS = Functional Assessment of Cancer Therapy-Disease Related Symptoms; IA1 = first interim analysis; KM = Kaplan-Meier; N = number of patients evaluable; TTD = time to deterioration
Note: Two-sided p-value=
Source: Pfizer Inc., 2018[68]

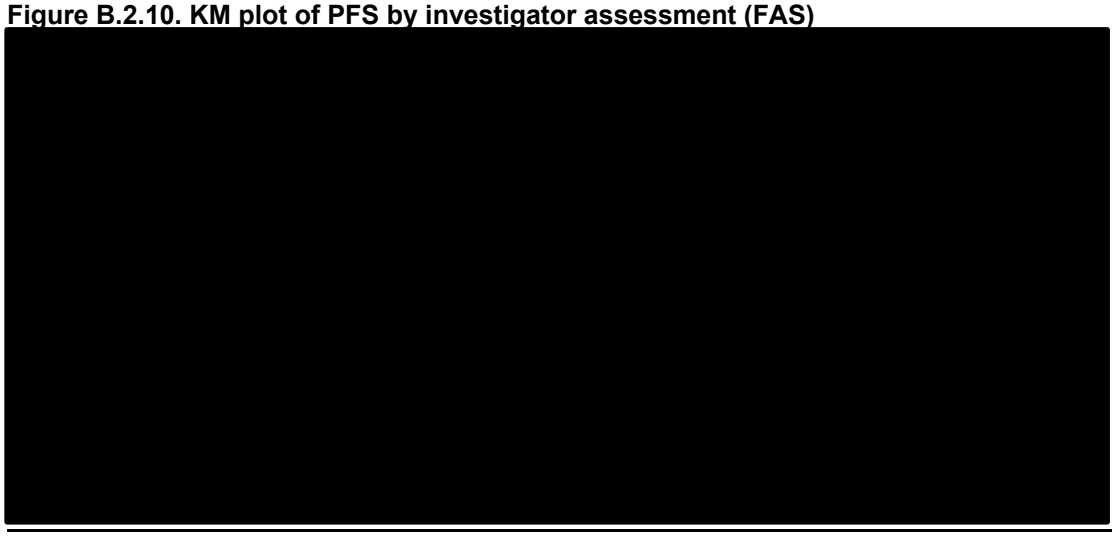
B.2.6.2 JAVELIN Renal 100

As OS data from JAVELIN Renal 101 are still maturing, supplemental evidence for the longer-term benefit of avelumab + axitinib is provided by JAVELIN Renal 100.

B.2.6.2.1 Progression-free survival

The median duration of follow-up for PFS in JAVELIN Renal 101 at IA1 was (95% CI: ,). A KM plot of PFS is shown in Figure B.2.10; the median PFS was (95% CI: ,), with a probability of being event-free at 24 months of (,).[70]

Figure B.2.10. KM plot of PFS by investigator assessment (FAS)

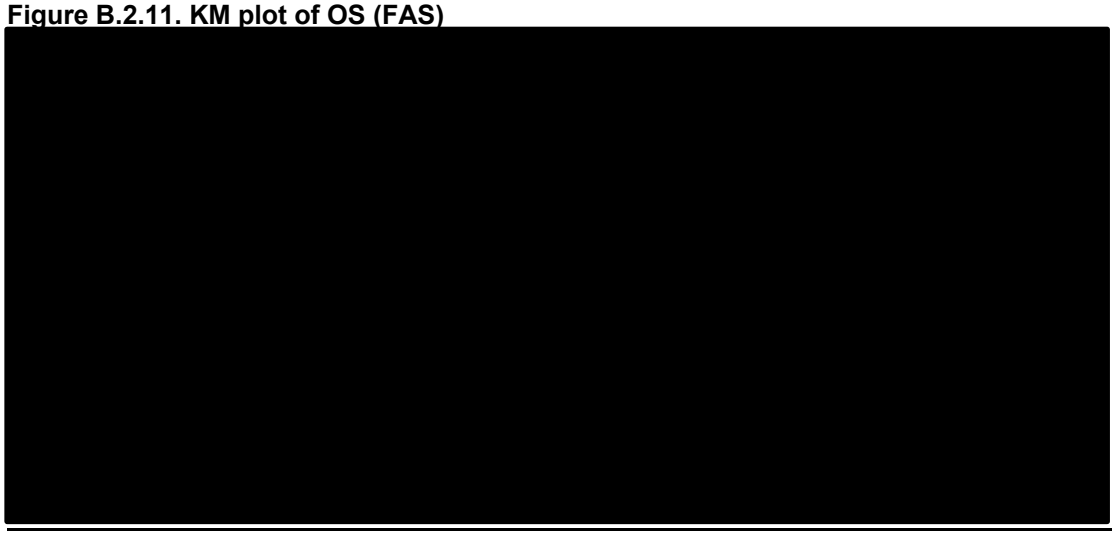


Abbreviations: CI = confidence interval; FAS = full analysis set; KM = Kaplan-Meier; N = number of patients evaluable; NE = not estimable; PFS = progression-free survival
Source: Pfizer Inc., 2018[70]

B.2.6.2.2 Overall survival

The median duration of follow-up for OS in JAVELIN Renal 100 was [redacted] (95% CI: [redacted], [redacted]), and at the time of the IA1 data cut-off (3 April 2018) [redacted] ([redacted]) patients had died. Although the [redacted], the probability of survival at 18 and 24 months was [redacted] (95% CI: [redacted], [redacted]) and [redacted] (95% CI: [redacted], [redacted]), respectively.[70] A KM plot of OS is shown in Figure B.2.11.

Figure B.2.11. KM plot of OS (FAS)



Abbreviations: CI = confidence interval; KM = Kaplan-Meier; N = number of patients evaluable; NE = no estimable; OS = overall survival
Source: Pfizer Inc., 2018[70]

B.2.6.2.3 Time to response and duration of response

As in JAVELIN Renal 101, responses to avelumab + axitinib in JAVELIN Renal 100 had an early onset (median TTR of [redacted] [range: [redacted], [redacted]]) and were durable (median DOR of [redacted] [95% CI: [redacted], [redacted]]). The probability of being event-free at 18 months was [redacted] (95% CI: [redacted], [redacted]).[70] A swimmer plot of time and duration of response is shown in Figure B.2.12.

Figure B.2.12. Swimmer plot of TTR and DOR for patients with a CR or PR by BICR assessment (FAS)

Abbreviations: BICR = blinded independent central review; CR = complete response; DOR = duration of response; FAS = full analysis set; PR = partial response; TTR = time to tumour response
Source: Pfizer Inc., 2018[70]

B.2.6.3 Efficacy conclusions

In the pivotal Phase 3 JAVELIN Renal 101 study, first-line treatment with avelumab + axitinib in patients irrespective of PD-L1 expression status led to a significant improvement in median PFS (13.8 months; 95% CI: 11.1, NE), compared with sunitinib (8.4 months; 95% CI: 6.9, 11.1), with a clinically meaningful and statistically significant 31% reduction in the risk of disease progression or death (one-sided p=0.0001).[67, 68] The results of IA2 reinforced the PFS benefit of avelumab + axitinib compared with sunitinib, maintaining a clinically meaningful [redacted] reduction in the risk of progression or death (one-sided p[redacted]).[69]

Although JAVELIN Renal 101 OS data were immature at the time of IA1 and IA2, the results suggest an OS benefit in favour of avelumab + axitinib (probability of survival at 30 months of [redacted] in IA2).[68, 69] In JAVELIN Renal 100, patients were followed up for a median time of 22 months, compared with 12 months in at IA1 in JAVELIN Renal 101, with a probability of survival at 18 and 24 months of [redacted] and [redacted], respectively.[70]

Analyses of objective response supported the benefit of avelumab + axitinib in patients with aRCC; at IA1, the ORR for avelumab + axitinib was doubled compared with sunitinib (51.4% and 25.7% in the combination and sunitinib arms, respectively; OR=3.10 [95% CI: 2.30, 4.15]), representing a potentially significant benefit for patients over a current first-line therapy.[67]

Responses to avelumab + axitinib had an earlier onset compared with responses to sunitinib (2.6 months and 3.2 months in the combination and sunitinib arms, respectively at IA1). The importance of early responses to avelumab has previously been demonstrated in patients with metastatic Merkel cell carcinoma (MCC), with patients with an early objective response achieving significantly longer OS.[71] The responses achieved with avelumab + axitinib were also more durable than those achieved with sunitinib; the probability of being event-free at 12 months was [redacted] and [redacted] in the combination and sunitinib arms, respectively.[68] In addition, 15 patients (3.4%) in the avelumab + axitinib arm had a CR, compared with 8 patients (1.8%) in the sunitinib arm.[67]

Although a formal comparison of PFS2 was not planned, the median PFS2 for patients in the combination arm appeared to be longer than for patients in the sunitinib arm (NE [95% CI: 19.9, NE] and 18.4 months [95% CI: 15.7, 23.6] in the combination and sunitinib arm, respectively).[75] As changes in tumour biology may alter the trajectory of disease and improve outcomes beyond first-line therapy, PFS2 may represent an important endpoint in first-line studies, especially when OS data are still maturing.[81]

In addition to the efficacy benefit observed with avelumab + axitinib, PRO analyses demonstrated that the combination was associated with similar HRQoL outcomes to sunitinib monotherapy. While the TTD in FKSI-DRS scores favoured sunitinib, the schedule of PRO assessments may have resulted in a significant impact favouring the sunitinib arm, and these data are not consistent with EQ-5D analyses, which indicated no difference between the treatments.[68]

Overall, the JAVELIN Renal 101 study demonstrates that avelumab + axitinib has the potential to be an efficacious first-line treatment (irrespective of PD-L1 expression status) for patients with aRCC. Where efficacy outcomes are available at IA2, the results are consistent with those seen at IA1, alongside a tightening of the 95% CI, which is expected to improve with time as data mature.[68-70]

B.2.7 Subgroup analysis

B.2.7.1 Methodology and statistical analysis

Pre-specified subgroup analyses were performed for PFS, objective response and DOR according to BICR assessment, and OS, based on the FAS for the following subgroups:

- Randomisation stratification factors
  - ECOG PS (0, 1)
  - Geographical region (US, Canada/Western Europe, rest of the world [RoW])
- Age (<65 years, ≥65 years)
- Gender (male, female)
- Race (Caucasian/White, Asian, Black/African American, other)
- Ethnicity (Hispanic/Latino, Non-Hispanic/Latino)
- Pooled geographic region (North America, Europe, Asia, RoW)
- Nephrectomy at baseline (yes, no)
- MSKCC prognostic criteria at baseline (favourable, intermediate, poor)
- IMDC prognostic criteria at baseline (favourable, intermediate, poor)[79]

All subgroup analyses were exploratory. Treatment arms were compared for PFS and OS using a two-sided unstratified log-rank test, and the unstratified HR and corresponding 95% CI calculated, for each subgroup level.[79]

In addition to the pre-specified subgroups, summaries were also provided for patients with PD-L1-negative tumours.[68]

B.2.7.2 Results of subgroup analyses

The PFS benefit of the combination arm compared with the sunitinib arm was consistently observed across pre-specified subgroups, including IMDC favourable risk groups.

Importantly, a treatment benefit was observed in the subgroup of patients with PD-L1 negative tumours, indicating that the benefit observed in patients irrespective of PD-L1 status was not solely driven by the benefit observed in patients with PD-L1 positive tumours (see Appendix E).[68]

As OS data are still maturing and median DOR was not yet reached at the time of IA1, definitive conclusions cannot be drawn based on the results of subgroup analyses of these endpoints.[68]

B.2.8 Meta-analysis

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

B.2.9 Indirect treatment comparisons

Two indirect treatment comparisons (ITCs) were conducted to evaluate the relative efficacy of avelumab + axitinib compared with other aRCC therapies in two distinct populations:

- First-line aRCC (equivalent to the JAVELIN Renal 101 ITT population)
- First-line aRCC with IMDC intermediate- or poor-risk risk status

B.2.9.1 Identification and selection of studies

As described in Section B.2.1 and Appendix D, an SLR was carried out in May 2018 and updated in March 2019 to identify published evidence from RCTs of treatment options for previously untreated patients with aRCC.

B.2.9.2 Summary of studies

In total, 59 studies were identified, with six studies considered for inclusion in the ITC for the ITT population[9, 18, 67, 84-86] and two studies considered for inclusion in the ITC for the IMDC intermediate- or poor-risk population.[67, 87] All studies were Phase 3, open-label, global studies,[9, 18, 67, 84-86] except that of cabozantinib, which was a Phase 2 study conducted in the US only.[87]

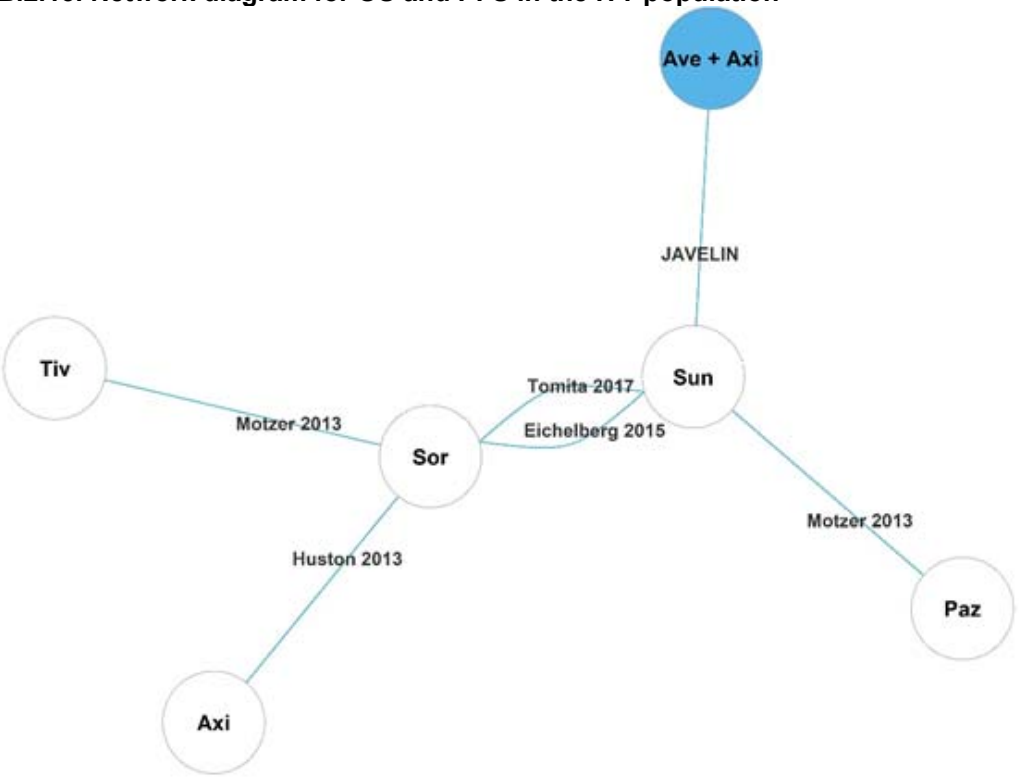
A summary of the included studies in both ITC networks is provided in Table B.2.20, with network diagrams presented in Figure B.2.13 and Figure B.2.14 (inclusion and exclusion criteria are detailed in Appendix D.

Table B.2.20. Studies included in the ITC

Trial	Design	Population	Treatment arms	Primary endpoint(s)
ITT population				
Motzer et al. 2019 (JAVELIN Renal 101/ NCT02684006)[67]	Phase 3; RCT; open label; multicentre; global	Advanced/ metastatic RCC	AVE+AXI SUN	PFS and OS
Eichelberg et al. 2015 (SWITCH/ NCT00732914)[85]	Phase 3; RCT; open label; multicentre; European	Advanced/ metastatic RCC	SOR→SUN SUN→SOR	PFS
Hutson et al. 2013 (NCT00920816)[9]	Phase 3; RCT; open label; multicentre; global	Metastatic clear-cell RCC	AXI SOR	PFS
Motzer et al. 2013 (COMPARZ/ NCT00720941)[84]	Phase 3; RCT; open label; multicentre; global	Advanced/ metastatic clear-cell RCC	PAZ SUN	PFS
Motzer et al. 2013 (TIVO-1/ NCT01030783)[18]	Phase 3; RCT; open label; multicentre; European	Advanced/ metastatic RCC	TIV SOR	PFS
Tomita et al. 2017 (CROSS-J-RCC/ NCT01481870)[86]	Phase 3; RCT; open label; multicentre; Japan	Advanced clear-cell RCC	SUN→SOR SOR→SUN	PFS
IMDC Intermediate- or poor-risk aRCC population				
Motzer et al. 2019 (JAVELIN Renal 101/ NCT02684006)[67]	Phase 3; RCT; open label; multicentre; global	Advanced/ metastatic RCC	AVE+AXI SUN	PFS
Choueiri et al. 2018 (CABOSUN/ NCT01835158)[87]	Phase 2; RCT; open label; multicentre; US	Advanced/ metastatic RCC	CAB SUN	PFS

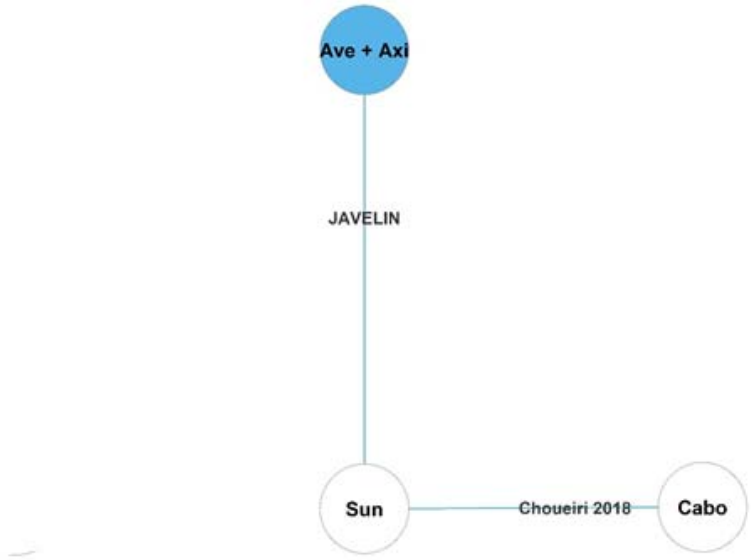
Abbreviations: AVE = avelumab; AXI = axitinib; CAB = cabozantinib; OS = overall survival; PAZ = pazopanib; PFS = progression-free survival; RCC = renal cell carcinoma; RCT = randomised controlled trial; SOR = sorafenib; SUN = sunitinib; TIV = tivozanib; US = United States

Figure B.2.13. Network diagram for OS and PFS in the ITT population



Abbreviations: Ave = avelumab; Axi = axitinib; OS = overall survival; Paz = pazopanib; PFS = progression-free survival; Sor = sorafenib; Sun = sunitinib; Tiv = tivozanib

Figure B.2.14. Network diagram for OS in the IMDC intermediate- or poor- risk population



Abbreviations: Ave = avelumab; Axi = axitinib; Cabo = cabozantinib; IMDC = International Metastatic RCC Database Consortium; OS = overall survival; Sun = sunitinib

B.2.9.3 Feasibility assessment

To provide indirect evidence for the comparisons to tivozanib and cabozantinib, the ITC was planned on two efficacy endpoints: OS and PFS. These represent key outcomes of interest to clinicians and patients and are consistently selected as primary and secondary efficacy endpoints in RCC and other oncology trials. The outputs of the ITC for these efficacy endpoints are utilised in the health economic analysis presented in Section B.3.

The feasibility assessment examined differences in study design, patient populations, treatment effects and relative outcomes. Publications were excluded from the analysis if they did not provide PFS or OS as an efficacy outcome either as a HR or in a KM plot. The assessment also compared study inclusion/exclusion criteria and baseline patient characteristics, including prognostic factors, risk score (IMDC and MSKCC), previous therapies and disease stage.

B.2.9.3.1 Data availability assessment

In order to assess the feasibility of performing an ITC, the availability of OS and PFS HRs or KM curves were assessed. A summary of the available data is provided in Table B.2.21.

Table B.2.21. Summary of survival outcomes of studies included in the ITCs

Study	Treatments	Population	N	OS (months)			PFS (months)		
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)
ITT population									
Motzer 2019 (JAVELIN Renal 101) [67]	AVE 10 mg/kg q2w + AXI 5 mg bid	Overall	442	NR	Not Reached	0.78 (0.55-1.08)	NR	12.5 (11.1-15.2)	0.64 (0.63-0.78)
	SUN 50 mg/d 4/2 schedule	Overall	444	NR	Not Reached	NR	NR	8.4 (8.2-9.7)	NR
	AVE 10 mg/ kg q2w + AXI 5 mg bid	Overall, IRC-assessed	442	NR	NR	NR	NR	13.8 (11.1-NE)	0.69 (0.56-0.84)
	SUN 50 mg/d 4/2 schedule	Overall, IRC-assessed	444	NR	NR	NR	NR	8.4 (6.9- 11.1)	NR
	AVE 10 mg/ kg q2w + AXI 5 mg bid	IMDC favourable risk	94	NR	NR	NR	NR	NE (16.1-NE)	0.54 (0.32-0.91)
	SUN 50 mg/d 4/2 schedule	IMDC favourable risk	96	NR	NR	NR	NR	13.8 (11.1-18.6)	NR
	AVE 10 mg/ kg q2w + AXI 5 mg bid	MSKCC favourable risk	96	NR	NR	NR	NR	NE (12.6-NE)	0.65 (0.40-1.10)
	SUN 50 mg/d 4/2 schedule	MSKCC favourable risk	100	NR	NR	NR	NR	16.7 (11.1-18.6)	NR
	AVE 10 mg/ kg q2w + AXI 5 mg bid	MSKCC intermediate risk	283	NR	NR	NR	NR	13.3 (8.5-NE)	0.72 (0.56-0.92)
	SUN 50 mg/d 4/2 schedule	MSKCC intermediate risk	293	NR	NR	NR	NR	7.9 (6.7-9.8)	NR
	AVE 10 mg/ kg q2w + AXI 5 mg bid	MSKCC poor risk	51	NR	NR	NR	NR	5.6 (2.6-11.2)	0.5 (0.30-0.83)
	SUN 50 mg/d 4/2 schedule	MSKCC poor risk	45	NR	NR	NR	NR	2.8 (1.5-2.9)	NR
Eichelberg 2015 (SWITCH/ NCT00732914) [85]	SOR 400 mg BD - SUN 50 mg/d 4/2 schedule	Overall	182	NR	NR	NR	NR	5.9	1.19
	SUN 50 mg/d 4/2 schedule-SOR 400 mg BD	Overall	183	NR	NR	NR	NR	8.5	NR
	SOR 400 mg BD-SUN 50 mg/d 4/2 schedule	MSKCC poor risk	NR	NR	NR	NR	NR	NR	1.3

	SUN 50 mg/d 4/2 schedule -SOR 400 mg BD	MSKCC poor risk	NR	NR	NR	NR	NR	NR	NR
	SOR 400 mg BD - SUN 50 mg/d 4/2 schedule	MSKCC intermediate risk	NR	NR	NR	NR	NR	NR	1.14
	SUN 50 mg/d 4/2 schedule-SOR 400mg BD	MSKCC intermediate risk	NR	NR	NR	NR	NR	NR	NR
Hutson 2013 (NCT00920816) [9]	AXI 5 mg BD	Overall	192	NR	NR	NR	NR	10.1 (7.2-12.1)	0.77 (0.56-1.05)
	SOR 400 mg BD	Overall	96	NR	NR	NR	NR	6.5 (4.7-8.3)	NR
	AXI 5 mg BD	Overall	NR	NR	NR	NR	NR	11.1	0.77 (0.57-1.04)
	SOR 400 mg BD	Overall	NR	NR	NR	NR	NR	7.4	NR
	AXI 5 mg BD	MSKCC favourable risk	NR	NR	NR	NR	NR	NR	0.64 (0.4-1.02)
	SOR 400 mg BD	MSKCC favourable risk	NR	NR	NR	NR	NR	NR	NR
	AXI 5 mg BD	MSKCC intermediate or poor risk	NR	NR	NR	NR	NR	NR	0.83 (0.54-1.28)
	SOR 400 mg BD	MSKCC intermediate or poor risk	NR	NR	NR	NR	NR	NR	NR
	AXI 5 mg BD	Overall	192	NR	21.7 (18-31.7)	0.995 (0.73-1.36)	NR	NR	NR
	SOR 400 mg BD	Overall	96	NR	23.3 (18.1-33.2)	NR	NR	NR	NR
Motzer 2013 (COMPARZ/ NCT00720941) [84]	PAZ 800 mg/day	Overall	557	NR	28.4 (26.2-35.6)	0.91 (0.76-1.08)	NR	10.5 (8.3-11.1)	1 (0.86-1.15)
	SUN 50 mg/day 4/2 schedule	Overall	553	NR	29.3 (25.3-32.5)	NR	NR	10.2 (8.3-11.1)	NR
	PAZ 800 mg/day	Overall	557	NR	NR	NR	NR	8.4 (8.3-10.9)	1.05 (0.9-1.22)
	SUN 50 mg/day 4/2 schedule	Overall	553	NR	NR	NR	NR	9.5 (8.3-11.1)	NR
	PAZ 800 mg/day	Overall	557	NR	28.3 (26-35.5)	0.92 (0.79-	NR	NR	NR

						1.06)			
	SUN 50 mg/day 4/2 schedule	Overall	553	NR	29.1 (25.4-33.1)	NR	NR	NR	NR
	PAZ 800 mg/day	MSKCC favourable risk	557	NR	42.5 (37.9-not reached)	0.88 (0.63-1.21)	NR	NR	NR
	SUN 50 mg/day 4/2 schedule	MSKCC favourable risk	553	NR	43.6 (37.1-47.4)	NR	NR	NR	NR
	PAZ 800 mg/day	MSKCC intermediate risk	557	NR	26.9 (23.1-35.6)	0.9 (0.74-1.09)	NR	NR	NR
	SUN 50 mg/day 4/2 schedule	MSKCC intermediate risk	553	NR	26.1 (20.7-31.6)	NR	NR	NR	NR
	PAZ 800 mg/day	MSKCC poor risk	557	NR	9.9 (7.3-12.3)	0.85 (0.56-1.28)	NR	NR	NR
	SUN 50 mg/day 4/2 schedule	MSKCC poor risk	553	NR	7.7 (5.4-11.9)	NR	NR	NR	NR
Motzer 2013 (TIVO-1/NCT01030783) [18]	TIV 1.5 mg OD	Overall	260	NR	NR	NR	NR	12.7	0.756 (0.58-0.99)
	SOR 400 mg BD	Overall	257	NR	NR	NR	NR	9.1	NR
Tomita 2017 (CROSS-J-RCC/ NCT01481870) [86]	SUN 50 mg/day 4/2 schedule-SOR 400 mg BD	Overall	60	NR	38.4	0.934 (0.59-1.49)	NR	8.7	0.67 (0.42-1.08)
	SOR 400 mg BD-SUN 50 mg/day 4/2 schedule	Overall	60	NR	30.9	NR	NR	7	NR
IMDC intermediate- or poor-risk population									
Motzer 2019 JAVELIN Renal 101[67]	AVE 10 mg/ kg q2w + AXI 5 mg bid	IMDC intermediate risk	271	NR	NR	NR	NR	13.8 (9.7-NE)	0.74 (0.57-0.95)
	SUN 50 mg/d 4/2 schedule	IMDC intermediate risk	276	NR	NR	NR	NR	8.4 (7-11.2)	NR
	AVE 10 mg/ kg q2w + AXI 5 mg bid	IMDC poor risk	72	NR	NR	NR	NR	6 (3.6-8.7)	0.57 (0.375-0.88)
	SUN 50 mg/d 4/2 schedule	IMDC poor risk	71	NR	NR	NR	NR	2.9 (2.7-5.5)	NR
Choueiri 2018 (Alliance A031203	CAB 60 mg/day	Overall	79	NR	26.6 (14.6-Not est)	0.8 (0.53-	NR	8.6 (6.8-14)	0.48 (0.31-0.74)

CABOSUN /NCT01835158) [87]						1.21)			
	SUN 37.5 mg/day	Overall	78	NR	21.2 (16.3-27.4)	NR	NR	5.3 (3-8.2)	NR
	CAB 60 mg/day	Overall	NR	NR	NR	NR	NR	8.3 (6.5-12.4)	0.56 (0.37-0.83)
	SUN 37.5 mg/day	Overall	NR	NR	NR	NR	NR	5.4 (3.4-8.2)	NR
	CAB 60 mg/day	Overall	79	NR	30.3 (14.6-35)	0.8 (0.5-1.26)	NR	NR	NR
	SUN 37.5 mg/day	Overall	78	NR	21.8 (16.3-27)	NR	NR	NR	NR
	CAB 60 mg/day	Overall	79	NR	26.4	0.87 (0.55-1.4)	NR	8.2 (6.2-8.8)	0.66 (0.46-0.95)
	SUN 37.5 mg/day	Overall	78	NR	23.5	NR	NR	5.6 (3.4-8.1)	NR
	CAB 60 mg/day	IMDC intermediate risk	NR	NR	NR	NR	NR	8.31	0.64 (0.43-0.96)
	SUN 37.5 mg/day	IMDC intermediate risk	NR	NR	NR	NR	NR	6.4	NR
	CAB 60 mg/day	IMDC poor risk	NR	NR	NR	NR	NR	6.14	0.75 (0.35-1.65)
	SUN 37.5 mg/day	IMDC poor risk	NR	NR	NR	NR	NR	2.77	NR
	CAB 60 mg/day	IMDC intermediate risk	NR	NR	NR	NR	NR	11.4	0.52 (0.32-0.82)
	SUN 37.5 mg/day	IMDC intermediate risk	NR	NR	NR	NR	NR	6.1	NR
	CAB 60 mg/day	IMDC poor risk	NR	NR	NR	NR	NR	6.8	0.31 (0.11-0.92)
	SUN 37.5 mg/day	IMDC poor risk	NR	NR	NR	NR	NR	2.7	NR

Abbreviations: AXI = axitinib; BD = twice daily; CAB = cabozantinib; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IPI = ipilimumab; kg = kilogram; mg = milligram; MSKCC = Memorial Sloan Kettering Cancer Center; N = number of patients evaluable; NIV = nivolumab; NR = not reported; OD = once daily; Q3W = every 3 weeks; RCC= renal cell carcinoma; SOR = sorafenib; SUN = sunitinib; TIV = tivozanib; US = United States

B.2.9.3.2 Assessment of heterogeneity

A key consideration of ITC is whether the studies included are homogenous in terms of study design and baseline patient characteristics. In general, study designs were similar – most were Phase 3, randomised, multicentre, international studies (Table B.2.20). Notably, two of studies in the ITT population network were crossover studies (Eichelberg 2015 and Tomita 2017). In each study, PFS data were available before and after the crossover, meaning true PFS values could be determined for each independent treatment.

In terms of baseline characteristics, the studies were generally similar (Table B.2.22). From a qualitative perspective, for studies that included the data, values for age (~60 years), proportion male (~70%), proportion with ≥2 metastatic sites (~75%), and proportion with clear-cell histology (~100%) were consistent. The primary metastatic site in all studies was the lung (~70%), followed by the liver (~20%) and bone (~20%). In most studies, ≥75% of patients had prior surgery and ≥80% patients were ECOG PS 0 or 1. In all of the studies included in the ITT population network, the majority of patients (≥85%) were low or intermediate MSKCC risk status. Of the two studies that reported IMDC risk status, 61–81% of patients were intermediate risk and 10–19% were poor risk.

Sunitinib was included as an experimental or control arm in multiple trials, with median PFS and OS generally consistent across trials (approximately 8–10 and –38 months, respectively).[67, 84-86] However, median PFS and OS in the sunitinib arm of the Phase 2 cabozantinib study (CABOSUN) were lower, at approximately 5 and 21 months, respectively.[87]

Table B.2.22. Summary of baseline characteristics in studies included in the ITC

Study	Treatment	Male, n (%)	Metastatic site, n (%)	Histology, n (%)	Prior therapy, n (%)	ECOG PS, n (%)	Risk group n (%)
ITT population							
Motzer 2019 (JAVELIN/ NCT02684006)[67]	AVE 10 mg/kg q2w + AXI 5 mg BD	316 (71.5)	NR	NR	352 (80)	NR	MSKCC: Favourable: 96 (21.7) Intermediate: 283 (64.0) Poor: 51 (11.5) IMDC: Favourable: 94 (21.3) Intermediate: 271 (61.3) Poor: 72 (16.3)
	SUN 50 mg/d 4/2 schedule	344 (77.5)	NR	NR	355 (80)	NR	MSKCC: Favourable: 100 (22.5) Intermediate: 293 (66) Poor: 45 (10.1) IMDC: Favourable: 96 (21.6) Intermediate: 276 (62.2) Poor: 71 (16.0)
Eichelberg 2015 (SWITCH/ NCT00732914)[85]	SOR 400 mg BD - SUN 50 mg/d 4/2 schedule	139 (77)	Lung: 139 (79) Liver: 36 (20) Bone: 22 (12) Adrenal: NR Brain: 6 (3.4) Pancreas: NR	Clear cell: 164 (90) Non-clear cell: NR Other:	Surgery: 167 (92) Radiotherapy: 16 (8.8)	0: 116 (66) 1: 55 (31) 2: 0 (0) 3: NR 4: NR	MSKCC Favourable: 71 (39) Intermediate:108 (59) Poor: 1 (0.5) IMDC NR
	SUN 50 mg/day 4/2 schedule - SOR 400 mg BD	135 (74)	Lung: 126 (72) Liver: 42 (24) Bone: 30 (17) Adrenal: NR Brain: 4 (2.3) Pancreas: NR	Clear cell: 154 (84) Non-clear cell: Other:	Surgery: 168 (92) Radiotherapy: 23 (13)	0: 106 (60) 1: 66 (38) 2: 1 (0.6) 3: NR 4: NR	MSKCC Favourable: 82 (45) Intermediate: 94 (51) Poor: 1 (0.5) IMDC NR
Hutson 2013 (NCT00920816)[9]	AXI 5 mg BD	134 (70)	Lung: 137 (72) Liver: 52 (27) Bone: 56 (29) Adrenal: NR Brain: NR Pancreas: NR	Clear cell: 192 (100)	Surgery: 164 (85) Radiotherapy: NR	0: 110 (57) 1: 82 (43) 2: NR 3: NR 4: NR	MSKCC Favourable: 94 (49) Intermediate: 84 (44) Poor: 7 (4) IMDC NR

	SOR 400 mg BD	74 (78)	Lung: 72 (75) Liver: 25 (26) Bone: 24 (25) Adrenal: NR Brain: NR Pancreas: NR	Clear cell: 96 (100)	Surgery: 86 (90) Radiotherapy: NR	0: 55 (57) 1: 41 (43) 2: NR 3: NR 4: NR	MSKCC Favourable: 53 (55) Intermediate: 40 (42) Poor: 2 (2) IMDC NR
Motzer 2013 (COMPARZ/ NCT00720941)[84]	PAZ 800 mg/day	398 (72)	Lung: 424 (77) Liver: 18 (15) Bone: 110 (20) Adrenal: NR Brain: NR Pancreas: NR	Clear cell: 557 (100)	Surgery: 459 (82) Radiotherapy: 46 (8)	NR	MSKCC Favourable: 151 (27) Intermediate: 322 (58) Poor: 67 (12) IMDC NR
	SUN 50 mg/day 4/2 schedule	415 (76)	Lung: 425 (77) Liver: 110 (20) Bone: 85 (15) Adrenal: NR Brain: NR Pancreas: NR	Clear cell: 553 (100)	Surgery: 465 (84) Radiotherapy: 42 (8)	NR	MSKCC Favourable: 152 (27) Intermediate: 328 (59) Poor: 52 (9) IMDC NR
Motzer 2013 (TIVO-1/ NCT01030783)[18]	TIV 1.5 mg OD	185 (71)	Lung: 212 (82) Liver: 182 (70) Bone: 61 (23) Adrenal: 78 (30) Brain: NR Pancreas: NR	NR	Systemic: 78 (30)	0: 116 (45) 1: 144 (55) 2: NR 3: NR 4: NR	MSKCC Favourable: 70 (27) Intermediate: 173 (67) Poor: 17 (7) IMDC NR
	SOR 400 mg BD	189 (74)	Lung: 204 (79) Liver: 166 (65) Bone: 52 (20) Adrenal: 57 (22) Brain: NR Pancreas: NR	NR	Systemic: 76 (30)	0: 139 (54) 1: 118 (46) 2: NR 3: NR 4: NR	MSKCC Favourable: 87 (34) Intermediate: 160 (62) Poor: 10 (4) IMDC NR
Tomita 2017 (CROSS-J-RCC/ NCT01481870)[86]	SUN 50 mg/day 4/2 schedule → SOR 400 mg BD	46 (81)	Lung: 40 (71) Liver: 4 (8) Bone: 13 (23) Adrenal: NR Brain: 5 (8.8) Pancreas: NR	Clear cell: 57 (100)	Surgery: 50 (88) Radiotherapy: NR	NR	MSKCC Favourable: 12 (21) Intermediate: 45 (75) Poor: NR IMDC NR
	SOR 400 mg BD → SUN	53 (85)	Lung: 47 (75) Liver: 6 (10)	Clear cell: 63 (100)	Surgery: 56 (89) Radiotherapy: NR	NR	MSKCC Favourable: 14 (22)

	50 mg/day 4/2 schedule		Bone: 21 (34) Adrenal: NR Brain: 1 (1.6) Pancreas: NR				Intermediate: 49 (78) Poor: NR IMDC NR
IMDC intermediate- or poor-risk population network							
Motzer 2019 (JAVELIN/ NCT02684006)[67]	AVE 10 mg/kg q2w + AXI 5 mg BD	316 (71.5)	NR	NR	352 (80%)	NR	MSKCC: Favourable: 96 (22.0) Intermediate: 283 (64.0) Poor: 51 (12.0) IMDC: Favourable: 94 (21.0) Intermediate: 271 (61.0) Poor: 72 (16.3)
	SUN 50 mg/d 4/2 schedule	344 (77.5)	NR	NR	355 (80%)	NR	MSKCC: Favourable: 100 (22.5) Intermediate: 293 (66.0) Poor: 45 (10.1) IMDC: Favourable: 96 (21.6) Intermediate: 276 (62.2) Poor: 71 (16.0)
Choueiri 2018 (Alliance A031203 CABOSUN/ NCT01835158)[87]	CAB 60 mg/day	66 (84.0)	Lung: 55 (70) Liver: 15 (19) Bone: 31 (39) Adrenal: NR Brain: 3 (4) Pancreas: NR	Clear cell: 79 (100)	Surgery: 57 (72) Radiotherapy: NR	0: 36 (46) 1: 33 (42) 2: 10 (13) 3: NR 4: NR	MSKCC NR IMDC Favourable: NR Intermediate: 64 (81.0) Poor: 15 (19.0)
	SUN 37.5 mg/day	57 (74)	Lung: 54 (70) Liver: 20 (26) Bone: 30 (38) Adrenal: NR Brain: 2 (3) Pancreas: NR	Clear cell: 78 (100)	Surgery: 60 (77) Radiotherapy: NR	0: 36 (46) 1: 32 (41) 2: 10 (13) 3: NR 4: NR	MSKCC NR IMDC Favourable: NR Intermediate: 63 (81.0) Poor: 15 (19.0)

Abbreviations: AVE = avelumab; AXI = axitinib; BD = twice daily; CAB = cabozantinib; ECOG = Eastern Cooperative Oncology Group; IRC = independent review committee; ITC = indirect treatment comparison; kg = kilogram; mg = milligram; NR = not reported; OD = once daily; PS = performance status; Q3W = every 3 weeks; SOR = sorafenib; SUN = sunitinib; TIV = tivozanib

B.2.9.4 ITC of parametric survival curves: methodology

The standard approach to network meta-analysis (NMA) estimates a constant relative treatment effect (usually either a HR or acceleration factor) for each treatment comparison, which is then applied to a parametric survival curve for the chosen reference treatment. This approach implies an assumption of proportional relative treatment effects, or proportional hazards (PH).

For comparators for which direct evidence versus avelumab + axitinib was not available (tivozanib, cabozantinib), an assessment of PH indicated potential violations for PFS and OS. Within the NICE technology appraisal for tivozanib (TA512)[12], it was acknowledged that tivozanib was expected to be overall less effective (lower OS) than sunitinib. Therefore, the assumption that tivozanib was equivalent to sunitinib (i.e. the approach taken for pazopanib) was not considered appropriate. The log-cumulative hazard (LCH) curves for the comparison of tivozanib to its comparator sorafenib in the TIVO-1 study indicate a potential violation of PH for OS, and a clear violation of PH for PFS (see Appendix D).

LCH curves for OS and PFS (see Appendix D) informed that assessment of the PH assumption for cabozantinib in the CABOSUN trial against sunitinib in patients with intermediate- or poor-risk status. The crossing of the LCH plots for OS demonstrate that the assumption of PH may be violated. The LCH plots for PFS begin to merge early on, before later separation, which provides some indication that the assumption of PH may not be appropriate for PFS. As such, ITC methods that do not rely on the PH assumption were applied for cabozantinib, which allows for greater flexibility in modelling the treatment effect over time. In addition, the treatment mechanism of action is common across the outcomes of OS and PFS within the cabozantinib comparison, as such maintaining a consistent approach to ITC is considered to be more appropriate.

An alternative approach to standard NMA has been previously published by Ouwens (2010).[88] This method of ITC does not assume PH (non-PH ITC) and is based on multi-parameter evidence synthesis of treatment effects that involves fitting parametric curves to each study and treatment in the evidence base in a frequentist framework that involves fitting parametric curves to each study and treatment.[88, 89] These curves allow the treatment effects to influence both the location (for example, scale in the Weibull distribution) and non-location (for instance, shape in the Weibull distribution) parameters of the parametric curve to reflect a time-varying treatment effect. In these analyses, the ITC is formed by using a covariate for study in the parametric models to maintain the randomisation within each trial. The study parameter acts as a proxy for all differences in study design and patient characteristics between studies.

The time-varying relative treatment effects are captured in a survival regression model by including terms for study and treatment in both the location and non-location elements of the following standard parametric distributions for the survival times:

- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalized gamma
- Generalized F

The exponential distribution is a special case of the Weibull distribution, so explicitly including the exponential distribution as a separate analysis was considered to be redundant. All analyses were carried out using the flexsurv package in R software.[90]

The generalized gamma distribution has three parameters (mean, sigma, and Q), and the generalized F distribution has four parameters (mean, sigma, Q, and P). For these two distributions, there are several alternative parameterisations. In each case, treatment and study effects can be applied to the location parameter (mean) and one of the non-location parameters (sigma, Q, or P). The use of sigma as the non-location parameter was the primary consideration in this case, to remain consistent with the other distributions.

The fit of the alternative models to the observed data can then be assessed using a combination of Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics, visual fit of the estimated parametric curve to the observed KM curve, and clinical plausibility of the extrapolations.

Given that there is some uncertainty around violations of the assumption of PH for OS and PFS for tivozanib and cabozantinib, a standard (Bayesian) NMA was also conducted assuming PH (PH ITC) between all comparators versus the reference treatment (sunitinib, informed based on the stratified curve from JAVELIN Renal 101). The output of the analyses is estimated HRs and 95% credible interval (CrIs) versus the reference treatment. The details of PH ITC methods are provided in Appendix D.

B.2.9.5 Outputs of the ITC

B.2.9.5.1.1 ITT population

The six distributions were fitted to the combined patient-level data (PLD) from JAVELIN Renal 101 and pseudo-PLD estimated from the comparator studies, using covariates for study and treatment, separately for PFS and OS. In the non-PH ITC, one parametric model is selected to fit the combined PLD for all included treatments. Treatment-specific parameter estimates (such as shape and scale for the Weibull) are then estimated, which allow changing relative treatment effects over time. Survival outcomes are then estimated for each treatment as though investigated within the JAVELIN Renal 101 trial. Table B.2.23 presents the AIC and BIC statistics for each model for PFS and OS in the ITT population.

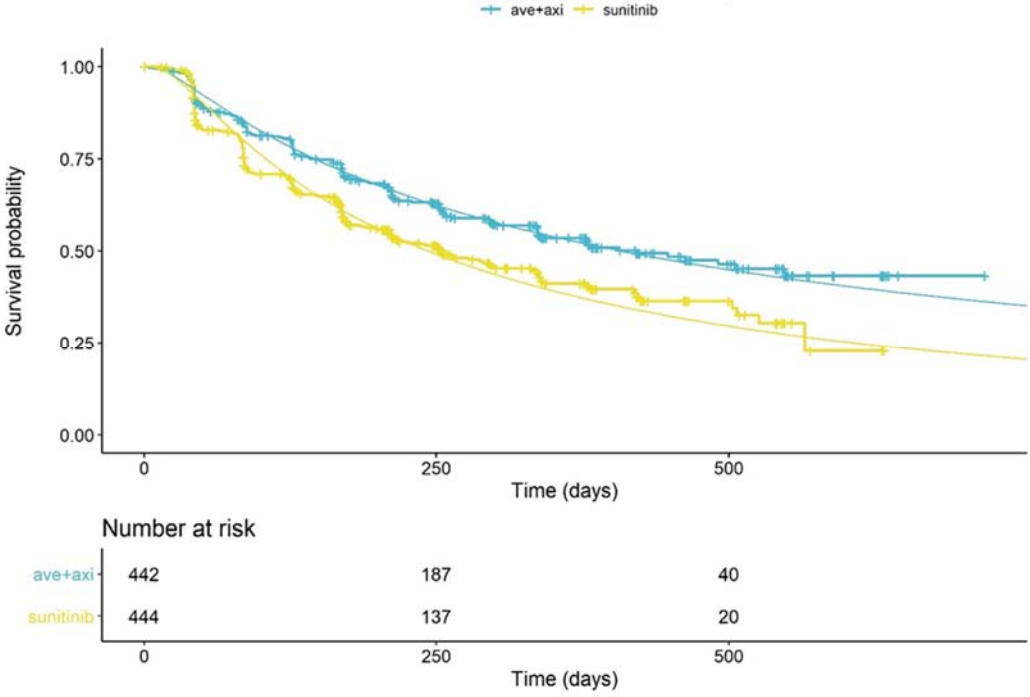
For both PFS and OS in the avelumab + axitinib arm of JAVELIN Renal 101, generalised gamma was selected for the base case as it had the lowest AIC and BIC scores and a good visual fit to the data. Fit statistics were relatively similar across parametric models; therefore, clinical plausibility was a key determining factor. A visual comparison of the estimated parametric survival curves using generalised gamma with the observed KM data from the JAVELIN Renal 101 study for PFS and OS is presented in Figure B.2.15 and Figure B.2.16, respectively.

Table B.2.23. Non-PH ITC AIC and BIC statistics – PFS and OS (ITT population)

Model	PFS		OS	
	AIC	BIC	AIC	BIC
Generalised gamma	**25351.33**	**25490.46**	**22128.34**	**22254.55**
Generalised F	25353.33	25498.51	22130.35	22262.57
Log-normal	25365.27	25498.35	22135.17	22255.38
Log-logistic	25436.25	25569.33	22136.94	22257.14
Weibull	25590.96	25724.04	22166.77	22286.98
Gompertz	25595.25	25728.33	22180.93	22301.14

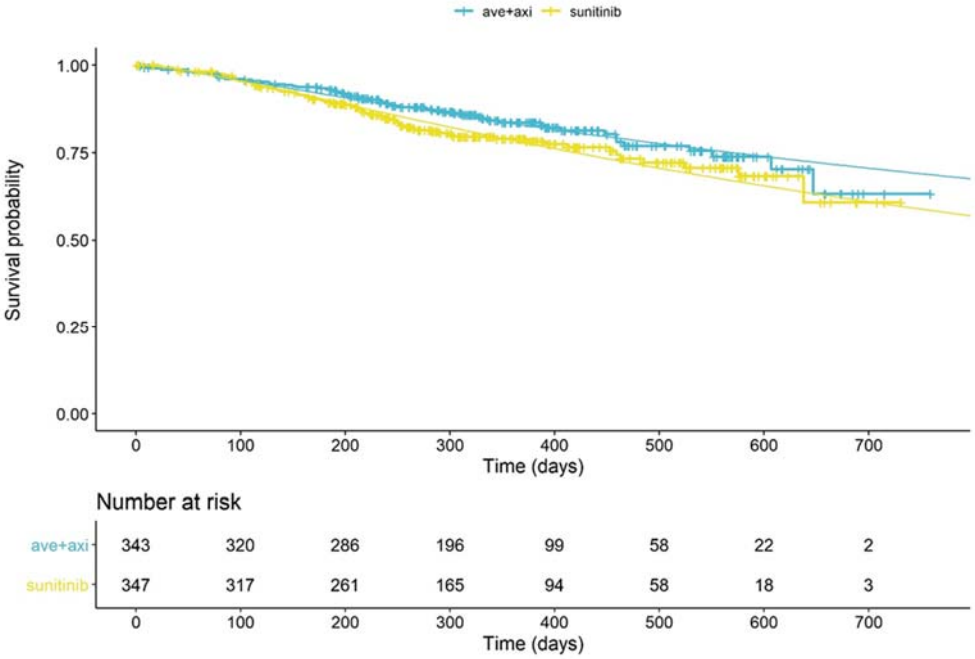
Abbreviations: AIC = Akaike information criteria; BIC = Bayesian information criteria; ITC = indirect treatment comparison; ITT = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; PH = proportional hazards

Figure B.2.15. Comparison of estimated generalised gamma curves from non-PH ITC to PFS KM curves from JAVELIN Renal 101 study (ITT population)



Abbreviations: ITC = indirect treatment comparison; ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; PH = proportional hazard

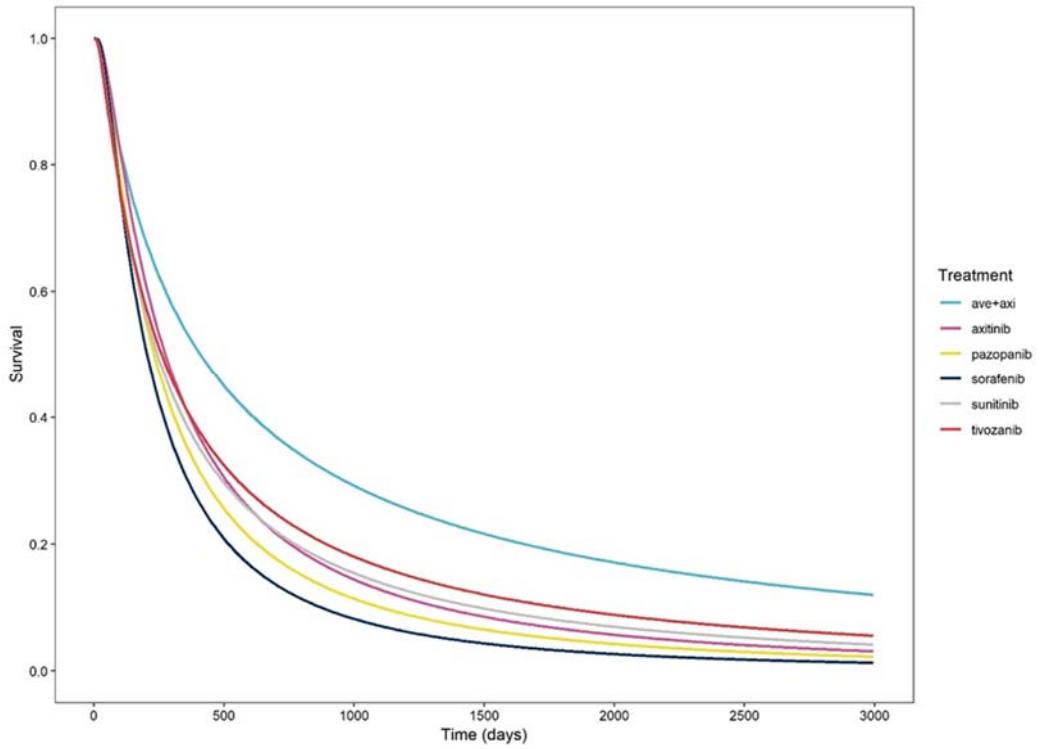
Figure B.2.16 Comparison of estimated generalised gamma curves from non-PH ITC to OS KM curves from JAVELIN Renal 101 study (ITT population)



Abbreviations: ITC = indirect treatment comparison; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; PH = proportional hazard

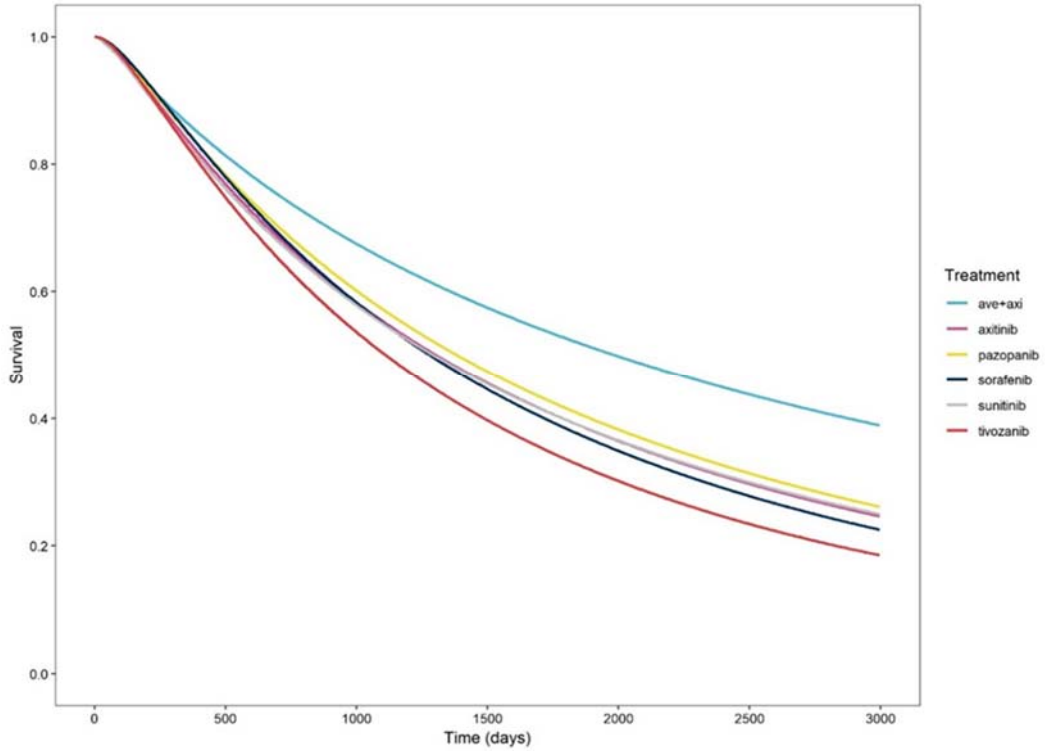
The extrapolated survival curves when using generalised gamma for both PFS and OS are reported for the treatments included within the non-PH ITC for the ITT population in Figure B.2.17 and Figure B.2.18. The crossing of the curves reflects the time-varying relative treatment effects estimated within the non-PH ITC. Estimated curves and landmark estimates for other parametric survival models with good fit are provided in Appendix D.

Figure B.2.17. Comparison of treatments based on estimated PFS – gen. gamma



Abbreviations: Ave = avelumab; Axi = axitinib; gen. = generalised; PFS = progression-free survival

Figure B.2.18. Comparison of treatments based on estimated OS – gen. gamma



Abbreviations: AVE = avelumab; AXI = axitinib; gen. = generalised; OS = overall survival

B.2.9.5.1.2 Intermediate- or poor-risk population

As with the ITT population, the six model distributions were fitted to the combined PLD from the IMDC intermediate- or poor-risk population of JAVELIN Renal 101 and pseudo-PLD estimated from the CABOSUN study, using covariates for study and treatment separately for PFS and OS.

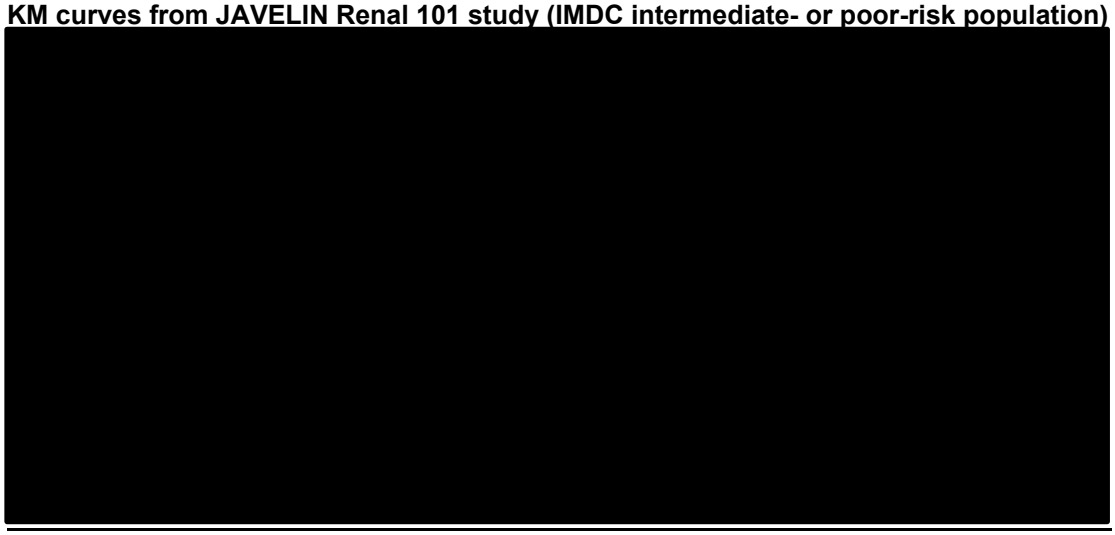
Table B.2.24 presents the AIC and BIC statistics for each model for PFS and OS in the IMDC intermediate- or poor- risk population. Based on the model fit statistics and visual inspection of the curves, generalised gamma was the most suitable curve for PFS. For OS, log-logistic was selected for the base case given its best statistical fit, although there was broad similarity across log-logistic, log-normal, Weibull, and generalized gamma for both statistical fit and visual inspection. A visual comparison of the estimated parametric survival curves using generalised gamma with the observed KM data from the JAVELIN Renal 101 study for PFS and OS is presented in Figure B.2.19 and Figure B.2.20, respectively.

Table B.2.24. Non-PH ITC AIC and BIC statistics – PFS and OS (IMDC intermediate- or poor-risk population)

Model	PFS		OS	
	AIC	BIC	AIC	BIC
Generalised gamma	**5815.03**	**5857.71**	3620.00	3662.68
Generalised F	5816.34	5863.76	3621.64	3669.05
Log-normal	5834.84	5872.77	3619.27	3657.21
Log-logistic	5860.58	5898.51	**3618.83**	**3656.76**
Gompertz	5902.13	5940.06	3627.57	3665.50
Weibull	5904.12	5942.05	3623.03	3660.96

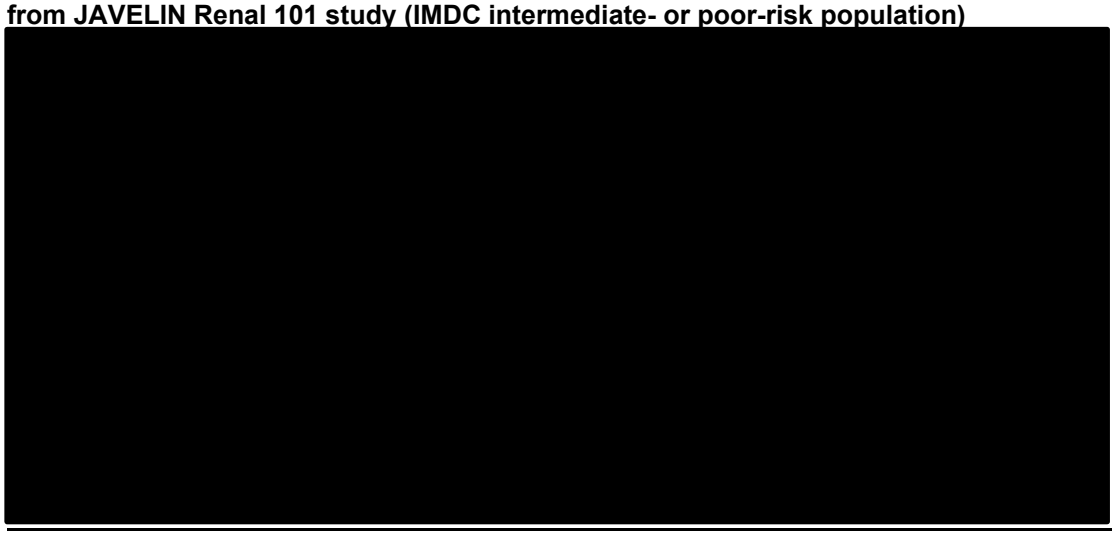
Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; PH = proportional hazards

Figure B.2.19 Comparison of estimated generalised gamma curves from non-PH ITC to PFS KM curves from JAVELIN Renal 101 study (IMDC intermediate- or poor-risk population)



Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; PH = proportional hazard

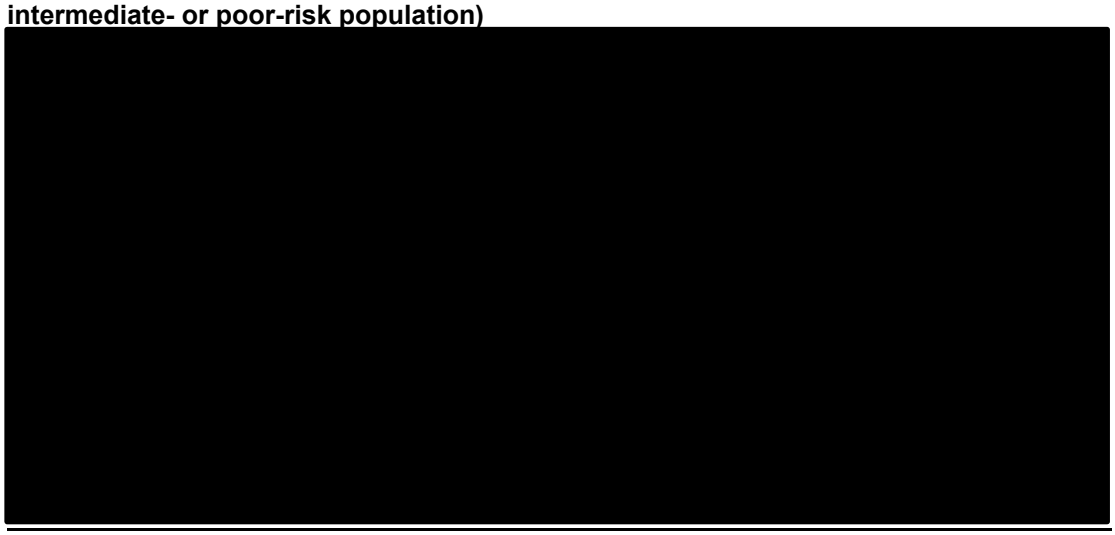
Figure B.2.20 Comparison of estimated log-logistic curves from non-PH ITC to OS KM curves from JAVELIN Renal 101 study (IMDC intermediate- or poor-risk population)



Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; PH = proportional hazard

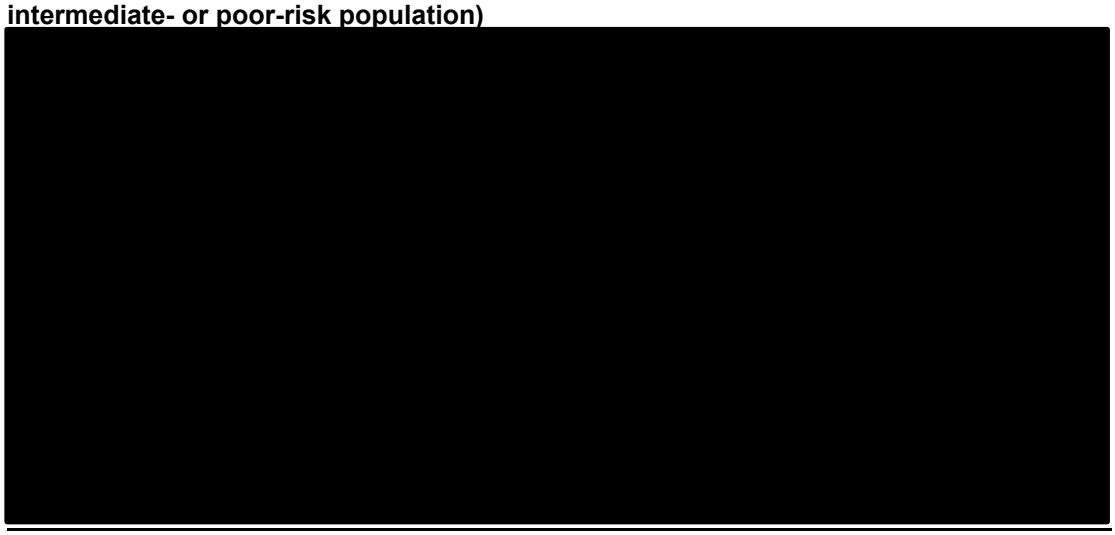
The extrapolated curves when using generalised gamma in the non-PH ITC for both PFS and OS for the intermediate- or poor-risk subgroup are reported below for avelumab + axitinib, sunitinib, and cabozantinib in Figure B.2.21 and Figure B.2.22. A crossing of the PFS curves reflects the time-varying relative treatment effects estimated within the non-PH ITC for this outcome. Estimated curves and landmark estimates for other parametric survival models with good fit are provided in Appendix D.

Figure B.2.21. Comparison of treatments based on estimated PFS – gen. gamma (IMDC intermediate- or poor-risk population)



Abbreviations: Ave = avelumab; Axi = axitinib; gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression-free survival

Figure B.2.22. Comparison of treatments based on estimated OS – log-logistic (IMDC intermediate- or poor-risk population)



Abbreviations: Ave = avelumab; Axi = axitinib; gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival

B.2.9.6 Uncertainties in the indirect treatment comparison of parametric survival curves

The ITC utilised a robust methodology with a systematic and comprehensive review and collection of data. However, there are inherent limitations in conducting SLRs and ITCs. For the SLR, although NICE methodology and guidance were followed, there is a risk of bias in the subjective review process. Two independent reviewers were used to mitigate this bias. Similarly, while the NICE checklist was used to assess quality of evidence, the grading process is subject to bias.

Investigation into the evidence available indicates that proportional hazards may not hold for comparators for which no direct evidence versus avelumab + axitinib is available (tivozanib, cabozantinib). Compared to standard NMA which assumes PH, the non-PH ITC approach

allows more flexibility into the shape of the comparator curves and was therefore selected to enable comparisons where no direct evidence is available. To assess the impact of the PH vs non-PH assumption, survival curves were modelled for all possible scenarios and were assessed using statistical tests, visual analysis, and clinical validity tests. Results based on non-PH and PH ITCs showed consistency in the ranking of included treatments (see Appendix D).

A final limitation of the ITC was the assumption that study design and patient populations were similar across the studies. Although potential differences were investigated, data were not available for all of the studies, so there is some uncertainty as to the heterogeneity of the studies. From the available data, however, there was evidence to indicate that the studies were generally similar, both in terms of design and patient baseline characteristics (e.g. age, metastatic sites, ECOG, histology, risk status) (see Section B.2.9.3.2). The non-PH ITC is conducted in a fixed effects framework and therefore no additional heterogeneity parameter is estimated. Investigations of study comparability did indicate studies to be generally similar in terms of design and patient population and as such this framework is considered appropriate.

B.2.10 Adverse reactions

B.2.10.1 Safety population

This submission is supported by safety data from the pivotal Phase 3 B9991003 study (JAVELIN Renal 101).[68] The safety and tolerability of avelumab + axitinib in patients with aRCC has also been assessed in the Phase 1b B9991002 study (JAVELIN Renal 100),[70] and safety data from a pooled aRCC population, comprising patients who received at least one dose of avelumab + axitinib in JAVELIN Renal 101 and JAVELIN Renal 100, are also presented. A summary of patients included in the SAS for each study is shown in Table B.2.25.

Table B.2.25. Safety population

Study	Data cut-off date	Study treatment, N	
		Avelumab + axitinib	Sunitinib
JAVELIN Renal 101 (B9991003)	20 June 2018	434	439
JAVELIN Renal 100 (B9991002)	3 April 2018	55	N/A

Abbreviations: N = number of patients evaluable; N/A = not applicable; SAS = safety analysis set
Sources: Pfizer Inc., 2018;[68] Pfizer Inc., 2018[70]

B.2.10.2 Extent of exposure

The extent of exposure to avelumab and axitinib in the pooled aRCC population, and avelumab, axitinib and sunitinib in JAVELIN Renal 101, is shown in Table B.2.26. The median duration of treatment with avelumab + axitinib was similar in the pooled aRCC population and JAVELIN Renal 101, at [redacted] and [redacted], respectively, for avelumab, and [redacted] and [redacted], respectively, for axitinib.[68, 91] In comparison, the median duration of treatment with sunitinib in JAVELIN Renal 101 was shorter, at [redacted].[68] In the pooled aRCC population, the median relative dose intensities for avelumab and axitinib were 92.3% and 88.4%, respectively.[91] In JAVELIN Renal 101, the median dose intensities were 91.5% for avelumab, 89.4% for axitinib and 83.9% for sunitinib.[67]

Table B.2.26. Extent of exposure to avelumab, axitinib and sunitinib (Pooled aRCC population; JAVELIN Renal 101 SAS)

	Pooled aRCC population		JAVELIN Renal 101		
	Avelumab (N=488)	Axitinib (N=489)	Avelumab (N=434)	Axitinib (N=434)	Sunitinib (N=439)
Median duration (range) of treatment, weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range) dose intensity					
Avelumab, mg/kg/6-week cycle	[redacted]	N/A	[redacted]	N/A	N/A
Axitinib, mg/week	N/A	[redacted]	N/A	[redacted]	N/A
Sunitinib, mg/6-week cycle	N/A	N/A	N/A	N/A	[redacted]
Median(range) relative dose intensity, %	92.3 ([redacted])	88.4 ([redacted])	91.5 ([redacted])	89.4 ([redacted])	83.9 ([redacted])

Abbreviations: aRCC = advanced renal cell carcinoma; kg = kilogram; mg = milligram; N = number of patients evaluable; N/A = not applicable; SAS = safety analysis set
Source: Motzer et al. 2019;[67] Pfizer Inc., 2018[91]

B.2.10.3 Adverse events

A summary of AEs in the pooled aRCC population and JAVELIN Renal 101 is shown in Table B.2.27. In JAVELIN Renal 101, AEs were well balanced in each treatment arm, with some exceptions, including:

- A higher percentage of patients with serious adverse events (SAEs) in the combination arm ([redacted]) compared with the sunitinib arm ([redacted])[68]
- Discontinuation of all study drugs due to AEs was reported in 7.6% of patients in the combination arm and 13.4% of patients in the sunitinib arm.[67] Discontinuation of all study drugs due to treatment-related AEs (TRAEs) was reported in [redacted] and [redacted] of patients in the combination and the sunitinib arms, respectively[68]
- Discontinuation of any study drug due to AEs was reported in [redacted] and [redacted] of patients in the combination and the sunitinib arms, respectively. Discontinuation of any study drug due to TRAEs was reported in [redacted] of patients in the combination arm and 8.0% of patients in the sunitinib arm.[68]

Table B.2.27. Summary of AEs (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population	JAVELIN Renal 101	
	Avelumab + axitinib (N=489)	Avelumab + axitinib (N=434)	Sunitinib (N=439)
TEAEs, n (%)	[redacted]	432 (99.5)	436 (99.3)
Grade ≥3	[redacted]	309 (71.2)	314 (71.5)
SAEs	[redacted]	[redacted]	[redacted]
AEs leading to death	[redacted]	[redacted]	[redacted]
Discontinuation of any study drug due to AEs	[redacted]	[redacted]	[redacted]
Discontinuation of all study drugs due to AEs	[redacted]	33 (7.6)	59 (13.4)
TRAEs, n (%)	[redacted]	414 (95.4)	423 (96.4)
Grade ≥3	[redacted]	246 (56.7)	243 (55.4)
SAEs	[redacted]	74 (17.1)	57 (13.0)
AEs leading to death	[redacted]	5 (1.2)	1 (0.2)
Discontinuation of any study drug due to AEs	[redacted]	[redacted]	[redacted]
Discontinuation of all study drug due to AEs	[redacted]	15 (3.5)	35 (8.0)

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; irAE = immune-related adverse event; IRR = infusion-related reactions; n = number of patients in the category; N = number of patients evaluable; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event

Source: Choueiri et al. 2019;[75] Motzer et al. 2019;[67] Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

As expected, based on the mechanism of action and the intravenous route of administration of avelumab, immune-related AEs (irAEs) were mostly reported in the combination arm (38.2% of patients [9.0% Grade ≥3], versus [redacted] [[redacted] Grade ≥3] in the sunitinib arm) and IRR was reported only in the combination arm (27.9% [1.6% Grade ≥3]; see Section B.2.10.3.6).[67, 68]

B.2.10.3.1 Commonly reported adverse events

The most frequent AEs (reported at any grade in ≥10% of patients or Grade ≥3 in ≥5% patients in either treatment arm) are shown in Table B.2.28.

In JAVELIN Renal 101, AEs were generally well balanced across treatment arms, with the exception of vascular disorders, which were more frequent in the combination arm ([redacted] and

[redacted] of patients for the combination and sunitinib arms, respectively), and appear to have been driven by hypertension. In the combination arm, a clinically relevant (>5%) higher frequency was reported for the following AEs:

- Diarrhoea, which is a known adverse drug reaction (ADR) for both avelumab and axitinib
- Hypertension, which is a known ADR for axitinib
- Dysphonia
- Hypothyroidism, which is a known ADR for both avelumab and axitinib
- Dyspnoea
- Arthralgia
- Weight decreased
- Alanine aminotransferase (ALT) increased, which is a known ADR for both avelumab and axitinib
- Chills
- Pruritus
- IRR.[68, 91]

In the sunitinib arm, a clinically relevant higher frequency was reported for nausea, dysgeusia, dyspepsia, anaemia, thrombocytopenia, platelet count decreased, neutropenia and neutrophil count decreased.[68]

Table B.2.28. Most common (any grade in ≥10% subjects or Grade ≥3 in ≥5% subjects in any treatment group) TEAEs (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population		JAVELIN Renal 101			
	Avelumab + axitinib (N=489)		Avelumab + axitinib (N=434)		Sunitinib (N=439)	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Diarrhoea	[redacted]	[redacted]	270 (62.2)	29 (6.7)	209 (47.6)	12 (2.7)
Hypertension	[redacted]	[redacted]	215 (49.5)	111 (25.6)	158 (36.0)	75 (17.1)
Fatigue	[redacted]	[redacted]	180 (41.5)	15 (3.5)	176 (40.1)	16 (3.6)
Nausea	[redacted]	[redacted]	148 (34.1)	6 (1.4)	172 (39.2)	7 (1.6)
PPE	[redacted]	[redacted]	145 (33.4)	25 (5.8)	148 (33.7)	19 (4.3)
Dysphonia	[redacted]	[redacted]	133 (30.6)	2 (0.5)	14 (3.2)	0 (0.0)
Decreased appetite	[redacted]	[redacted]	114 (26.3)	9 (2.1)	126 (28.7)	4 (0.9)
Hypothyroidism	[redacted]	[redacted]	108 (24.9)	1 (0.2)	61 (13.9)	1 (0.2)
Cough	[redacted]	[redacted]	100 (23.0)	1 (0.2)	83 (18.9)	0 (0.0)
Stomatitis	[redacted]	[redacted]	102 (23.5)	8 (1.8)	103 (23.5)	4 (0.9)
Headache	[redacted]	[redacted]	89 (20.5)	1 (0.2)	71 (16.2)	1 (0.2)
Arthralgia	[redacted]	[redacted]	85 (19.6)	4 (0.9)	50 (11.4)	2 (0.5)
Dyspnoea	[redacted]	[redacted]	86 (19.8)	13 (3.0)	57 (13.0)	7 (1.6)
Weight decreased	[redacted]	[redacted]	85 (19.6)	12 (2.8)	30 (6.8)	4 (0.9)
Constipation	[redacted]	[redacted]	77 (17.7)	0 (0.0)	64 (14.6)	0 (0.0)
Vomiting	[redacted]	[redacted]	80 (18.4)	4 (0.9)	87 (19.8)	7 (1.6)
ALT increased	[redacted]	[redacted]	74 (17.1)	26 (6.0)	50 (11.4)	11 (2.5)
Back pain	[redacted]	[redacted]	77 (17.7)	2 (0.5)	65 (14.8)	8 (1.8)
Rash	[redacted]	[redacted]	62 (14.3)	2 (0.5)	49 (11.2)	2 (0.5)
AST increased	[redacted]	[redacted]	63 (14.5)	17 (3.9)	52 (11.8)	9 (2.1)
Chills	[redacted]	[redacted]	69 (15.9)	1 (0.2)	33 (7.5)	0 (0.0)
Mucosal inflammation	[redacted]	[redacted]	61 (14.1)	5 (1.2)	61 (13.9)	5 (1.1)
Pruritus	[redacted]	[redacted]	61 (14.1)	0 (0.0)	22 (5.0)	0 (0.0)
Abdominal pain	[redacted]	[redacted]	59 (13.6)	5 (1.2)	43 (9.8)	8 (1.8)
Asthenia	[redacted]	[redacted]	64 (14.7)	11 (2.5)	72 (16.4)	13 (3.0)
Dysgeusia	[redacted]	[redacted]	57 (13.1)	0 (0.0)	142 (32.3)	0 (0.0)
IRR	[redacted]	[redacted]	53 (12.2)	7 (1.6)	0 (0.0)	0 (0.0)
Pyrexia	[redacted]	[redacted]	56 (12.9)	0 (0.0)	62 (14.1)	1 (0.2)
Dizziness	[redacted]	[redacted]	51 (11.8)	2 (0.5)	47 (10.7)	3 (0.7)
Pain in extremity	[redacted]	[redacted]	52 (12.0)	1 (0.2)	46 (10.5)	3 (0.7)
Myalgia	[redacted]	[redacted]	43 (9.9)	2 (0.5)	26 (5.9)	0 (0.0)
Oropharyngeal pain	[redacted]	[redacted]	44 (10.1)	0 (0.0)	27 (6.2)	0 (0.0)

Dry skin	[redacted]	[redacted]	43 (9.9)	0 (0.0)	44 (10.0)	0 (0.0)
Oedema peripheral	[redacted]	[redacted]	39 (9.0)	2 (0.5)	45 (10.3)	1 (0.2)
Epistaxis	[redacted]	[redacted]	37 (8.5)	0 (0.0)	49 (11.2)	0 (0.0)
Dyspepsia	[redacted]	[redacted]	35 (8.1)	0 (0.0)	83 (18.9)	0 (0.0)
Anaemia	[redacted]	[redacted]	26 (6.0)	7 (1.6)	101 (23.0)	36 (8.2)
Thrombocytopenia	[redacted]	[redacted]	15 (3.5)	1 (0.2)	85 (19.4)	27 (6.2)
Platelet count decreased	[redacted]	[redacted]	8 (1.8)	0 (0.0)	63 (14.4)	22 (5.0)
Neutropenia	[redacted]	[redacted]	6 (1.4)	1 (0.2)	83 (18.9)	35 (8.0)
Neutrophil count decreased	[redacted]	[redacted]	1 (0.2)	0 (0.0)	45 (10.3)	25 (5.7)

Abbreviations: ALT = alanine aminotransferase; aRCC = advanced renal cell carcinoma; AST = aspartate aminotransferase; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; PPE = palmar-plantar erythrodysaesthesia; SAS = safety analysis set; TEAE = treatment-emergent adverse event
Source: Motzer et al. 2019;[67] Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

The most frequent TRAEs (reported at any grade in ≥10% of patients or Grade ≥3 in ≥5% patients in either treatment arm) are shown in Table B.2.29

The profile of TRAEs was consistent with that of all-causality AEs. In addition to the events above, a clinically relevant higher frequency of treatment-related decreased appetite and vomiting was reported for the sunitinib arm in JAVELIN Renal 101.[68]

Table B.2.29. Most common (any grade in ≥10% subjects or Grade ≥3 in ≥5% subjects in any treatment group) TRAEs (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population		JAVELIN Renal 101			
	Avelumab + axitinib (N=489)		Avelumab + axitinib (N=434)		Sunitinib (N=439)	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Diarrhoea	[redacted]	[redacted]	235 (54.1)	22 (5.1)	196 (44.6)	11 (2.5)
Hypertension	[redacted]	[redacted]	208 (47.9)	106 (24.4)	142 (32.3)	67 (15.3)
Fatigue	[redacted]	[redacted]	156 (35.9)	13 (3.0)	159 (36.2)	16 (3.6)
PPE	[redacted]	[redacted]	144 (33.2)	25 (5.8)	148 (33.7)	19 (4.3)
Dysphonia	[redacted]	[redacted]	116 (26.7)	2 (0.5)	12 (2.7)	0 (0.0)
Hypothyroidism	[redacted]	[redacted]	105 (24.2)	1 (0.2)	59 (13.4)	1 (0.2)
Nausea	[redacted]	[redacted]	107 (24.7)	3 (0.7)	148 (33.7)	5 (1.1)
Stomatitis	[redacted]	[redacted]	96 (22.1)	8 (1.8)	100 (22.8)	4 (0.9)
Decreased appetite	[redacted]	[redacted]	86 (19.8)	7 (1.6)	115 (26.2)	4 (0.9)
ALT increased	[redacted]	[redacted]	57 (13.1)	21 (4.8)	43 (9.8)	9 (2.1)
Mucosal inflammation	[redacted]	[redacted]	58 (13.4)	5 (1.2)	60 (13.7)	4 (0.9)
Rash	[redacted]	[redacted]	54 (12.4)	2 (0.5)	42 (9.6)	2 (0.5)
Chills	[redacted]	[redacted]	62 (14.3)	1 (0.2)	16 (3.6)	0 (0.0)
AST increased	[redacted]	[redacted]	49 (11.3)	12 (2.8)	48 (10.9)	6 (1.4)
Dysgeusia	[redacted]	[redacted]	56 (12.9)	0 (0.0)	141 (32.1)	0 (0.0)
IRR	[redacted]	[redacted]	52 (12.0)	7 (1.6)	0 (0.0)	0 (0.0)
Arthralgia	[redacted]	[redacted]	52 (12.0)	1 (0.2)	24 (5.5)	0 (0.0)
Pruritus	[redacted]	[redacted]	53 (12.2)	0 (0.0)	19 (4.3)	0 (0.0)
Dyspnoea	[redacted]	[redacted]	53 (12.2)	6 (1.4)	24 (5.5)	1 (0.2)
Weight decreased	[redacted]	[redacted]	49 (11.3)	7 (1.6)	17 (3.9)	1 (0.2)
Vomiting	[redacted]	[redacted]	42 (9.7)	1 (0.2)	68 (15.5)	7 (1.6)
Asthenia	[redacted]	[redacted]	41 (9.4)	5 (1.2)	54 (12.3)	8 (1.8)
Dyspepsia	[redacted]	[redacted]	24 (5.5)	0 (0.0)	74 (16.9)	0 (0.0)
Thrombocytopenia	[redacted]	[redacted]	12 (2.8)	1 (0.2)	78 (17.8)	24 (5.5)
Anaemia	[redacted]	[redacted]	9 (2.1)	1 (0.2)	73 (16.6)	22 (5.0)
Platelet count decreased	[redacted]	[redacted]	7 (1.6)	0 (0.0)	61 (13.9)	22 (5.0)
Neutropenia	[redacted]	[redacted]	6 (1.4)	1 (0.2)	79 (18.0)	34 (7.7)
Neutrophil count decreased	[redacted]	[redacted]	1 (0.2)	0 (0.0)	44 (10.0)	25 (5.7)

Abbreviations: ALT = alanine aminotransferase; aRCC = advanced renal cell carcinoma; AST = aspartate aminotransferase; IRR = infusion-related reaction; n = number of patients in the category; N = number of patients evaluable; PPE = palmar-plantar erythrodysaesthesia; SAS = safety analysis set; TRAE = treatment-related adverse event
Source: Motzer et al. 2019;[67] Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

B.2.10.3.2 Serious adverse events

A summary of SAEs is shown in Table B.2.30. In JAVELIN Renal 101, more patients in the avelumab + axitinib arm reported SAEs compared with the sunitinib arm ([redacted] and [redacted] of patients, respectively; Table B.2.27).[68] The frequency of SAEs was also slightly higher in the pooled aRCC population compared with the sunitinib arm of JAVELIN Renal 101 (Table B.2.27); however, the frequency of patients with Grade ≥3 SAEs was similar.[91]

Table B.2.30. Most common (any grade in ≥2% subjects or Grade ≥3 in ≥2% subjects in any treatment group) SAEs (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population		JAVELIN Renal 101			
	Avelumab + axitinib (N=489)		Avelumab + axitinib (N=434)		Sunitinib (N=439)	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: aRCC = advanced renal cell carcinoma; n = number of patients in the category; N = number of patients evaluable; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event
Source: Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

For treatment-related SAEs, the difference between treatments was less evident, with [redacted] of patients in the combination arm and [redacted] of patients in the sunitinib arm reporting treatment-related SAEs in JAVELIN Renal 101, and 17.8% in the pooled aRCC population (Table B.2.27). No treatment-related SAEs occurred in ≥2% of patients in either treatment arm of JAVELIN Renal 101. The largest difference between treatment arms was reported for hepatobiliary disorders ([redacted] of patients in the combination arm and [redacted] in the sunitinib arm.[68]

B.2.10.3.3 Deaths

A summary of deaths is shown in Table B.2.31. As of the data cut-off date (20 June 2018), [redacted] of patients in the avelumab + axitinib arm of JAVELIN Renal 101 and [redacted] of patients in the sunitinib arm had died. The most common cause of death was disease progression for both the combination ([redacted]) and sunitinib ([redacted]) arms.[68]

During the on-treatment period the frequency of fatal AEs was similar in the combination and the sunitinib arms of JAVELIN Renal 101, as well as the pooled aRCC population, for both all-cause and treatment-related events. Fatal AEs other than disease progression were predominantly of cardiovascular nature for both avelumab + axitinib and sunitinib, consistent with the safety profiles of axitinib and sunitinib.[68, 91]

Table B.2.31. Summary of deaths (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population	JAVELIN Renal 101	
	Avelumab + axitinib (N=489)	Avelumab + axitinib (N=434)	Sunitinib (N=439)
Deaths, n (%)	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Study treatment toxicity	[redacted]	3 (0.7)	1 (0.2)
AE not related to study treatment	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
TEAEs leading to death, n (%)	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]	[redacted]
Malignant neoplasm progression	[redacted]	[redacted]	[redacted]
Neoplasm progression	[redacted]	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]	[redacted]
Cardiopulmonary failure	[redacted]	[redacted]	[redacted]
Renal cancer	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]
Ileus	[redacted]	[redacted]	[redacted]
Intestinal perforation	[redacted]	[redacted]	[redacted]
TRAEs leading to death, n (%)	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]	[redacted]
Intestinal perforation	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; n = number of patients in the category; N = number of patients evaluable; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event
Source: Motzer et al. 2019;[67] Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

Among the TRAEs leading to death (other than disease progression) in the pooled aRCC population, there were two cases of myocarditis, which is a known ADR for avelumab and other checkpoint inhibitors. In the sunitinib arm of JAVELIN Renal 101, the only TRAE leading to death was intestinal perforation in 1 patient (0.2%).[67]

B.2.10.3.4 Adverse events associated with treatment discontinuation

A summary of AEs associated with permanent discontinuation is shown in Table B.2.32. In JAVELIN Renal 101, patients in the combination arm received two study drugs which could be discontinued independently of each other, while patients in the sunitinib arm received only one study drug. As such, permanent discontinuations of all study drugs were higher in the sunitinib arm (13.4%) compared with the combination arm (7.6%).[67] Conversely, AEs leading to permanent discontinuations of any study drug were higher in the avelumab + axitinib arm ([redacted]) compared with the sunitinib arm (13.4%).[68]

Table B.2.32. AEs associated with permanent discontinuation of study treatment (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population	JAVELIN Renal 101	
	Avelumab + axitinib (N=489)	Avelumab + axitinib (N=434)	Sunitinib (N=439)
TEAEs, n (%)			
Discontinuation of any study drug	[redacted]	[redacted]	[redacted]
Discontinuation of all study drugs	[redacted]	33 (7.6)	59 (13.4)
Discontinuation of avelumab	[redacted]	[redacted]	N/A
Discontinuation of axitinib	[redacted]	[redacted]	N/A
Discontinuation of sunitinib	[redacted]	N/A	[redacted]
TRAEs, n (%)			
Discontinuation of any study drug	[redacted]	[redacted]	[redacted]
Discontinuation of all study drugs	[redacted]	15 (3.5)	35 (8.0)
Discontinuation of avelumab	[redacted]	[redacted]	N/A
Discontinuation of axitinib	[redacted]	[redacted]	N/A
Discontinuation of sunitinib	[redacted]	N/A	[redacted]

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; n = number of patients in the category; N = number of patients evaluable; N/A = not applicable; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event
Source: Choueiri et al. 2019;[75] Motzer et al. 2019;[67] Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

In the pooled aRCC population, the most frequent AEs leading to discontinuation of avelumab were alanine aminotransferase (ALT) increased ([redacted]) and aspartate aminotransferase (AST) increased ([redacted]). [redacted] AEs leading to discontinuation of axitinib or sunitinib were reported in ≥2% of patients.[91]

B.2.10.3.5 Adverse events associated with dose modification

A summary of AEs associated with dose reduction or treatment interruption is shown in Table B.2.33.

Table B.2.33. AEs associated with dose reduction or treatment interruption (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population	JAVELIN Renal 101	
	Avelumab + axitinib (N=489)	Avelumab + axitinib (n=434)	Sunitinib (n=439)
TEAEs leading to dose reduction, n (%)			
Avelumab	[redacted]	[redacted]	N/A
Axitinib	[redacted]	[redacted]	N/A
Sunitinib	N/A	N/A	[redacted]
TEAEs leading to interruption, n (%)			
Avelumab	[redacted]	[redacted]	N/A
Axitinib	[redacted]	[redacted]	N/A
Sunitinib	N/A	N/A	[redacted]
TEAEs leading to interruption and dose reduction, n (%)			
Avelumab	[redacted]	[redacted]	N/A
Axitinib	[redacted]	[redacted]	N/A
Sunitinib	N/A	N/A	[redacted]

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; n = number of patients in the category; N = number of patients evaluable; N/A = not applicable; SAS = safety analysis set; TEAE = treatment-emergent adverse event
Source: Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

While avelumab dose reductions were not permitted in JAVELIN Renal 101, a dose reduction was reported for one patient ([redacted]) following Grade 1 hypersensitivity. However, in this case the recording of a dose reduction reflected that the infusion was not completed as planned. In the pooled aRCC population, the most frequent AEs leading to interruption of avelumab (≥2% of patients) were [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted] each). No patient had a AE leading to both interruption and dose reduction of avelumab.[91]

In the pooled aRCC population, the most frequent reported AEs leading to interruption of axitinib (≥2% of patients) were [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]. The most common AEs leading to dose reduction of axitinib were [redacted] and [redacted]. The most frequent AE leading to both interruption and dose reduction of axitinib was [redacted].[91]

In the sunitinib arm of JAVELIN Renal 1010, the most frequent AEs leading to interruption of sunitinib (≥2% of patients) were [redacted], [redacted], [redacted], [redacted], [redacted]; [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted]. The most common AEs leading to dose reduction of sunitinib were [redacted], [redacted], [redacted], and [redacted]. The most frequent AE leading to both interruption and dose reduction of sunitinib was [redacted].[91]

B.2.10.3.6 Adverse events of special interest

Adverse events of special interest (AESIs) were defined as irAEs and infusion-related reactions. The definition of infusion-related reactions included the Preferred Terms in the Medical Dictionary for Regulatory Activities 'IRRs SIGNS and SYMPTOMS' (when the AE onset date was the day of the infusion, the timing was during or after the infusion and the AE resolved within 2 days of infusion) and 'IRRs CORE' (when the AE onset date was the day of

the infusion and the timing was during or after the infusion, or the onset date was the day after the infusion) lists.

B.2.10.3.6.1 Immune-related adverse events

A summary of irAEs is shown in Table B.2.34. As expected based on avelumab's mechanism of action, irAEs were more frequent in the combination arm of JAVELIN Renal 101 compared with the sunitinib arm (38.2% of patients and [redacted], respectively).[67, 68]

In the pooled aRCC population, the most frequent irAEs (≥2% of patients) of any grade were [redacted], [redacted], [redacted], [redacted], [redacted]. The most frequent Grade ≥3 irAEs (≥1% of patients) were [redacted] and [redacted]. There were three fatal irAEs in the avelumab + axitinib arm: [redacted] and [redacted], with the latter occurring after the treatment period.[91]

In the sunitinib arm of JAVELIN Renal 101, the only irAEs were [redacted] and [redacted] clusters. There was only one Grade 3 event ([redacted]) and [redacted] Grade 4 or 5 events.[68]

Table B.2.34. Summary of irAEs by cluster (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population		JAVELIN Renal 101			
	Avelumab + axitinib (N=489)		Avelumab + axitinib (N=434)		Sunitinib (N=439)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
irAEs, n(%)	[redacted]	[redacted]	166 (38.2)	39 (9.0)	[redacted]	[redacted]
Immune-related endocrinopathies: thyroid disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related endocrinopathies: adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related endocrinopathies: type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other immune-related adverse events: myocarditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related nephritis and renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other immune-related adverse events: pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-related endocrinopathies: pituitary dysfunction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: aRCC = advanced renal cell carcinoma; irAE = immune-related adverse event; n = number of patients in the category; N = number of patients evaluable; SAS = safety analysis set
Source: Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

B.2.10.3.6.2 Infusion-related reactions

A summary of infusion-related reactions in the pooled aRCC population and avelumab + axitinib arm of JAVELIN Renal 101 is shown in Table B.2.35. The infusion-related reaction profile in the pooled aRCC population was generally consistent with that previously reported for avelumab monotherapy. The majority of infusion-related reactions were Grade 1 or 2 in severity ([redacted]), and most occurred for the first time within the first two infusions. Grade 3 infusion-related reactions were reported in [redacted] and there were [redacted] Grade 4 or Grade 5 infusion-related reactions.[91]

Table B.2.35. Summary of infusion-related reactions in patients receiving avelumab + axitinib (Pooled aRCC population; JAVELIN Renal 101 SAS)

Event	Pooled aRCC population (N=489)		JAVELIN Renal 101 (N=434)	
	All grades	Grade ≥3	All grades	Grade ≥3
Infusion-related reactions, n (%)	[redacted]	[redacted]	121 (27.9)	7 (1.6)
IRR	[redacted]	[redacted]	52 (12.0)	6 (1.4)
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; aRCC = advanced renal cell carcinoma; n = number of patients in the category; N = number of patients evaluable; N/A = not applicable; SAS = safety analysis set; TEAE = treatment-emergent adverse event
Source: Motzer et al. 2019;[67] Pfizer Inc. 2018;[68] Pfizer Inc., 2018[91]

B.2.10.3.7 Other significant adverse events

Cardiovascular events have been reported in patients treated with VEGFR TKIs, such as axitinib and sunitinib, and myocarditis has been reported with avelumab and other immune checkpoint inhibitors. In JAVELIN Renal 101, cardiac AEs were reported for [redacted] of patients in the combination arm and [redacted] of patients in the sunitinib arm, with [redacted], [redacted], [redacted], [redacted] and [redacted] reported in [redacted] of patients in the avelumab + axitinib arm.[68]

Grade 3 cardiac AEs reported by ≥1 patient in either treatment arm were [redacted] and [redacted]. Grade 3 [redacted] was reported in [redacted] in the combination arm (assessed as treatment-related) and [redacted] patients in the sunitinib arm. There were [redacted] Grade 4 cardiac AEs that were reported in more than one patient in either treatment arm, but [redacted] in the combination arm ([redacted]) and [redacted] in the sunitinib arm ([redacted]), neither of which were assessed as treatment-related) with a Grade 5 cardiac AE. Immune-mediated myocarditis is a known ADR for avelumab, [redacted][68]

B.2.10.4 Safety conclusions

In the JAVELIN Renal 101 study, avelumab + axitinib for the first-line treatment of aRCC was generally well tolerated. AEs were typically manageable and were consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies. While no new safety concerns were identified for the combination beyond those already described for each individual agent, the following AEs were reported at higher frequencies than observed with the single agents:

- Diarrhoea, a known ADR for both avelumab and axitinib, was reported at a higher frequency for the combination treatment than each agent as monotherapy
- Hypertension, a known ADR for axitinib, was reported at a higher frequency for Grade ≥3 in the combination treatment compared with axitinib alone. However, this may have been due to more stringent criteria than those used for axitinib monotherapy studies
- Hypothyroidism, a known ADR for both avelumab and axitinib, was reported at a higher frequency for the combination treatment than that of each agent as monotherapy
- ALT increased, a known ADR for both avelumab and axitinib, was reported at a higher frequency for the combination treatment than each agent as monotherapy. The frequency of Grade ≥3 events was also higher for the combination treatment, compared with the single agents.[91]

B.2.11 Ongoing studies

Other than JAVELIN Renal 100 and JAVELIN Renal 101, there are currently no ongoing studies of avelumab + axitinib for the treatment of aRCC.

B.2.12 Innovation

Prior to the relatively recent development of targeted therapies, immunotherapy with interleukins and interferons was the only systemic therapy indicated for aRCC. Targeted therapies were first approved in 2005, and the treatment landscape has since become dominated by TKI monotherapies. RCC, like many other tumour types, is characterised by complex interactions between the host immune response and a variety of immune pathways.[92] As such, the current treatment landscape is shifting to include the use of IO agents, either as monotherapy or in combination with other agents.[93]

Avelumab + axitinib is a novel and innovative treatment approach in aRCC, as demonstrated by the designation of Promising Innovative Medicine status in January 2019 and EAMS scientific opinion in July 2019. The combination builds on the established efficacy of TKI monotherapy through the addition of an IO agent targeting the PD-1/PD-L1 checkpoint pathway. This TKI/IO combination is currently unique in aRCC, and will be the only combination therapy indicated for use across all risk groups. Inhibition of the PD-1/PD-L1 interaction by avelumab releases the inhibitory effects of PD-L1, leading to restoration of the anti-tumour immune response, which is complemented by the immune-supportive tumour environment created through blockade of VEGFR by axitinib. As well as its role in promoting angiogenesis, VEGF has a diverse range of effects on the immune system, including tumour-induced immunosuppression.[94] Inhibition of VEGFR by TKIs such as axitinib has been shown to promote an immune-stimulatory tumour microenvironment through increased

T-cell infiltration, reduced accumulation and activity of immune suppressor cells, and a reduction in inflammatory signalling.[27-29]

Through their complementary mechanisms of action,[21, 22] the combination of avelumab and axitinib has the potential to achieve rapid and high rates of responses, combined with durable responses, as demonstrated by preliminary data from JAVELIN Renal 101.[68, 69] Avelumab + axitinib therefore provides clinicians and patients in England and Wales with a step-changing treatment option, which offers the opportunity to significantly delay disease progression for patients across all risk groups.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Interim findings from the clinical evidence

In the UK, current first-line treatment options for aRCC are limited to the VEGFR TKIs sunitinib, pazopanib, tivozanib and cabozantinib (the latter in patients with intermediate- or poor-risk status only). Outcomes with TKI monotherapy are modest, with response rates of 12–33% and median PFS of 5.6–12.7 months.[17-20] Although the IO combination of nivolumab and ipilimumab has demonstrated improved objective response compared with sunitinib, the median PFS remained below 13 months,[95] and this combination is restricted to use in patients in the poor- and intermediate-risk groups only.[96] Therefore, despite the improvements since the introduction of targeted therapies, current first-line monotherapies often fail to achieve sustained therapeutic responses, outcomes for patients with aRCC remain poor, and there remains a clear unmet need for a treatment with improved response rates and survival outcomes.

At the time of IA1, avelumab + axitinib demonstrated a statistically significant and clinically meaningful improvement in PFS compared with sunitinib, in patients with aRCC irrespective of PD-L1 expression status (median PFS of in 13.8 months in the combination arm, compared with 8.4 months in the sunitinib arm; HR: 0.69; one-sided p=0.0001). As with PD–L1 expression status, the improvement in PFS was observed across all risk groups (according to IMDC criteria).[67, 68]

In addition to the PFS benefit, the objective response for avelumab + axitinib was doubled compared with sunitinib in patients irrespective of PD-L1 expression (51.4% and 25.7% in the combination and sunitinib arms, respectively; OR: 3.10) and responses had an earlier onset (median TTR of 2.6 months and 3.2 months in the combination and sunitinib arms, respectively). The proportion of patients with a CR was also higher in the combination arm than in the sunitinib arm (3.4% and 1.8%, respectively). Although the median DoR for patients who responded was not reached for both treatment arms, for patients irrespective of PD-L1 expression status, the probability of being event-free at 12 months was [redacted] (95% CI: [redacted], [redacted]) and [redacted] (95% CI: [redacted], [redacted]) in the combination and sunitinib arms, respectively.[67, 68]

Although OS data were immature at the time of IA1 (25.8% of the 535 deaths required for the final OS analyses), a trend in favour of avelumab + axitinib was observed among patients irrespective of PD-L1 status (HR: 0.78 [95% CI: 0.55, 1.08]).[68] With longer follow-up in the Phase 1b JAVELIN Renal 100 ([redacted], compared with 12 months in JAVELIN Renal 101),[68, 70] median OS for patients treated with avelumab + axitinib was [redacted]. The

probability of survival at 18 and 24 months was [redacted] (95% CI: [redacted], [redacted]) and [redacted], (95% CI: [redacted], [redacted]) respectively.[70]

Regardless of the immaturity of OS data, the potential for durable responses and long-term survival following treatment with IOs (including avelumab) has previously been established,[71-74] and is supported by the immunogenic nature of RCC.[92] A long-term survival plateau following IO therapy was first observed in patients with melanoma treated with ipilimumab; in a pooled analysis of 1,861 patients across 12 studies, the survival curve began to plateau at 3 years and extended up to 10 years in some patients.[73] For avelumab, an early objective response in patients with metastatic MCC was associated with improved OS in the Phase 2 EMR 100070-003 (JAVELIN Merkel 200; NCT02155647) study; patients with an objective response by 7 or 13 weeks had significantly longer OS than patients without (90% of these patients were still alive 18 months after treatment initiation, compared with 20–26% of patients without response at weeks 7 and 13).[71] [redacted].[72] In RCC, nivolumab monotherapy has demonstrated 3- and 5-year OS rates of 41% and 34%, respectively. [97] Therefore, patients who achieve a durable response to avelumab + axitinib have the potential to achieve extended survival without the need for further systemic therapies, thereby avoiding AEs of further treatment and the associated impact on QoL. In addition, approximately 50% of patients with metastatic RCC receive a second-line therapy, highlighting the importance of a durable response to first-line therapies.[65]

Avelumab + axitinib was generally well tolerated, and TEAEs (including Grade 3–4 TEAEs and TRAEs) were reported with similar incidence in each treatment arm (99.5% and 99.3% of patients in the combination and sunitinib arms, respectively). Grade ≥3 TEAEs were reported in 71.2% and 71.5% of patients in the combination and sunitinib arms, respectively, and TRAEs were reported in 95.4% and 96.4% of patients in the combination and sunitinib arms, respectively. Of the TRAEs, 56.7% in the combination arm were Grade ≥3, compared with 55.4% in the sunitinib arm.[67] Diarrhoea, hypertension, hypothyroidism and alanine aminotransferase increased were reported at higher frequencies than observed with the single agents; however, these are all known adverse drug reactions for avelumab, axitinib or both.[91] Overall, avelumab + axitinib for the first-line treatment of aRCC was generally well tolerated, and adverse events were typically manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies. No new safety concerns were identified for the combination beyond those already described for each individual agent.[68]

B.2.13.2 Strengths and limitations of the clinical evidence base

Overall, clinical data for avelumab + axitinib provide an appropriate evidence base for assessment of its clinical and cost-effectiveness for the treatment of aRCC. The strengths of the clinical evidence base are:

- JAVELIN Renal 101 is a robust, multicentre RCT which randomised 886 patients with previously untreated aRCC across all risk groups

- The safety and efficacy of avelumab + axitinib was assessed in comparison to that of sunitinib, a current standard of care in the UK and NICE-recommended first-line treatment option
- The trial included six sites in the UK and enrolled patients representative of those who would receive avelumab + axitinib in routine clinical practice in the UK. Therefore, it is expected that the reported benefits of avelumab + axitinib are likely to be reflected in clinical practice in England and Wales
- JAVELIN Renal 101 assessed the primary outcomes of PFS and OS, which are widely regarded as appropriate endpoints to assess the efficacy of anti-cancer therapies
    - The primary outcome of PFS in patients with PD-L1-positive tumours was met, with a significant and clinically meaningful improvement in PFS
    - Multiple sensitivity analyses of PFS endpoint were consistent with the primary analysis, demonstrating the robustness of the clinical benefit of avelumab + axitinib
    - Although OS data were immature at the time of IA1, there was a trend in favour of the combination arm
- A gatekeeping procedure was used to allow further testing of PFS and OS in patients irrespective of PD-L1 expression. According to the statistical analysis plan, if PFS was statistically significant in the PD-L1-positive group, PFS in the entire study population was to be analysed for statistical significance
    - As with patients with PD-L1-positive tumours, treatment with avelumab + axitinib demonstrated a significant and clinically meaningful improvement in PFS among patients irrespective of PD-L1 expression status
    - Multiple sensitivity analyses of PFS endpoint were consistent with the main analysis, demonstrating the robustness of the clinical benefit of avelumab + axitinib
    - OS data in patients among patients irrespective of PD-L1 expression status were also immature. However, as with patients with PD-L1-positive tumours, a trend in favour of avelumab + axitinib was observed
- Importantly, avelumab + axitinib demonstrated efficacy across all risk groups
- The secondary efficacy endpoints of objective response, TTR, DoR and PFS2 are relevant to routine clinical practice and analyses supported the outcome of the primary efficacy analysis
- The study also included an assessment of HRQoL, as measured by the generic EQ-5D-5L instrument, and the disease-specific FKSI-19 and FKSI-DRS instruments
- In the first-line aRCC population (equivalent to the JAVELIN Renal 101 ITT population), ITC and stratified analysis demonstrated that avelumab + axitinib was associated with higher rates of PFS and OS at each time point against all comparators (see Sections B.3.3.2 and B.3.3.3)
- In the IMDC intermediate- or poor-risk population, avelumab + axitinib demonstrated a longer-term PFS and OS benefit compared with cabozantinib by ITC, with cabozantinib offering higher PFS and OS in the short-term (see Sections B.3.3.2 and B.3.3.3)

The limitations of the clinical evidence base include:

- Due to the different routes of administration (IV for avelumab; orally for axitinib and sunitinib), JAVELIN Renal 101 was an open-label study. However, BICR was used to minimise bias (including expedited BICR review was for investigator-assessed disease

progression). All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory

- OS data are currently immature. However, JAVELIN Renal 101 is ongoing and further OS data will be collected (third IA and final analysis expected in April 2020 and July 2023, respectively). In the meantime, PFS2 results in JAVELIN Renal 101 demonstrated a benefit in favour of avelumab + axitinib in a clinically meaningful endpoint, which may be a prognostic-factor of long-term survival[81, 82]

B.2.13.3 End-of-life criteria

In pivotal trials of the current NICE-recommended first-line monotherapies for aRCC (sunitinib, pazopanib, tivozanib, and cabozantinib), median OS ranged from 21.8 to 30.3 months.[17-20, 84, 98] As such, avelumab + axitinib does not meet the criteria for consideration as a life-extending treatment at the end of life for patients with aRCC with favourable- to poor-risk status.

B.3. Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted on 4 June 2019 to identify economic evaluations of avelumab + axitinib in aRCC (see Appendix D). No such studies were identified. The SLR did, however, identify a number of previous NICE technology appraisals (TAs) of first-line therapies for aRCC, including: NICE TA581 (nivolumab + ipilimumab)[57], NICE TA169 (sunitinib)[14], NICE TA542 (cabozantinib)[15], NICE TA215 (pazopanib)[13], and NICE TA512 (tivozanib).[12] These models helped to inform the methodology and inputs of the economic evaluation of avelumab + axitinib in first-line aRCC. A summary of the model characteristics of previous NICE TAs is shown in Table B.3.1.

Table B.3.1. Previous NICE TAs for first-line aRCC therapies

Characteristic	Appraisal				
	TA581 (nivolumab + ipilimumab)	**TA169 (sunitinib)**	**TA542 (cabozantinib)**	**TA215 (pazopanib)**	**TA512 (tivozanib)**
Year	2018	2009	2018	2010	2017
Appraisal	Nivolumab + ipilimumab for untreated aRCC	Sunitinib for the first-line treatment of advanced and/or metastatic RCC	Cabozantinib for untreated aRCC	Pazopanib for the first-line treatment of aRCC	Tivozanib for treating aRCC
Model methodology	Cost-utility, partitioned survival model	Cost-utility, partitioned survival model	Cost-utility, partitioned survival model	Cost-utility, partitioned survival model	Cost-utility, partitioned survival model
Population	1L aRCC (IMDC intermediate- or poor-risk)	1L aRCC	1L aRCC (IMDC intermediate- or poor-risk)	1L aRCC	1L aRCC
Time horizon	40 years	10 years	20 years	10 years	10 years
Extrapolation of treatment effectiveness	Parametric survival model based on CheckMate 214 study, with a curative IO therapy survival effect for some patients with durable response	Parametric survival model of bevacizumab plus IFN versus IFN RCT, with HR for sunitinib applied from sunitinib versus IFN RCT	Parametric survival model based on CABOSUN study, comparing cabozantinib with sunitinib. ITC used for cabozantinib versus pazopanib	Parametric survival model based on an RCT in which patients crossed-over from placebo to pazopanib (adjustments made for cross-over effect). Comparison with sunitinib made by ITC	Parametric survival model based on TIVO-1 study comparing tivozanib with sunitinib. ITC used for pazopanib and IFN
Source of utilities	EQ-5D-3L data from CheckMate 214; UK valuation tariff	Estimated from EQ-5D-3L data from Phase 2 and 3 sunitinib trials; UK valuation tariff	Published literature	Progression-free state: EQ-5D-3L data from pazopanib RCT; UK valuation tariff. Post-progression state: published literature	EQ-5D-3L data from TIVO-1
Source of costs	Based on UK reference costs, literature, and expert opinion	Based on UK reference costs, literature, and expert opinion	Based on UK reference costs, literature, and expert opinion	Based on UK reference costs, literature, and expert opinion	Based on UK reference costs, literature, and expert opinion

Abbreviations: 1L = first-line; aRCC = advanced renal cell carcinoma; EQ-5D-3L = EuroQol 5-Dimension 3-Level; HR = hazard ratio; IFN = interferon; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immune-oncology; ITC = indirect-treatment comparison; RCC = renal cell carcinoma; RCT = randomised controlled trial; TA = technology appraisal; UK = United Kingdom

B.3.2 Economic analysis

B.3.2.1 Patient population

As described in Section B.1.2, the anticipated marketing authorisation for avelumab + axitinib is for the first-line treatment of adult patients with aRCC across all risk groups (comprising stage III–IV disease). The economic analysis focuses on clinical outcomes for these patients, which aligns with the NICE Final scope and the JAVELIN Renal 101 ITT population. A subgroup analysis of first-line aRCC with IMDC intermediate- or poor- risk status was considered for comparisons with cabozantinib, as this aligns with the population considered in the NICE TA of cabozantinib in first-line aRCC (TA542).[15]

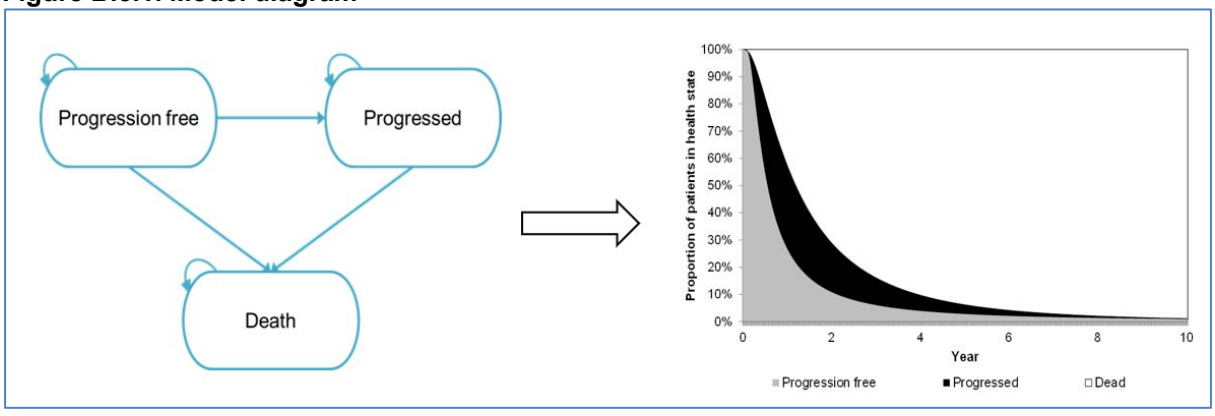
B.3.2.2 Model structure

In line with the approaches in previous NICE TAs in aRCC (nivolumab + ipilimumab [TA581][57], cabozantinib [TA542][15], pazopanib [TA215[13]] and tivozanib [TA512][12], the cost-effectiveness model was developed in Microsoft Excel® using an area under the curve (partitioned survival analysis) structure.

The model structure (Figure B.3.1) has three health states: progression-free survival (PFS), progressed disease (PPS) and death. All patients enter the model in PFS state and are at risk of progression. Death can occur in either the PFS or progressed disease health states, and Death is an 'absorbing state'. The occupancy in the PFS state is calculated as the area under the progression-free survival (PFS) curve, while the progressed disease state is calculated as the area between the overall survival (OS) curve and the PFS curve, and Death is calculated as 1-OS. The progression-free health state was designed to capture the relatively higher quality of life while the disease is controlled prior to progression, as patients are benefitting from an active treatment. The progressed disease state was designed to capture the relatively poor quality of life following disease progression. The model therefore captures the changes in quality of life between the progression-free and progressed disease states.

The model structure is fully aligned with two of the key objectives of treatment in aRCC; specifically, delaying disease progression and prolonging life. This structure is considered appropriate for capturing the health effects and complexities of natural history/disease progression in aRCC and aligns with the efficacy outcomes of JAVELIN Renal 101.

Figure B.3.1. Model diagram



The analysis used a lifetime time horizon, with a maximum time horizon of 40 years. This aligns with the most recent NICE TA in aRCC,[57] and enabled the long-term effects of treatment of IO therapies in some patients to be captured. A cycle length of 7 days (1 week) was applied – this was sufficiently short to accurately capture key clinical outcomes and dosing regimens of avelumab + axitinib and its comparators. Given the short cycle length, a half-cycle correction was not applied to costs or health outcomes. A summary of the key components of the analysis is presented in Table B.3.2.

Table B.3.2. Summary and justification of model structure

Factor	Chosen method	Justification
Model type	Partitioned survival analysis	Aligns with prior NICE submissions[12, 13, 15, 57, 58] Considered most appropriate to reflect chronic nature of disease and care pathway of aRCC
Health states	PFS, PPS, death	Aligns with prior NICE submissions[12, 13, 15, 57, 58]
Time horizon	Lifetime (40 years)	Considered most appropriate to fully capture the potential long-term outcomes associated with treatment
Cycle length	7 days	Considered appropriate length of time to best capture the dosing regimens of the intervention and comparator therapies
Half-cycle correction	No	Cycle length too short to justify use of half-cycle correction
Are health effects measured in QALYs?	Yes	NICE Guide to the Methods of Technology Appraisals, 2013[99]
Costs, LYs and QALYs included as outcomes	Yes	
Discount of 3.5% for utilities and costs	Yes	
Perspective	NHS/PSS	

Abbreviations: ITC = indirect treatment comparison; LY = life years; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PFS = progression-free survival; PPS = post-progression survival; PSS = personal social services; QALY = quality-adjusted life year

B.3.2.3 Intervention technology and comparators

In line with the proposed licensed indication, the intervention investigated in the analysis was a flat IV dose of 800 mg avelumab Q2W + 5 mg axitinib orally BD. A scenario was included in which patients received a 10 mg/kg dose of avelumab Q2W and 5 mg axitinib BD, consistent with the avelumab dose in JAVELIN Renal 101. The duration of therapy was based on stratified time on treatment (ToT) data from JAVELIN Renal 101 (see Section B.3.3.4).

A list of comparators in the analysis, and their dosing schedules, is provided in Table B.3.3. All comparators are part of the current clinical pathway for first-line aRCC. Sunitinib, tivozanib and pazopanib are the relevant comparators in the first-line aRCC (ITT) population, which is the primary and broadest population considered in the analysis and aligns with both the proposed indication for avelumab + axitinib (first-line treatment of adult patients [comprising stage III–IV disease]), and the JAVELIN Renal 101 ITT population.[25] Cabozantinib was not included as a comparator in the ITT population, as it is indicated for use only in patients with IMDC intermediate- or poor-risk status.[100] Therefore, we provide a

subgroup analysis of patients with intermediate- or poor-risk status, with cabozantinib being the only comparator.

Table B.3.3. Comparator treatments and dosing details

Comparator	Dosing	Relevant population	Reference
Sunitinib	50mg orally OD for 4 consecutive weeks followed by a 2-week off-treatment period (Schedule 4/2).	1L aRCC patients (used in NMA as a reference curve for all populations)	JAVELIN Renal 101[67]
Tivozanib	1.34 mg OD for 21 days followed by a 7-day rest period	1L aRCC patients	Fotivda® SmPC[101]
Pazopanib	800 mg daily	1L aRCC patients	Votrient SmPC[102]
Cabozantinib	60 mg OD	1L aRCC patients with IMDC intermediate- or poor-risk status	Cabometyx® SmPC[100]

Abbreviations: 1L = first-line; aRCC = advanced renal cell carcinoma; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; mg = milligram; OD = once daily; NMA = network meta-analysis; SmPC = summary of product characteristics

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data in the model

The primary data source for the model was JAVELIN Renal 101, which directly compared avelumab + axitinib with sunitinib in patients with untreated aRCC (see Section B.2.3). In the absence of direct evidence, an ITC was required to allow comparison with tivozanib in the ITT population, and with cabozantinib in the subgroup of patients with IMDC intermediate- or poor- risk status (see Section B.2.9). Pazopanib was assumed equivalent to sunitinib following previous NICE committee conclusions and clinical feedback, which indicated that these treatments have the same effectiveness in a real-world setting.[57]

The PFS and OS curves in JAVELIN Renal 101 were estimated using the KM method. PFS data reflected the assessment by BICR in the base-case analysis given that PFS by BICR was the primary outcome of JAVELIN Renal 101.[68]

Extrapolations for time-to-event data (PFS, OS and TTD) were assessed using standard parametric curves (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) as recommended by the NICE Decision Support Unit (DSU).[103] An additional curve (generalised F) was also explored for fitting PFS data, based on health economic expert recommendations (see Section B.3.10.2) to broaden the scope of approaches to be investigated. Experts suggested that the fourth covariate of the generalised F would allow modelling of the long-term shape of the survival curve, an aspect not captured by standard parametric survival models. The model selection process included testing model fit and plausibility, according to the following NICE DSU guidance:[104]

- Goodness-of-fit measures (AIC and BIC) – the lower the AIC or BIC, the better the model fit to the observed data. A nominal difference of ≥5 in AIC and/or BIC is considered to imply a meaningful difference between the fit of the parametric survival models and the observed data
- Visual inspection – the fitted survival curves were overlaid on KM data to assess how closely the curves matched the observed data

- Clinical validation – clinical experts were asked in advisory boards and one-to-one meetings for their opinions on the expected outcomes based on real-world clinical practice

Whilst goodness-of-fit measures to the observed data and visual inspection were taken into account when selecting the most appropriate parametric survival model, clinical validation was particularly influential due to the anticipated long-term benefit of IO therapies. IO therapies have been shown to have a long-term durable treatment effect – for example, 42% of first-line aRCC patients treated with nivolumab + ipilimumab are responders at 30 months,[105] while 86% of melanoma patients were progression-free 20.3 months after completing 2 years of pembrolizumab treatment.[106] Given that the median follow-up time for JAVELIN Renal 101 data presented in B.2.6.1 is ≤12 months, it is reasonable to assume that the JAVELIN Renal 101 data are not mature enough to sufficiently predict long-term outcomes with avelumab + axitinib. Therefore, expert clinical opinion was influential when determining the most plausible parametric survival models for long-term treatment outcomes.

The parametric survival options for PFS and OS selected in the base-case analysis are summarised below in Table B.3.4 and further detailed in Section B.3.3.2 and Section B.3.3.3.

Table B.3.4 Summary of selected of parametric survival options for PFS and OS in the base-case and subgroup analyses

Comparator	Parametric survival model selected in the base case	Population	Assumption
Avelumab + axitinib	Stratified survival curves from JAVELIN Renal 101 for PFS and OS	ITT	Using stratified survival curves of JAVELIN Renal 101 data does not require the assumption of proportional hazards and reflects time-varying hazards.
Sunitinib	Stratified survival curves from JAVELIN Renal 101 for PFS and OS		
Pazopanib	Stratified survival curves from JAVELIN Renal 101 for sunitinib for PFS and OS		Pazopanib is assumed clinically similar to sunitinib; JAVELIN Renal 101 can therefore provide direct comparative data for avelumab + axitinib to pazopanib for both PFS and OS
Tivozanib	Non-PH ITC, generalised gamma parametric survival model for PFS and OS for both tivozanib and avelumab + axitinib in a pairwise comparison	ITT	The evidence from the TIVO-1 trial indicated violations of assumption of proportional hazards, therefore the non-PH ITC was selected as it allows greater flexibility with time-varying hazards. Generalised gamma was the best statistical fit to the PFS and OS data for the non-PH ITC and produced plausible estimates of survival. To avoid the risk of bias by combining elements of different methods (e.g. stratified curves combined with non-PH ITC estimates), the non-PH ITC was also used to inform the avelumab + axitinib arm for PFS and OS in this comparison.
Avelumab + axitinib (for comparison to tivozanib)			
Cabozantinib	Non-PH ITC, generalised gamma parametric survival model for PFS and log-logistic for OS for both cabozantinib and avelumab + axitinib in the subgroup analysis.	Intermediate- or poor risk status	Given the indications of violation of the PH assumption, the non-PH ITC was used to estimate PFS and OS for both avelumab + axitinib and cabozantinib. For PFS, statistical fit and visual analysis indicated that generalised gamma was the most appropriate choice of parametric survival. For OS, log-logistic was most appropriate based on best statistical fit and visual analysis, and produced plausible survival estimates.
Avelumab + axitinib (for comparison to cabozantinib)			

B.3.3.2 Progression-free survival

B.3.3.2.1 ITT population

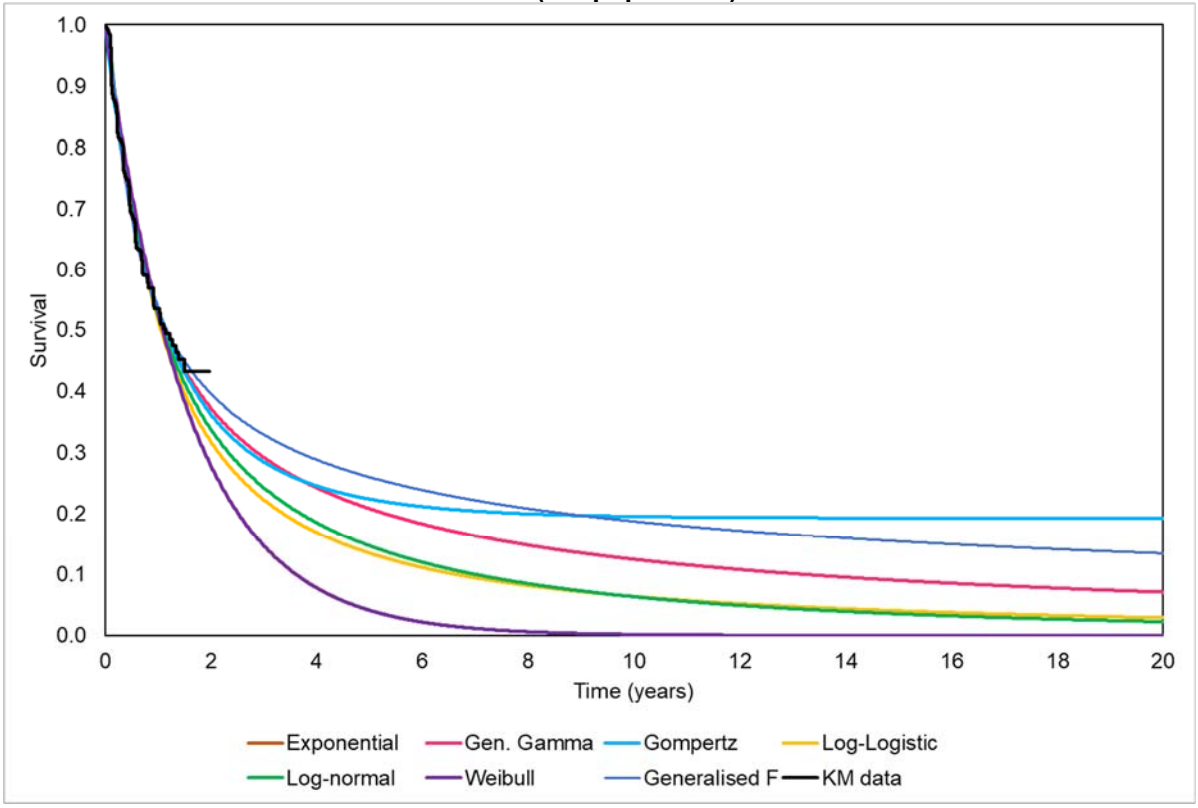
B.3.3.2.1.1 Avelumab + axitinib

Stratified analysis was used to fit parametric curves to the available PLD from JAVELIN Renal 101 for avelumab + axitinib and sunitinib. Based on the assumption of clinical equivalence between pazopanib and sunitinib, JAVELIN Renal 101 notably provided a direct

comparison of avelumab + axitinib with two of the three comparators in the ITT population as per the Final NICE scope, and reflected the current expected outcomes associated with first-line treatment with TKIs and the availability of IO treatment in subsequent line of therapy.

The parametric survival models fit to the avelumab + axitinib PFS data are presented in Figure B.3.2, with AIC and BIC statistics reported in Table B.3.5. Landmark PFS estimates at 6 months and 1, 2, 5 and 10 years are presented in Table B.3.6. Aside from the log-normal curve, which was excluded due to a lack of clinical plausibility, all curves were potentially clinically plausible in the shorter term but varied in their long-term outcomes. Consultant oncologists from various hospitals in the UK provided feedback on the available parametric survival models fitted to the data and the corresponding landmark PFS estimates. The generalised gamma curve was considered to be the most appropriate for avelumab + axitinib PFS data due to having good visual fit, long-term plausibility, and having the best statistical fit.

Figure B.3.2. Avelumab + axitinib PFS extrapolations from parametric survival models of stratified curves from JAVELIN Renal 101 (ITT population)



Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; PFS = progression-free survival

Table B.3.5. Avelumab + axitinib PFS model fit statistics (ITT population)

Model	AIC	BIC
Exp.	2648.59	2652.68
Gen. gamma	**2629.74**	2642.02
Gompertz	2645.62	2653.80
Log-logistic	2639.76	2647.94
Log-normal	2630.65	**2638.83**
Weibull	2650.59	2658.77
Gen. F	2630.38	2646.75

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; PFS = progression-free survival
Note: Underlined bold values indicate the lowest AIC or BIC value

Table B.3.6. Landmark avelumab + axitinib PFS estimates from parametric survival curves (ITT population)

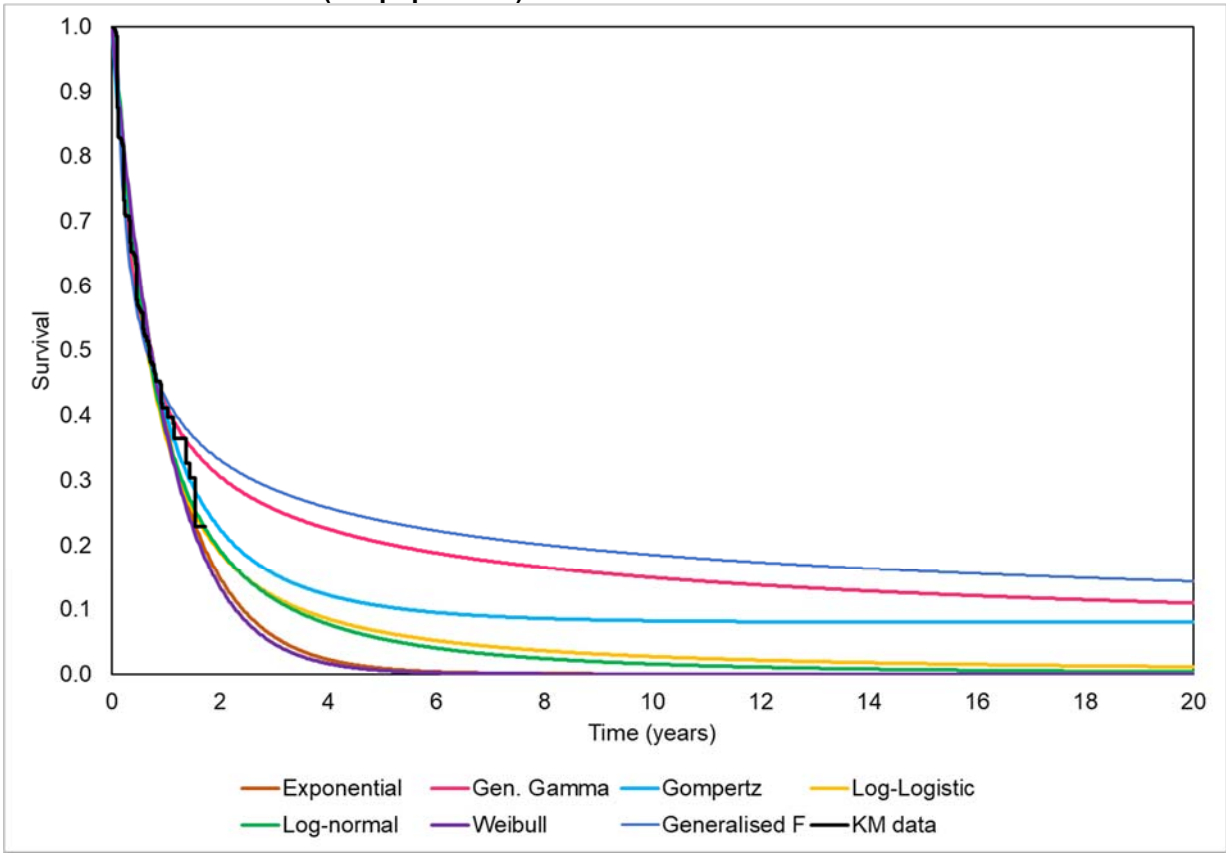
Time	PFS estimate (%)						
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull	Gen. F
6 months	72.80	69.70	70.56	71.18	70.69	72.81	68.93
1 year	53.01	53.23	53.61	51.87	52.62	53.00	53.35
2 years	28.10	37.40	36.40	31.97	33.98	28.08	39.71
5 years	4.18	20.92	22.48	13.57	14.78	4.17	26.10
10 years	0.17	12.51	19.59	6.39	6.35	0.17	18.79

Abbreviations: Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; PFS = progression-free survival

B.3.3.2.1.2 Sunitinib

Parametric survival models fit to sunitinib PFS data are presented in Figure B.3.3, with AIC and BIC statistics reported in Table B.3.7, and landmark PFS estimates in Table B.3.8. Generalised F was the best statistical fit according to both AIC and BIC, but clinicians considered this extrapolation to be too optimistic. Similarly, generalised gamma was also considered optimistic.[107] Instead, log-logistic had a good statistical fit to the data and produced landmark estimates that were consistent with PFS rates in the COMPARZ trial[84] (in which approximately 25% of patients were in PFS at 2 years), and were consistent long-term extrapolations of sunitinib PFS in NICE TA581[57] (in which approximately 9% were estimated in PFS at 5 years). Whilst Gompertz showed closer alignment to previous PFS estimates at 2- and 5-years, the longer-term outcomes based on log-logistic were deemed more realistic based on feedback received from UK consultant oncologists following a review of the curves and landmark estimates. Log-logistic was therefore selected for sunitinib PFS for the base-case analysis.

Figure B.3.3. Sunitinib PFS extrapolations from parametric survival models of stratified curves from JAVELIN Renal 101 (ITT population)



Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM, Kaplan–Meier; PFS, progression-free survival

Table B.3.7. Sunitinib PFS model fit statistics (ITT population)

Model	AIC	BIC
Exp.	3005.71	3009.81
Gen. gamma	2939.45	2951.74
Gompertz	3003.54	3011.73
Log-logistic	2986.35	2994.54
Log-normal	2968.61	2976.80
Weibull	3007.04	3015.23
Gen. F	**2911.13**	**2927.52**

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; PFS = progression-free survival
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.8. Landmark sunitinib PFS estimates from parametric survival curves (ITT population)

Time	PFS estimate (%)						
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull	Gen. F
6 months	62.32%	56.36%	60.48%	59.66%	59.82%	62.80%	55.05%
1 year	38.84%	41.74%	40.42%	37.08%	37.89%	38.21%	42.75%
2 years	15.09%	30.69%	22.60%	19.02%	19.34%	13.67%	33.20%
5 years	0.88%	20.37%	10.50%	6.51%	5.46%	0.55%	23.77%
10 years	0.01%	14.92%	8.21%	2.69%	1.54%	0.00%	18.45%

Abbreviations: Exp. = exponential; ITT = intention-to-treat; PFS = progression-free survival

B.3.3.2.1.3 Tivozanib

Review of the log-cumulative hazard (LCH) curves for tivozanib and sorafenib in TIVO-1 indicated a clear violation of the PH assumption for PFS (see Appendix D). Therefore, for the comparison of avelumab + axitinib and tivozanib, the non-PH ITC was used to estimate PFS for both therapies. The advantage of ITC methods is that it allows all treatments to be compared within one cohesive analysis. To avoid the risk of bias by combining elements of different methods, such as selecting stratified JAVELIN Renal 101 curves for avelumab and a curve for tivozanib derived from the non-PH ITC (which incorporates other comparators including sunitinib and avelumab data from JAVELIN Renal 101), the non-PH ITC output was also used to inform the avelumab + axitinib arm in this comparison.

AIC and BIC statistics are presented in Table B.3.9, and landmark PFS estimates for avelumab + axitinib and tivozanib are presented in Table B.3.10 and Table B.3.11, respectively. Generalised gamma was the best statistical fit to the PFS data and was selected for the base-case analysis. Extrapolations for PFS for avelumab + axitinib and tivozanib using generalised gamma and the non-PH ITC are presented in Figure B.3.4. A comparison of estimated PFS curves using alternative parametric models from the non-PH ITC is provided in Appendix D.

As seen in Table B.3.11, the PFS estimates for avelumab + axitinib are approximately 2.5% lower at 5 and 10 years when using the non-PH ITC compared with its stratified PFS curve from JAVELIN Renal 101. This underestimate is acknowledged and would potentially underestimate the incremental PFS benefit for avelumab + axitinib compared with tivozanib.

Table B.3.9. Non-PH ITC PFS model fit statistics (ITT population)

Model	AIC	BIC
Gen. gamma	**25351.33**	**25490.46**
Gompertz	25595.25	25728.33
Log-logistic	25436.25	25569.33
Log-normal	25365.27	25498.35
Weibull	25590.96	25724.04
Gen. F	25353.33	25498.51
Gen. gamma	25351.33	25490.46

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Gen. = generalised; ITT = intent-to-treat; PFS = progression-free survival
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.10. Landmark tivozanib PFS estimates from parametric survival curves (ITT population)

Time	PFS estimate (%)					
	Gen. gamma	**Gompertz**	**Log-logistic**	**Log-normal**	**Weibull**	**Gen. F**
6 months	60.17	60.50	60.89	60.80	62.38	60.17
1 year	40.57	42.21	39.09	40.00	38.61	40.57
2 years	23.93	27.11	20.92	21.75	14.66	23.93
5 years	9.82	18.10	7.58	6.98	0.78	9.82
10 years	4.37	17.03	3.26	2.24	0.01	4.37

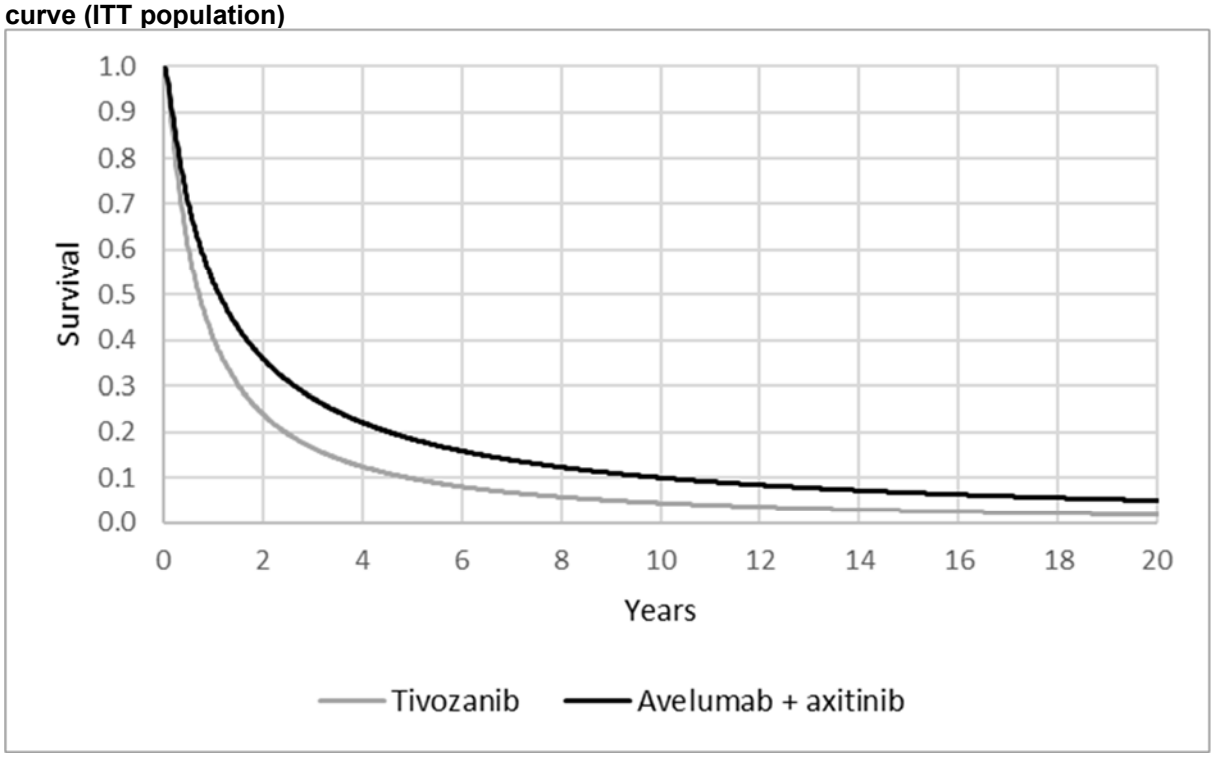
Abbreviations: Gen. = generalised; ITT = intention-to-treat; PFS = progression-free survival

Table B.3.11. Landmark avelumab + axitinib PFS estimates from non-PH ITC (ITT population)

Time	PFS estimate (%)					
	Gen. gamma	**Gompertz**	**Log-logistic**	**Log-normal**	**Weibull**	**Gen. F**
6 months	70.06	70.56	71.18	70.69	72.81	70.06
1 year	52.92	53.60	51.87	52.62	53.00	52.92
2 years	36.03	36.39	31.97	33.98	28.08	36.03
5 years	18.50	22.45	13.57	14.79	4.17	18.51
10 years	9.97	19.55	6.39	6.35	0.17	9.97

Abbreviations: gen. = generalised; ITC = indirect treatment comparison; ITT = intention-to-treat; PFS = progression-free survival

Figure B.3.4. Avelumab + axitinib and tivozanib PFS extrapolations – Non-PH ITC gen. gamma curve (ITT population)



Abbreviations: gen. generalised; ITC = indirect treatment comparison; ITT = intention-to-treat; PFS = progression-free survival; PH = proportional hazards

B.3.3.2.1.4 Summary of landmark PFS estimates

Base-case landmark PFS estimates for avelumab + axitinib, sunitinib and tivozanib are presented in Table B.3.12 (as pazopanib was assumed to be equivalent to sunitinib, PFS estimates for pazopanib are not presented). Avelumab + axitinib demonstrated a higher proportion of patients in PFS at each time point against all comparators.

Table B.3.12. Landmark PFS estimates (ITT population)

Time	PFS estimate (%)			
	Avelumab + axitinib	**Sunitinib**	**Avelumab + axitinib (non-PH ITC)**	**Tivozanib (non-PH ITC)**
6 months	69.70	59.66	70.06	60.17
1 year	53.23	37.08	52.92	40.57
2 years	37.40	19.02	36.03	23.93
5 years	20.92	6.51	18.50	9.82
10 years	12.51	2.69	9.97	4.37

Abbreviations: ITC = indirect treatment comparison; ITT = intention-to-treat; PH = proportional hazards; PFS = progression-free survival

B.3.3.2.2 Intermediate- or poor-risk population

Although review of the LCH curves of cabozantinib and sunitinib in CABOSUN for PFS did not provide clear conclusions on the suitability of the PH assumption, there was indication that the PH assumption may not be appropriate (see Appendix D). Furthermore, there was indication of PH violation for OS (see Section B.3.3.2.2), and selecting the non-PH ITC for PFS also helps to ensure consistency in the survival estimates between PFS and OS.

Therefore, as with tivozanib, the non-PH ITC was used to estimate PFS for the comparison of avelumab + axitinib with cabozantinib in patients with intermediate- or poor risk status. AIC and BIC statistics are reported in Table B.3.13 and landmark PFS estimates in Table B.3.14. Generalised gamma and generalised F provided the best statistical fit, with visual analysis indicating that generalised gamma was a better fit. Generalised gamma was therefore considered to be the most appropriate for the base-case analysis.

Table B.3.13. Non-PH ITC PFS model fit statistics (IMDC intermediate- or poor-risk population)

Model	AIC	BIC
Gen. gamma	**5815.03**	**5857.71**
Gompertz	5902.13	5940.06
Log-logistic	5860.58	5898.51
Log-normal	5834.84	5872.77
Weibull	5904.12	5942.05
Gen. F	5816.34	5863.76

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; PFS = progression-free survival; PH = proportional hazard
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.14. Landmark cabozantinib PFS estimates from non-PH ITC (IMDC intermediate- or poor-risk population)

Time	PFS estimate (%)					
	Gen. gamma	**Gompertz**	**Log-logistic**	**Log-normal**	**Weibull**	**Gen. F**
6 months	70.12	70.12	74.03	71.94	72.11	75.00
1 year	53.28	53.28	59.50	53.33	53.63	55.82
2 years	37.99	37.99	45.24	33.75	34.31	30.68
5 years	22.69	22.69	34.82	14.89	14.50	4.95
10 years	14.83	14.83	33.35	7.22	6.00	0.22

Abbreviations: Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; PH = proportional hazards; PFS = progression-free survival

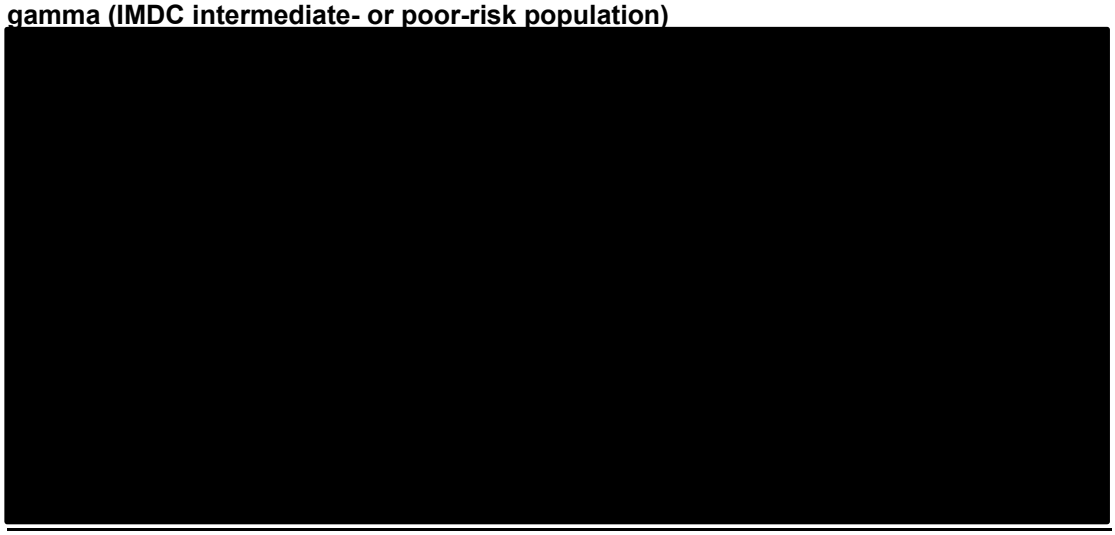
Table B.3.15. Landmark avelumab + axitinib PFS estimates from non-PH ITC (IMDC intermediate- or poor-risk population)

Time	PFS estimate (%)					
	Gen. gamma	**Gompertz**	**Log-logistic**	**Log-normal**	**Weibull**	**Gen. F**
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year						
2 years						
5 years						
10 years						

Abbreviations: Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression-free survival

Parametric survival models for avelumab + axitinib and cabozantinib in patients with intermediate- or poor-risk status are presented in Figure B.3.5, and landmark PFS estimates in Table B.3.16. Avelumab + axitinib demonstrated a longer-term PFS benefit, with cabozantinib offering higher PFS in the short-term. A comparison of estimated PFS curves using alternative parametric models from the non-PH ITC is provided in Appendix D.

Figure B.3.5. Avelumab + axitinib and cabozantinib PFS extrapolations – Non-PH ITC gen. gamma (IMDC intermediate- or poor-risk population)



Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression-free survival

Table B.3.16. Landmark PFS estimates – generalised gamma (IMDC intermediate- or poor-risk population)

Time	PFS estimate (%)	
	Avelumab + axitinib	Cabozantinib
6 months	[redacted]	70.12
1 year	[redacted]	53.28
2 years	[redacted]	37.99
5 years	[redacted]	22.69
10 years	[redacted]	14.83

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression-free survival

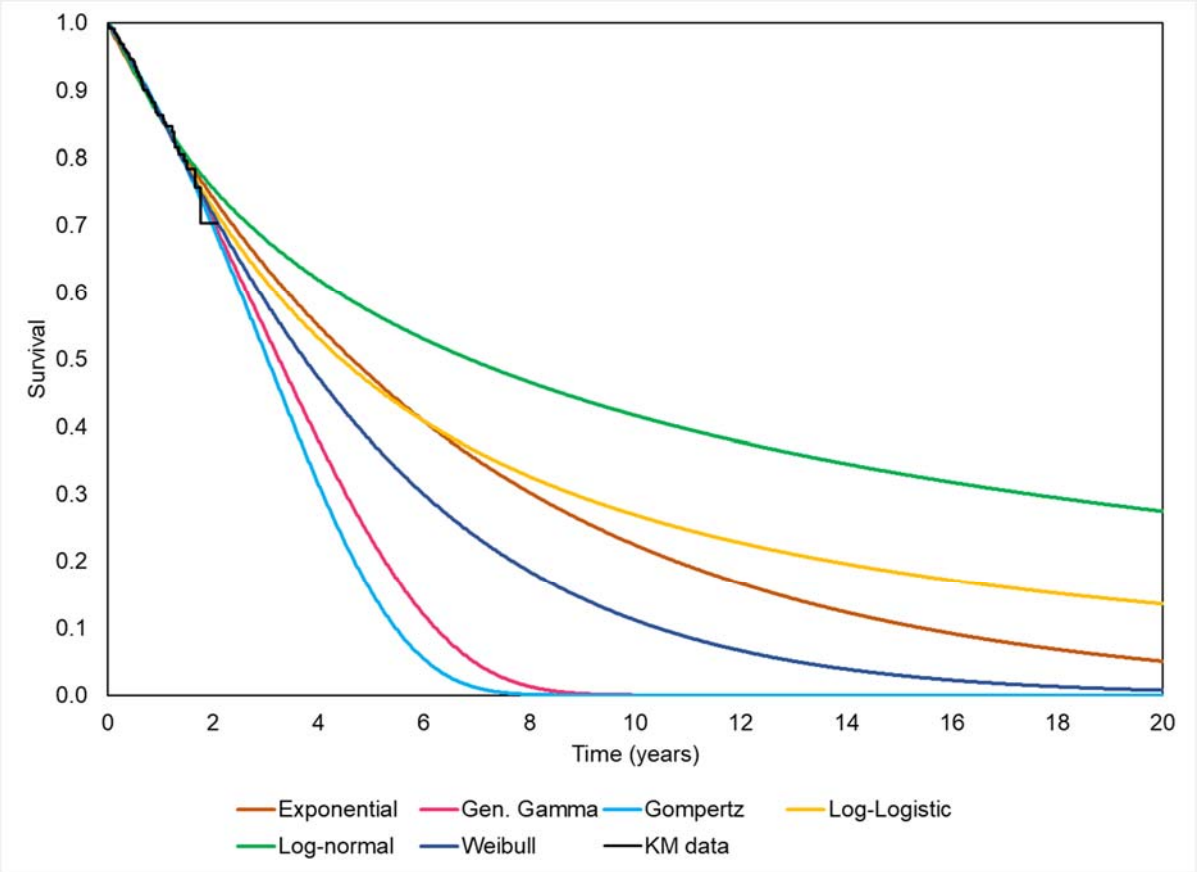
B.3.3.3 Overall survival

B.3.3.3.1 ITT population

B.3.3.3.1.1 Avelumab + axitinib

As with PFS, OS extrapolations for avelumab + axitinib and sunitinib were informed directly by stratified survival curves based on JAVELIN Renal 101 data. The parametric survival model fits to the avelumab + axitinib OS data are presented in Figure B.3.6, with AIC and BIC statistics reported in Table B.3.17. Landmark OS estimates at 6 months and 1, 2, 5 and 10 years are presented in Table B.3.18. The exponential curve provided the best statistical fit to the avelumab + axitinib OS data, although the log-logistic curve was also a good fit. Log-logistic was considered more reflective of the expected long-term survival outcomes associated with IO therapy following a presentation of potential OS extrapolations and landmark OS estimates to consultant oncologists from various hospitals in the UK who treat aRCC. Thus, log-logistic was selected as the most appropriate parametric survival model for avelumab + axitinib OS extrapolation.

Figure B.3.6. Avelumab + axitinib OS extrapolations from parametric survival curves of stratified curve from JAVELIN Renal 101 (ITT population)



Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; OS = overall survival

Table B.3.17. Avelumab + axitinib OS model fit statistics (ITT population)

Model	AIC	BIC
Exp.	**1110.93**	**1115.02**
Gen. gamma	1112.99	1125.26
Gompertz	1111.14	1119.32
Log-logistic	1111.39	1119.57
Log-normal	1115.25	1123.44
Weibull	1111.11	1119.29

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; OS = overall survival
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.18. Landmark avelumab + axitinib OS estimates from parametric survival curves (ITT population)

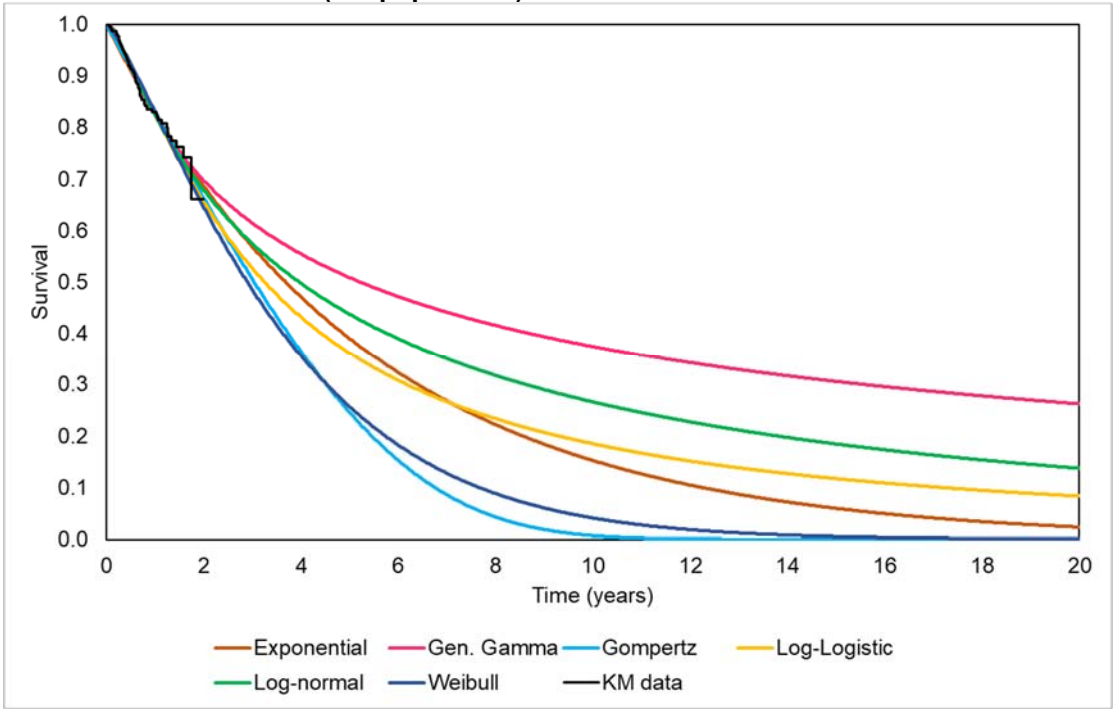
Time	OS estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	92.82	93.76	93.74	93.63	92.95	93.69
1 year	86.16	86.49	86.63	86.24	86.07	86.34
2 years	74.23	70.76	69.97	72.77	75.63	71.81
5 years	47.48	23.56	15.66	46.42	57.15	37.92
10 years	22.47	0.02	0.00	26.93	41.69	11.18

Abbreviations: Exp. = exponential; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; OS = overall survival

B.3.3.3.1.2 Sunitinib

Parametric survival models fit to sunitinib OS data are presented in Figure B.3.7, with AIC and BIC statistics reported in Table B.3.19 and landmark OS estimates in Table B.3.20. Log-normal was the best statistical fit, but was considered to produce an overestimate of likely survival outcomes with sunitinib following discussions with clinical experts. Of the remaining curves, log-logistic was a good fit and aligned with sunitinib OS (although slightly overestimating) reported at two years in the COMPARZ[84] trial (~55% at two years) and with long-term sunitinib OS extrapolations in TA581[57] (~28% at 5 years; ~12% at 10 years in the intermediate- or poor-risk status population). Log-logistic also aligned with UK consultant oncologists' experience of outcomes with sunitinib and was therefore chosen for the base-case analysis.

Figure B.3.7. Sunitinib OS extrapolations from parametric survival curves of stratified curve from JAVELIN Renal 101 (ITT population)



Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; OS = overall survival

Table B.3.19. Sunitinib OS model fit statistics (ITT population)

Model	AIC	BIC
Exp.	1287.58	1291.68
Gen. gamma	1281.62	1293.91
Gompertz	1289.14	1297.34
Log-logistic	1284.17	1292.36
Log-normal	**1280.43**	**1288.62**
Weibull	1285.73	1293.92

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; OS = overall survival
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.20. Sunitinib OS survival estimates from parametric survival curves (ITT population)

Time	OS estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	91.05	91.57	91.54	92.28	91.96	92.41
1 year	82.89	82.36	83.08	82.70	82.47	83.05
2 years	68.71	69.78	66.42	65.65	67.90	64.60
5 years	39.14	50.94	24.73	36.26	43.86	25.81
10 years	15.26	37.48	0.68	18.49	26.62	4.10

Abbreviations: Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; OS = overall survival

B.3.3.3.1.3 Tivozanib

Given that TIVO-1 OS curves indicated potential violations of the PH assumption for OS (see Appendix D), the non-PH ITC was used to estimate OS for the comparison of avelumab + axitinib and tivozanib. AIC and BIC statistics are reported in Table B.3.21, and landmark PFS estimates for tivozanib and avelumab + axitinib are presented in Table B.3.22 and Table B.3.23, respectively.

Generalised gamma was the best statistical fit to the OS data and produced plausible estimates of survival and was therefore selected to inform the base-case analysis. The OS estimates for avelumab + axitinib using generalised gamma showed slightly higher survival than would be expected for aRCC patients at approximately 35-40 years of the time horizon (or patient age 95-100). To account for this, and as detailed in Section B.3.3.7, mortality rates for aRCC patients were programmed in the model calculations to follow general population mortality rates in any cycle where the extrapolated OS curve produced mortality transition probabilities lower than mortality in the general population. Parametric survival models for avelumab + axitinib and tivozanib OS are presented in Figure B.3.8. A comparison of estimated OS curves using alternative parametric models from the non-PH ITC is provided in Appendix D.

Table B.3.21. Non-PH ITC OS model fit statistics (ITT population)

Model	AIC	BIC
Gen. gamma	**22128.34**	**22254.55**
Gompertz	22180.93	22301.14
Log-logistic	22136.94	22257.14
Log-normal	22135.17	22255.38
Weibull	22166.77	22286.98
Gen. F	22130.35	22262.57

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITC = indirect treatment comparison; ITT = intention-to-treat; OS = overall survival; PH = proportional hazard
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.22. Landmark tivozanib OS estimates from non-PH ITC (ITT population)

Time	OS estimate (%)					
	Gen. gamma	**Gompertz**	**Log-logistic**	**Log-normal**	**Weibull**	**Gen. F**
6 months	92.61	88.78	91.66	93.43	91.43	92.61
1 year	82.11	78.61	80.78	83.03	80.89	82.12
2 years	64.04	61.12	61.65	65.63	60.55	64.06
5 years	33.19	26.72	31.10	37.11	20.88	33.24
10 years	13.95	5.07	14.69	18.85	2.44	14.00

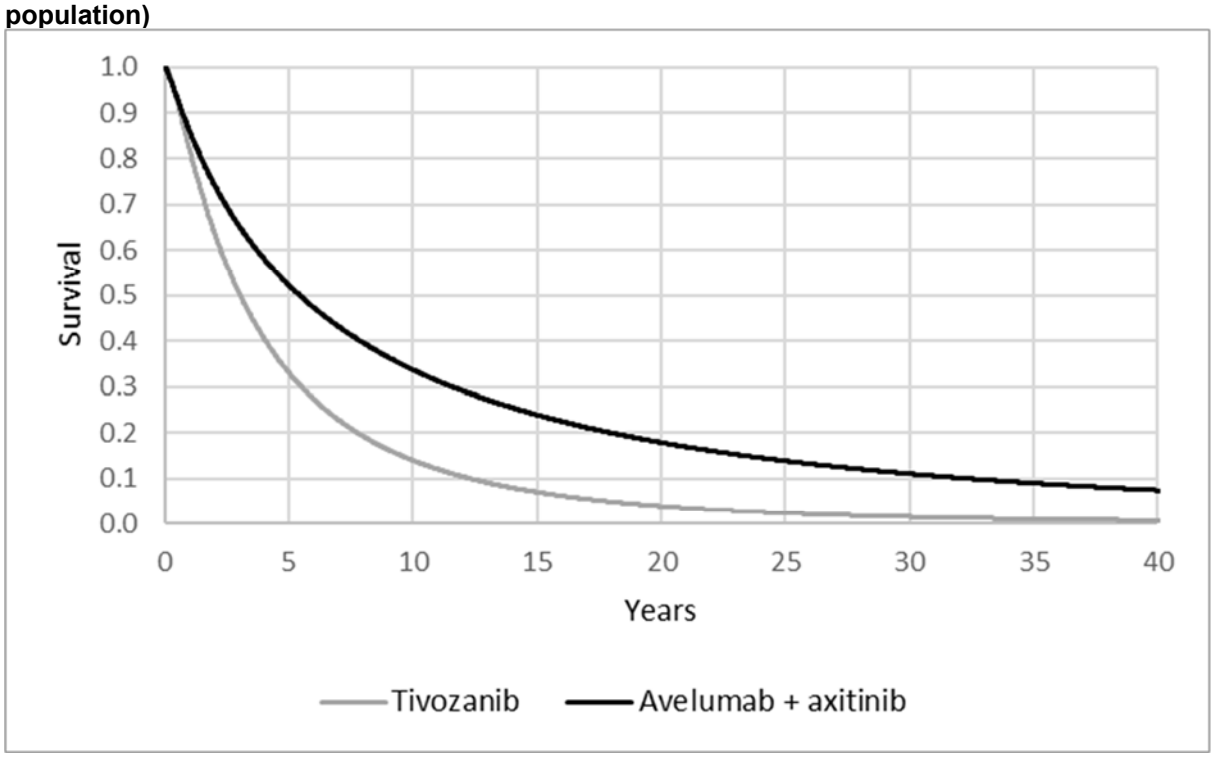
Abbreviations: Gen. = generalised; ITT = intention-to-treat; OS = overall survival

Table B.3.23. Landmark avelumab + axitinib OS estimates from non-PH ITC (ITT population)

Time	OS estimate (%)					
	Gen. gamma	**Gompertz**	**Log-logistic**	**Log-normal**	**Weibull**	**Gen. F**
6 months	93.24	93.74	93.63	92.95	93.69	93.24
1 year	86.10	86.63	86.24	86.07	86.34	86.08
2 years	74.44	69.97	72.77	75.63	71.81	74.38
5 years	52.37	15.69	46.42	57.15	37.92	52.26
10 years	33.73	0.00	26.93	41.69	11.18	33.60

Abbreviations: Gen. = generalised; ITT = intention-to-treat; OS = overall survival

Figure B.3.8. Avelumab + axitinib and tivozanib OS extrapolations – gen. gamma (ITT population)



Abbreviations: Gen. = generalised; ITT = intention-to-treat; OS = overall survival

B.3.3.3.1.4 Summary of landmark OS estimates

Base-case landmark OS estimates for avelumab + axitinib, sunitinib and tivozanib are presented in Table B.3.24 (as with PFS, pazopanib was assumed to be equivalent to sunitinib and is not presented below). Avelumab + axitinib was associated with the longest OS at all time points versus comparators in the ITT population.

Table B.3.24. Landmark OS estimates (ITT population)

Time	OS estimate (%)			
	Avelumab + axitinib	**Sunitinib**	**Avelumab + axitinib (non-PH ITC)**	**Tivozanib (non-PH ITC)**
6 months	93.63	92.28	93.24	92.61
1 year	86.24	82.70	86.10	82.11
2 years	72.77	65.65	74.44	64.04
5 years	46.42	36.26	52.37	33.19
10 years	26.93	18.49	33.73	13.95

Abbreviations: ITT = intention-to-treat; OS = overall survival

B.3.3.3.2 Intermediate- or poor-risk patients

As with PFS, comparison of OS for avelumab + axitinib and cabozantinib in the intermediate- or poor-risk population was informed by the non-PH ITC. AIC and BIC statistics are reported in Table B.3.25 and landmark OS estimates for cabozantinib and avelumab + axitinib are presented in Table B.3.26 and Table B.3.27, respectively. Log-logistic provided the best statistical fit and was used to estimate OS for avelumab + axitinib and cabozantinib in the base-case analysis.

Table B.3.25. Cabozantinib OS model fit statistics (IMDC intermediate- or poor-risk population)

Model	AIC	BIC
Gen. Gamma	3620.00	3662.68
Gompertz	3627.57	3665.50
Log-logistic	**3618.83**	**3656.76**
Log-normal	3619.27	3657.21
Weibull	3623.03	3660.96
Gen. F	3621.64	3669.05

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.26. Landmark cabozantinib OS estimates from non-PH ITC (IMDC intermediate- or poor-risk population)

Time	OS estimate (%)					
	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull	Gen. F
6 months	94.36	91.37	94.02	94.51	93.83	94.41
1 year	85.33	82.71	84.87	85.43	85.02	85.24
2 years	68.42	65.70	66.68	69.55	66.12	68.10
5 years	36.83	23.47	33.88	41.81	24.04	38.62
10 years	15.69	0.51	15.42	22.60	2.62	20.49

Abbreviations: Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival

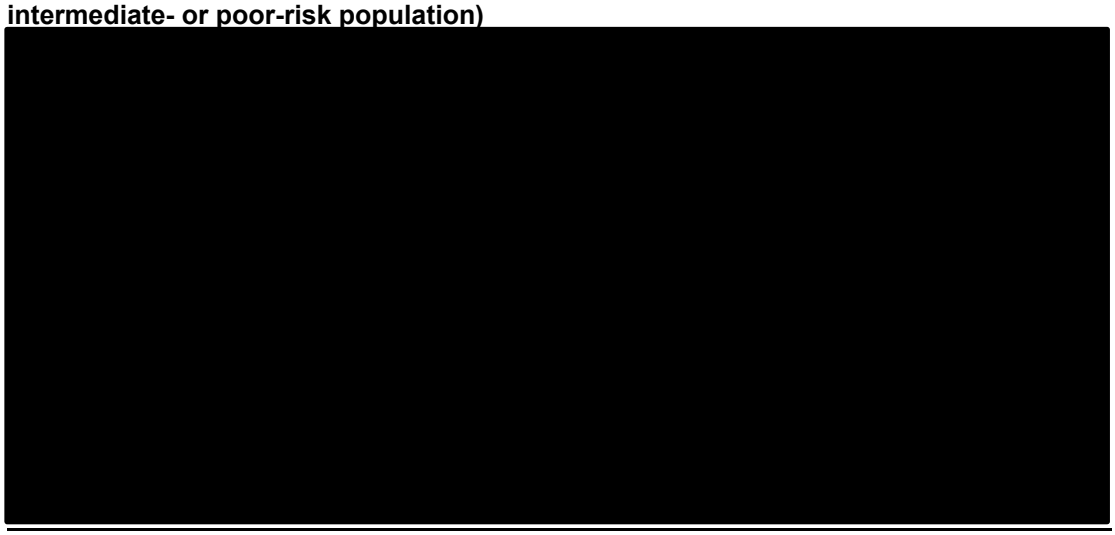
Table B.3.27. Landmark avelumab + axitinib OS estimates from non-PH ITC (IMDC intermediate- or poor-risk population)

Time	OS estimate (%)					
	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull	Gen. F
6 months	[redacted]					
1 year						
2 years						
5 years						
10 years						

Abbreviations: Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival

Parametric survival models for avelumab + axitinib and cabozantinib in patients with intermediate- or poor-risk status are presented in Figure B.3.9, with landmark OS estimates in Table B.3.28. A comparison of estimated OS curves using alternative parametric models from the non-PH ITC is provided in Appendix D. Avelumab + axitinib demonstrated a longer-term OS benefit, with cabozantinib offering marginally higher OS in the short term.

Figure B.3.9. Avelumab + axitinib and cabozantinib OS extrapolations – log-logistic (IMDC intermediate- or poor-risk population)



Abbreviations: Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival

Table B.3.28. Landmark OS estimates – log-logistic (IMDC intermediate- or poor-risk population)

Time	OS estimate (%)	
	Avelumab + axitinib	Cabozantinib
6 months		94.02
1 year		84.87
2 years		66.68
5 years		33.88
10 years		15.42

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival

B.3.3.4 Time on treatment (ToT)

ToT was used to inform drug and administration costs for all treatments. For avelumab, axitinib and sunitinib, time to treatment discontinuation (TTD) was based on the treatment exposure observed in PLD of JAVELIN Renal 101.

Given that the PLD reflected the first interim analysis, many patients were still on treatment at the time of the data cut. Therefore, for many patients the last dose received would unlikely reflect their treatment end date and thus their estimated ToT. To account for this, true discontinuations were identified by assessing the proximity of treatment end date against the trial cut-off date (20 June 2018), to identify patients who were likely to continue treatment beyond IA1. A 30-day interval prior to the trial cut-off date was applied, with patients considered to be censored for treatment discontinuation if treatment ended within this interval. Thirty days was considered to be an appropriate cut-off, as a gap of >30 days between last dose of avelumab and end of follow-up would indicate >2 missed doses, which is indicative of discontinuation.

TTD was reported separately for avelumab and axitinib in the JAVELIN Renal 101 PLD; therefore, parametric model fits were conducted separately for avelumab and axitinib. ToT data for avelumab and axitinib were derived individually for each treatment, reflecting the possibility of patients discontinuing avelumab and axitinib independently. The ToT curves for

avelumab and axitinib showed some variation from the PFS estimates of avelumab + axitinib over time due to the possibility to continue on study treatment post-progression in JAVELIN Renal 101 (see Section B.2.3.3.2).

For pazopanib, ToT in the base-case analysis was assumed to be equal to sunitinib ToT. Limited data were available for ToT of tivozanib; therefore, tivozanib ToT was assumed equal to tivozanib PFS. For cabozantinib, ToT was estimated by digitising the ToT curve reported in the NICE TA of cabozantinib (TA542).[15]

B.3.3.4.1 ITT population

B.3.3.4.1.1 Avelumab

Parametric models fit to avelumab ToT data are presented in Figure B.3.10, with AIC and BIC statistics reported in Table B.3.29. Landmark ToT estimates at 6 months and 1, 2, 5 and 10 years are presented in Table B.3.30. The log-normal distribution was the best fit according to AIC and BIC statistics, and was therefore selected as the most appropriate to estimate avelumab ToT in the base-case analysis.

Figure B.3.10. Avelumab ToT extrapolations from parametric survival curves of stratified curve from JAVELIN Renal 101 (ITT population)

Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; ToT = time on treatment

Table B.3.29: Avelumab ToT model fit statistics (ITT population)

Model	AIC	BIC
Exp.	3019.28	3023.35
Gen. gamma	3007.53	3019.75
Gompertz	3012.97	3021.12
Log-logistic	3011.62	3019.76
Log-normal	**3006.09**	**3014.23**
Weibull	3019.85	3028.00

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.30. Landmark avelumab ToT estimates from parametric survival curves (ITT population)

Time	ToT estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	[redacted]					
1 year						
2 years						
5 years						
10 years						

Abbreviations: Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment

B.3.3.4.1.2 Axitinib

Parametric models fit to axitinib ToT data are presented in Figure B.3.11, with AIC and BIC statistics reported in Table B.3.31 and landmark ToT estimates in Table B.3.32. Although the exponential curve was statistically the best-fitting curve for axitinib ToT data, the extrapolated results appeared to underestimate axitinib ToT compared with avelumab ToT as well as with the avelumab + axitinib PFS curve, both of which were observed to be lower than the axitinib ToT curve based on JAVELIN Renal 101 PLD. Therefore, the log-logistic distribution was selected due to closer alignment with PFS and a good relative fit according to AIC and BIC scores.

Figure B.3.11. Axitinib ToT extrapolations from parametric survival curves of stratified curve from JAVELIN Renal 101 (ITT population)

Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; ToT = time on treatment

Table B.3.31. Axitinib ToT model fit statistics (ITT population)

Model	AIC	BIC
Exp.	**2812.43**	**2816.50**
Gen. gamma	2815.85	2828.07
Gompertz	2813.33	2821.48
Log-logistic	2814.03	2822.17
Log-normal	2827.02	2835.16
Weibull	2813.98	2822.12

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.32. Landmark axitinib ToT estimates from parametric survival curves (ITT population)

Time	ToT estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	[redacted]					
1 year						
2 years						
5 years						
10 years						

Abbreviations: Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment

B.3.3.4.1.3 Sunitinib

Parametric survival models fit to sunitinib ToT data are presented in Figure B.3.12, with AIC and BIC statistics reported in Table B.3.33 and landmark ToT estimates in Table B.3.34. The generalised gamma and exponential distributions produced the best statistical fit according to AIC and BIC scores, respectively; however, the log-normal distribution produced similar outcomes to the sunitinib PFS curve and was therefore selected for the base-case analysis, given that sunitinib treatment duration is typically aligned to time spent in PFS.

Figure B.3.12. Sunitinib ToT extrapolations from parametric survival curves (ITT population)

[redacted]

Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; ToT = Time on treatment

Table B.3.33. Sunitinib ToT model fit statistics (ITT population)

Model	AIC	BIC
Exp.	3812.94	**3817.02**
Gen. gamma	**3809.33**	3821.59
Gompertz	3814.45	3822.62
Log-logistic	3810.08	3818.25
Log-normal	3809.34	3817.51
Weibull	3814.61	3822.78

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.34. Landmark sunitinib ToT estimates from parametric survival curves (ITT population)

Time	ToT estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	[redacted]					
1 year						
2 years						
5 years						
10 years						

Abbreviations: Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment

B.3.3.4.2 Intermediate- or poor-risk population

ToT data for avelumab + axitinib were derived individually for each treatment for the intermediate- or poor-risk subgroup (with the same approach taken as for the ITT population). Given the intermediate- or poor-risk subgroup is expected to have a poorer prognosis than the ITT population, ToT was estimated separately for the intermediate- and poor-risk patients in JAVELIN Renal 101.

B.3.3.4.2.1 Avelumab

Parametric models fit to avelumab ToT data are presented in Figure B.3.10, with AIC and BIC statistics reported in Table B.3.29. Landmark ToT estimates at 6 months and 1, 2, 5 and 10 years are presented in Table B.3.30. The log-normal distribution was the best fit according to AIC and BIC statistics provided a mid-range estimate of ToT from the derived parametric survival models and was therefore selected as the most appropriate to estimate avelumab ToT in the base-case analysis.

Figure B.3.13. Avelumab ToT extrapolations from parametric survival curves of stratified curve from JAVELIN Renal 101 (ITT population)

Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; ToT = time on treatment

Table B.3.35: Avelumab ToT model fit statistics (IMDC intermediate- or poor-risk patients)

Model	AIC	BIC
Exp.	2486.92	2490.74
Gen. gamma	2482.12	2493.59
Gompertz	2484.96	2492.60
Log-logistic	2483.46	2491.11
Log-normal	**2480.12**	**2487.77**
Weibull	2488.17	2495.82

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; ToT = time on treatment
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.36. Landmark avelumab ToT estimates from parametric survival curves (IMDC intermediate- or poor-risk populations)

Time	ToT estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	[redacted]					
1 year						
2 years						
5 years						
10 years						

Abbreviations: Exp. = exponential; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; ToT = time on treatment

B.3.3.4.2.2 Axitinib

Parametric models fit to axitinib ToT data are presented in Figure B.3.11, with AIC and BIC statistics reported in Table B.3.37 and landmark ToT estimates in Table B.3.38.

Although the exponential curve was statistically the best-fitting curve for axitinib ToT data, the extrapolated results appeared to be lower beyond two years for axitinib than avelumab. This outcome would not be aligned to clinical rationale where it would be anticipated that typically, patients would be more likely to remain on axitinib for the same time or slightly

longer than avelumab. Therefore, the log-logistic distribution was selected as it aligned better with the avelumab ToT curve and was in the middle of the derived parametric survival models. The AIC and BIC statistics for log-logistic were closely aligned to the exponential curve. Given the visual fit to the KM data at the end of follow-up, the log-logistic curve was selected, which may overestimate the ToT of axitinib if this tail is not representative.

Figure B.3.14. Axitinib ToT extrapolations from parametric survival curves of stratified curve from JAVELIN Renal 101 (ITT population)

Abbreviations: Gen. = generalised; ITT = intention-to-treat; KM = Kaplan–Meier; ToT = time on treatment

Table B.3.37. Axitinib ToT model fit statistics (IMDC intermediate- or poor-risk population)

Model	AIC	BIC
Exp.	**2321.25**	**2325.07**
Gen. gamma	2325.21	2336.68
Gompertz	2323.13	2330.77
Log-logistic	2324.87	2332.52
Log-normal	2336.69	2344.33
Weibull	2323.22	2330.86

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; ITT = intention-to-treat; ToT = time on treatment
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.38. Landmark axitinib ToT estimates from parametric survival curves (IMDC intermediate- or poor-risk population)

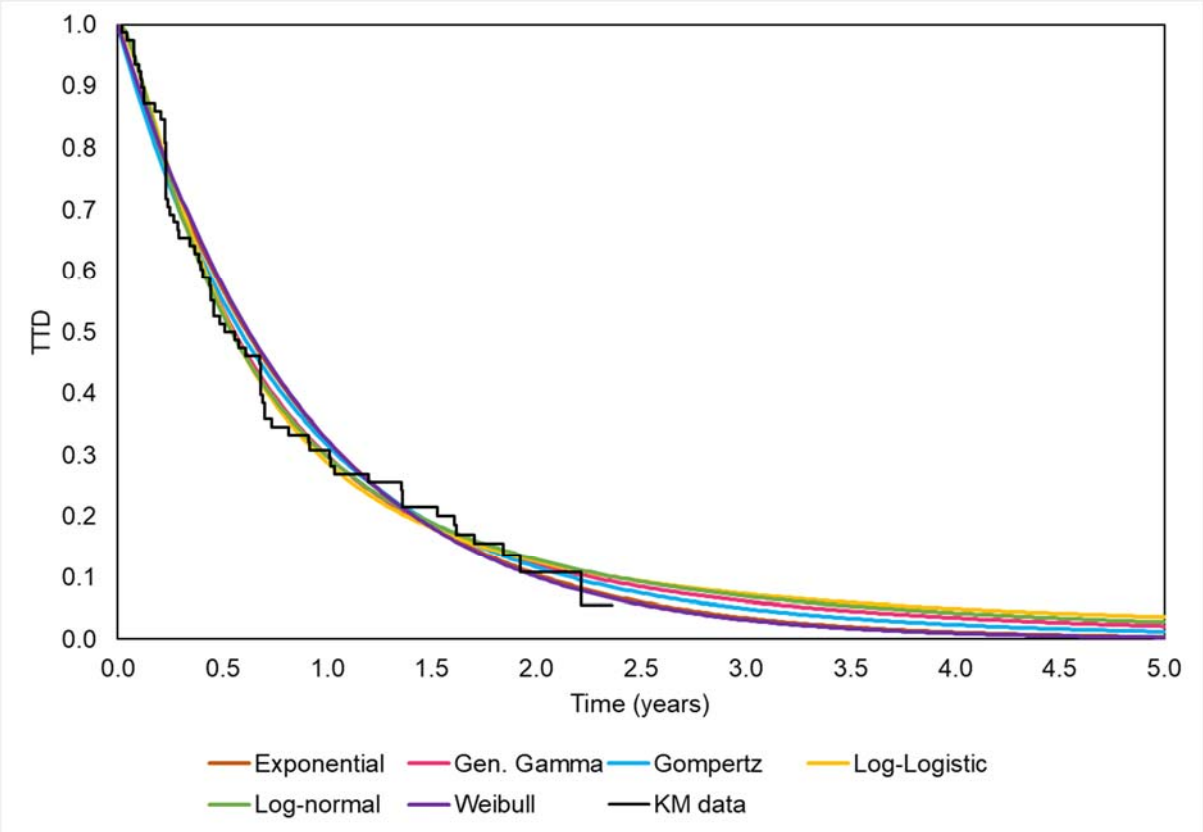
Time	ToT estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	[redacted]					
1 year						
2 years						
5 years						
10 years						

Abbreviations: Exp. = exponential; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; ToT = time on treatment

B.3.3.4.2.3 Cabozantinib

ToT for cabozantinib was derived from the CABOSUN trial based on pseudo-PLD replicated using the algorithm developed by Guyot et al. (2012).[108] Parametric survival models fit to these data are presented in Figure B.3.15, with AIC and BIC statistics reported in Table B.3.39 and landmark ToT estimates in Table B.3.40. Given the completeness of the CABOSUN KM curve, all extrapolated curves provided a similar visual fit to the data. The log-normal distribution provided the best statistical fit and was considered an appropriate distribution to inform ToT for cabozantinib in the intermediate- or poor-risk population.

Figure B.3.15. Cabozantinib ToT extrapolations from parametric survival curves (IMDC intermediate- or poor-risk population)



Abbreviations: Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KM = Kaplan–Meier; ToT = time on treatment

Table B.3.39. Cabozantinib ToT model fit statistics (IMDC intermediate- or poor-risk population)

Model	AIC	BIC
Exp.	459.93	462.29
Gen. gamma	459.17	466.24
Gompertz	461.56	466.27
Log-logistic	457.87	462.58
Log-normal	**457.37**	**462.09**
Weibull	461.85	466.56

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; Exp. = exponential; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ToT = time on treatment
Note: Underlined bold values indicate the lowest AIC or BIC score

Table B.3.40. Landmark cabozantinib ToT estimates from parametric survival curves (IMDC intermediate- or poor-risk population)

Time	ToT estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	57.09	53.82	55.31	53.41	52.96	57.79
1 year	32.59	30.13	31.84	28.99	29.97	32.69
2 years	10.62	12.34	11.78	12.69	13.03	10.23
5 years	0.37	2.09	1.22	3.58	2.76	0.29
10 years	0.00	0.32	0.14	1.30	0.59	0.00

Abbreviations: Exp. = exponential; Gen. = generalised; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ToT = time on treatment

B.3.3.5 Stopping rule

In the base case analysis, a two-year treatment stopping rule was applied for both avelumab and axitinib.

The primary rationale for a two-year stopping rule was the immune-modifying effect of avelumab. Avelumab is a checkpoint inhibitor and IO agent that blocks PD-L1, allowing the immune system to continue targeting tumour cells.[23] This alteration of the immune response by IO therapies can have a long-term effect – for example, among intermediate- or poor-risk RCC patients treated with first-line nivolumab + ipilimumab in the CheckMate-214 study, the ORR at 30 months was 42%, while PFS at 24 months was 30%.[105] In line with this, data from JAVELIN Renal 101 show that 45% of RCC patients treated with avelumab + axitinib are progression-free at 18 months, with approximately 37% predicted to be progression-free at two years (see Section B.2.6.1.2).[68] While this does not directly support the assumption that patients would continue to benefit after stopping treatment, it does demonstrate a durable effect with IO therapies in RCC. In addition, a stopping rule has recently been accepted in an SMC technology appraisal for nivolumab + ipilimumab for the first-line treatment of aRCC.[109]

To provide additional data on long-term outcomes with IO therapies in aRCC, data from IO therapies in other indications can lend support to a two-year stopping rule for avelumab + axitinib. Among 65 real-world melanoma patients who stopped pembrolizumab while progression-free, the best objective response rate (BORR) remained stable 26 weeks after stopping treatment (80% on treatment, 77% at 26 weeks after stopping),[110] indicating negligible short-term effect of discontinuing treatment. Similarly, among 104 melanoma patients who completed two years of pembrolizumab treatment in KEYNOTE-006, 91%

remained progression-free 9.7 months after stopping pembrolizumab.[111] Among these, 95% of CRs and 91% of PRs were maintained after stopping pembrolizumab. In fact, 20.3 months after stopping pembrolizumab, 86% of patients were progression-free, demonstrating the durable efficacy of IO therapies after stopping treatment. This data from other indications provides support for a two-year stopping rule for avelumab + axitinib in RCC.[106]

Clinicians also agree that IO therapies can have a long-term benefit beyond treatment discontinuation. During one-to-one meetings, consultant oncologists from various hospitals in the UK agreed that it was acceptable to stop treatment at two years in progression-free patients, with benefits expected to continue in most cases. Clinicians agreed that implementing a stopping rule at two years would unlikely cause a sudden loss of response in most patients, with a gradual waning of effect being more likely. In those who do experience a loss of response, a sudden loss would be driven by axitinib discontinuation, as the IO effect is expected to be more durable. Thus, prescribing oncologists are supportive of a stopping rule and would be amenable to implementing it in their practice.[107]

Patients are also likely to benefit from the convenience, costs and safety of a stopping rule. If treated to progression, some patients could conceivably be treated for five years or longer, given that ~30% of pembrolizumab-treated melanoma patients are progression-free at five years.[112] This would mean patients would have the inconvenience and costs of making 130 hospital visits over five years for avelumab treatment administration alone, while the possibility of an AE would typically increase with the prolonged treatment duration. Increased NHS resources would also be required, including additional drug, staff and equipment costs. The combination's long-term efficacy is predicated on the activation of the previously dormant immune response. By this point, treatment is expected to result in the restoration of the immune response, including the anti-tumour immune response. For this reason, treatment can often be discontinued, thereby removing the risk of potential AEs and the costs and inconvenience of ongoing hospital visits.[113]

Assumptions regarding stopping treatment after a pre-determined period of time and the maintenance of benefits have previously been studied for IO therapies. NICE has previously approved a two-year stopping rule for other IO therapies despite the absence of stopping rules in clinical trials or summaries of product characteristics.[114-117] These decisions were reached based on clinical advice suggesting that the risk of treatment-related toxicities would make it inadvisable to continue treatment indefinitely. Furthermore, representatives from NHS England and clinical leads from the Cancer Drugs Fund have suggested in multiple appraisals that a 2-year stopping rule for IO therapies is acceptable to both patients and clinicians and can be implemented.[114, 116, 117]

B.3.3.6 Treatment effect waning

A treatment waning effect was incorporated in the base-case analysis to reflect the uncertainty around the extent of disease progression following treatment discontinuation. Treatment effect waning assumed that, once avelumab + axitinib treatment is stopped at two years, a proportion of patients gradually lose some of the accumulated treatment benefit, and instead eventually follow the PFS and OS hazard associated with sunitinib. Based on discussions with clinicians, the upper and lower ranges of responding patients who may lose some benefit following discontinuation was estimated to be 50% and 20%, respectively.

Therefore, a treatment waning effect was applied for a third of patients following discontinuation of avelumab + axitinib in the base-case analysis.

In a real-world setting, the loss of treatment effect is unlikely to occur instantaneously and is instead likely to occur gradually over time. As such, the model accounted for this by producing a weighted hazard based on the stratified PFS and OS curves for avelumab + axitinib and sunitinib from JAVELIN Renal 101 over a 2-year period post-discontinuation. The gradual transition from the avelumab + axitinib hazard to the sunitinib hazard was estimated linearly, and the PFS and OS curves were weighted such that a new survival curve was estimated for avelumab + axitinib at each cycle as a construct of the hazard of the two treatments.

For the remaining two-thirds of patients still benefiting from treatment after two years, it was assumed that, after stopping avelumab + axitinib, they would continue receiving treatment benefit and follow the PFS and OS hazard associated with avelumab + axitinib.

B.3.3.7 Adjusting for general population mortality

To ensure model validity, all curves used to produce economic and survival estimates were capped to ensure that patients' transition to death was never lower than that of the general population. In any cycle where the OS curves were associated transition probabilities to the death state that were lower than general population mortality rates, patients instead faced a mortality risk equal to that of the general population.

B.3.3.8 Summary of modelled outcomes

Figure B.3.16, Figure B.3.17 and Figure B.3.18 present PFS, OS and ToT as estimated within the cost-effectiveness model for comparisons of avelumab + axitinib versus sunitinib based on stratified curves from JAVELIN Renal 101, versus tivozanib based on the non-PH ITC (in ITT population) and versus cabozantinib based on the non-PH ITC (in intermediate- or poor-risk status patients), respectively.

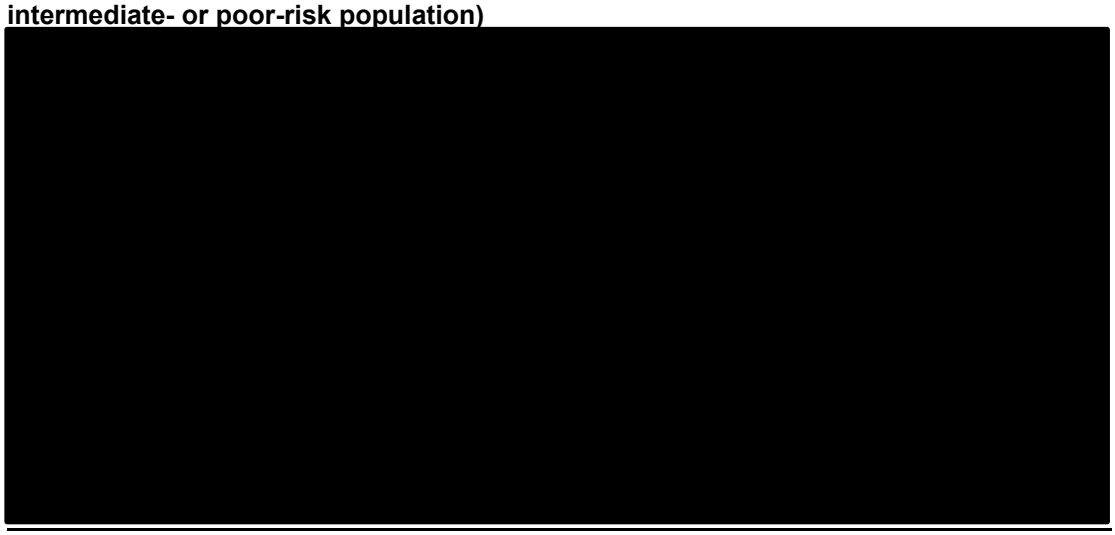
Figure B.3.16. Modelled PFS, OS and ToT for avelumab + axitinib versus sunitinib (ITT population)

Abbreviations: ITT = intention-to-treat; KM = Kaplan–Meier; OS = overall survival; PFS = progression-free survival; ToT = time on treatment

Figure B.3.17. Modelled PFS, OS and ToT for avelumab + axitinib versus tivozanib (ITT population)

Abbreviations: ITT = intention-to-treat; KM = Kaplan–Meier; OS = overall survival; PFS = progression-free survival; ToT = time on treatment

Figure B.3.18. Modelled PFS, OS and ToT for avelumab + axitinib versus cabozantinib (IMDC intermediate- or poor-risk population)



Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; KM = Kaplan–Meier; OS = overall survival; PFS = progression-free survival; ToT = time on treatment

B.3.4 Measurement and valuation of health effects

To capture the impact of symptoms of aRCC on patient quality of life, HRQoL is reflected in the analysis, informed by an SLR to identify utility studies relevant to the decision problem (see Appendix H). Thirty-eight studies were identified, including 13 conducted in the UK.

Utility values were applied to both health states in the model (PFS, PPS) to capture patient HRQoL associated with treatment and disease outcomes. Trial data were preferred as a source of utility inputs given that this allowed utility and efficacy data to be derived from the same population.

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

B.3.4.1.1 JAVELIN Renal 101

EQ-5D-5L data were collected in the JAVELIN Renal 101 clinical trial. According to NICE guidelines, EQ-5D (EQ-5D-3L) is the preferred descriptive system.[118] Therefore, the EQ-5D-5L responses were mapped to EQ-5D-3L using the van Hout crosswalk mapping algorithm.[119] The mapped responses were then used within a standard mixed effects regression model to identify significant factors that influence utility.

As seen in the utility values calculated based on the UK general population tariff and the EQ-5D questionnaire values from the JAVELIN Renal 101 study (Table B.3.41), there are large differences in utility between on-treatment and off-treatment patients in PPS. In JAVELIN Renal 101, the EQ-5D questionnaire was administered to patients at tumour assessment every 6 weeks. As patients with radiologic progression could remain on treatment in post-progression in JAVELIN Renal 101 there were numerous records of patients in the PPS health state but still receiving first-line treatment. However, given continued receipt of first-line treatment, these EQ-5D records were elicited in the absence of clinical progression. To reflect this, the regression analysis accounted for whether the record was captured on- or off- treatment in the estimation of the predicted utility values.

Table B.3.41. Observed EQ-5D questionnaire values in the JAVELIN Renal 101 study

Progression status	On/off treatment	Mean	Median	SD	Min	Max	Observations	Subjects
Post-progression	Off	0.639	0.701	0.273	-0.429	1	90	71
Post-progression	On	0.737	0.768	0.221	-0.429	1	1105	325
Pre-progression	Off	0.765	0.768	0.150	0.419	1	15	12
Pre-progression	On	0.777	0.768	0.184	-0.594	1	3479	696

Abbreviations: SD = standard deviation

To determine which baseline covariates were included in the final regression model for use in the base-case analysis, backward stepwise variable selection by AIC was used. Stepwise variable selection is a parsimonious approach to inclusion of covariates, chosen to avoid unnecessary complexity without additional statistical gain. The results of the regression model for each treatment arm, as well as the pooled treatment-independent utilities split by progression status, are presented in Table B.3.42.

Table B.3.42. Utility analysis – predicted results from regression model

Health state	Treatment	Utility
PFS	Avelumab + axitinib	0.722
	Sunitinib	0.737
	Pooled	0.730
PPS: on-treatment	Avelumab + axitinib	0.710
	Sunitinib	0.702
	Pooled	0.706
PFS: on-treatment	Pooled	0.753
PPS: off-treatment	Pooled	0.683

Abbreviations: PFS = progression-free survival; PPS = post-progression survival

Following discussions with UK consultant oncologists, there was agreement that, despite avelumab being well tolerated, there would be no difference in patient utility between the avelumab + axitinib and sunitinib treatment arms. This is aligned with the small differences shown between PFS and PPS utility estimates between treatments. Furthermore, treatment arm was not a significant covariate in the regression model. Therefore, pooled utility values across treatments for progression-free, on-treatment patients were considered to be most relevant to represent the HRQoL for patients in PFS (0.753). It was also agreed that the post-progression value for off-treatment utility (0.683) reflected the expected impact of progression on QoL.[107]

Base-case utilities estimated from the regression model using JAVELIN Renal 101 PLD are presented in Table B.3.43. The pooled progression-free (including on-treatment and off-treatment patients) utility value is explored in scenario analysis.

Table B.3.43. Base case utilities informed from the regression model using JAVELIN Renal 101 PLD

	Mean	SE	Lower bound	Upper bound
PFS: on-treatment	0.753	0.026	0.702	0.804
PPS: off treatment	0.683	0.026	0.632	0.734

Abbreviations: PFS = progression-free survival; PLD = patient-level data; PPS = post-progression survival; SE = standard error

B.3.4.1.2 Summary of utility values from PLD and literature sources

The selected base case PFS and PPS utility values calculated from the JAVELIN-Renal-101-mapped EQ-5D data are plotted in Table B.3.44 alongside utilities used in previous NICE TAs in aRCC. Both PFS and PPS utility values from the mapped analysis were in the approximate middle of the range of values extracted from the previous NICE TAs (Figure B.3.19).

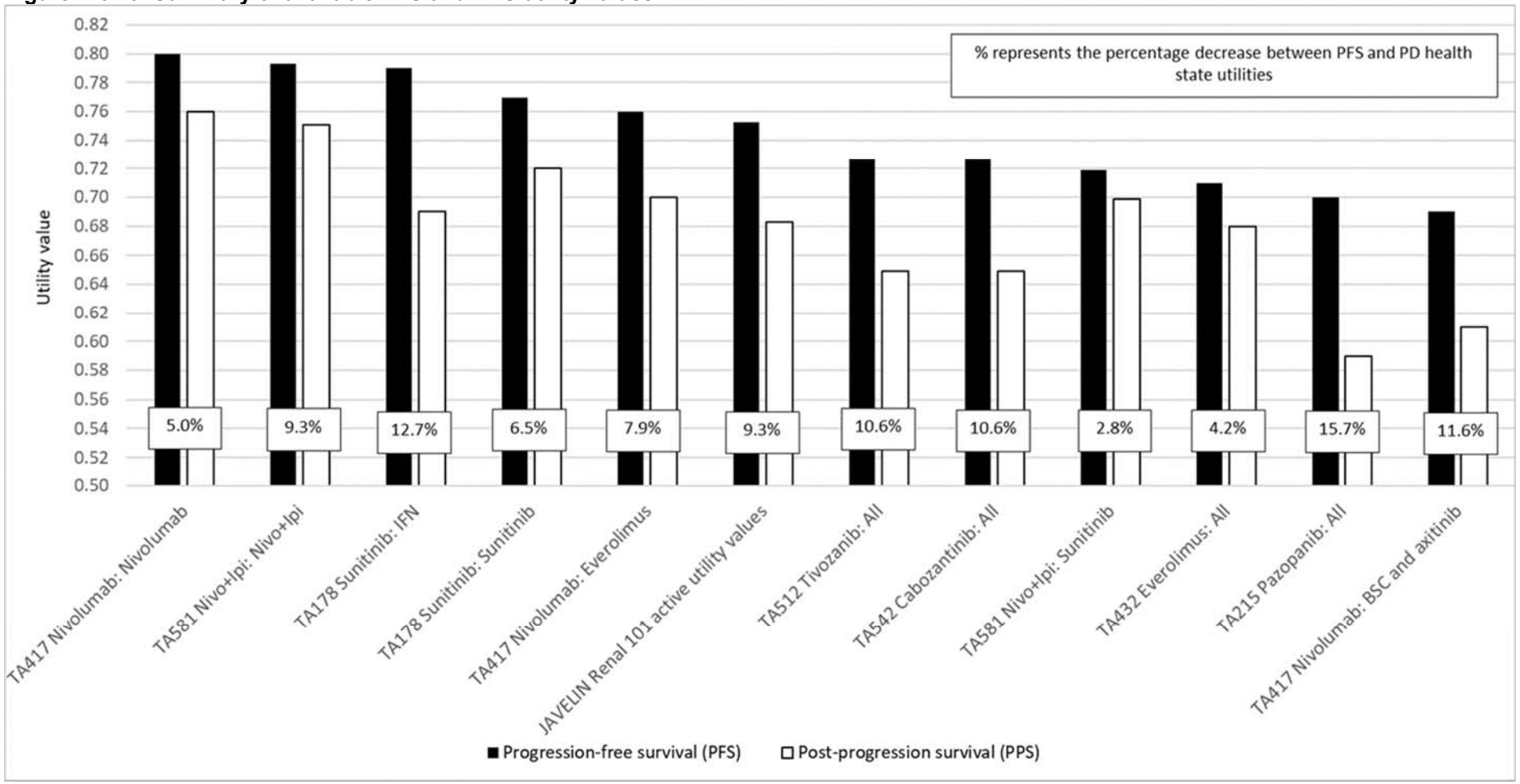
The percentage differences between the PFS and PPS utility values compared with the corresponding values in prior NICE TAs are presented in Figure B.3.19. The percentage difference for the base-case JAVELIN Renal 101 PFS and PPS values (6.42%) were comparable to those of previous NICE TAs. Therefore, the base-case analysis used the JAVELIN Renal 101 pooled treatment arm PFS and PPS utility values for all comparators not included as treatment arms in JAVELIN Renal 101.

Table B.3.44. Comparator utility values from previous NICE TAs

NICE TA	TA intervention	Indication	Treatment arm applied	PFS utility	PPS utility	Assumptions used
TA178[58]	Sunitinib	1L aRCC	Sunitinib	0.7700	0.7200	TA178: All arms have sunitinib with the exception of the placeholders, which are assumed to have IFN utility
	Sunitinib		IFN	0.7900	0.6900	
TA215[13]	Pazopanib	1L aRCC	All	0.7000	0.5900	N/A
TA512[12]	Tivozanib	1L aRCC	All	0.7260	0.6490	N/A
TA542[15]	Cabozantinib	1L aRCC	All	0.7260	0.6490	N/A
TA581[57]	Nivolumab + ipilimumab	1L aRCC	Nivolumab + ipilimumab	0.7930	0.7510	TA581: All therapies using antibodies have nivolumab + ipilimumab utility, all other have sunitinib utility
			Sunitinib	0.7190	0.6990	
TA432[61]	Everolimus	2L+ aRCC	All	0.7100	0.6800	N/A
TA417[60]	Nivolumab	2L+ aRCC	Nivolumab	0.8000	0.7600	TA417: All therapies using antibodies have nivolumab utility, all other have everolimus
			Everolimus	0.7600	0.7000	
			BSC and axitinib	0.6900	0.6100	
Average across all appraisals				0.7440	0.6816	N/A
Average % utility decrement				N/A	8.85%	N/A

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

Figure B.3.19. Summary of available PFS and PPS utility values



Abbreviations: BSC = best supportive care; IFN = interferon; PFS = progression-free survival; PPS = post-progression survival; TA = technology appraisal.
Note: Values represent the percentage reduction in QoL between the PFS and PPS health states

B.3.4.2 Age adjustment of utility values

As the interim analysis for JAVELIN Renal 101 had a relatively short follow-up period, age was not considered within the utility regression model. However, age is a significant covariate for utility in the general UK population.[120] To incorporate these findings in the base-case analysis, utility weights were calculated using the average age of the selected population to create the average age-adjusted general population utility per cycle. The relative utility decrement to the starting age is then calculated and applied as a multiplier to the QALYs per cycle.

The formula used was:

$$General\ population, EQ\text{-}5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

B.3.4.3 Adverse reactions

JAVELIN Renal 101 utilities were calculated using pooled utilities from PLD independent of whether patients experienced a TRAE. It was therefore assumed that the derived utility values were reflected any disutility from AEs, as applying disutilities related to adverse events would double count the quality of life impact of treatment already captured within the health state utility values for PFS and PPS. Scenario analyses were conducted to explore the effect of applying AE disutilities for Grade ≥3 TRAEs experienced by ≥5% of patients in JAVELIN Renal 101 and in comparator trials.

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

An SLR was conducted to identify published costs and resource use associated with previously untreated aRCC in the UK (see Appendix I). Fifteen studies reporting relevant cost and resource use evidence in the UK were identified, including ten HTAs and four economic evaluations.

B.3.5.1 Intervention and comparator costs and resource use

B.3.5.1.1 Acquisition costs

Acquisition costs associated with the intervention and comparators are presented in Table B.3.45. List prices were sourced from the Monthly Index of Medical Specialities. The discounted price for pazopanib reflects a non-confidential PAS discount of 12.5%;[13] while a non-confidential PAS is also in place for sunitinib, a discounted price is not shown in in Table B.3.45, as the first cycle of sunitinib is provided free of charge to the NHS.[14] Due to confidential nature of each PAS, discounted prices of tivozanib and cabozantinib were not known.[12, 62]

Table B.3.45. Acquisition costs of the intervention and comparators

Drug name	Drug form	Available unit amounts	Units in packet	List price	Discounted price
Avelumab[121]	Vial	200 mg	1	£768.00	[redacted]
Axitinib*[122]	Tablet	1 mg	56	£703.40	[redacted]
		3 mg	56	£2,110.20	[redacted]
		5 mg	56	£3,517.00	[redacted]
		7 mg	56	£4,923.80	[redacted]
Pazopanib[123]	Tablet	200 mg	30	£560.50	£490.44
		400 mg	30	£1,121.00	£980.88
Sunitinib[124]	Tablet	12.5 mg	28	£784.70	First 4-week cycle provided free of charge
		25 mg	28	£1,569.40	
		50 mg	28	£3,138.80	
Tivozanib[125]	Tablet	1.34 mg	21	£2,052.00	Unknown
Cabozantinib[126]	Tablet	20 mg	84	£4,800.00	Unknown
		80 mg	28	£4,800.00	

Abbreviations: mg = milligram
* For axitinib, the 7mg option is stated on the Monthly Index of Medical Specialities but is not included in the calculations of drug costs

In the base-case analysis, the avelumab dose was 800 mg (reflecting the proposed licensed dose), comprising 4 × 200mg vials, meaning no wastage was accrued. The 800 mg avelumab dose was used, rather than the weight-based dose used in the JAVELIN Renal 101 trial, because the cost-effectiveness analysis aims to reflect the costs likely to be incurred by the NHS, which, at the time of writing, is likely to be the 800 mg dose included within the proposed license. The 800 mg dose is similar to the mean weight-based dose observed in JAVELIN Renal 101. For axitinib and comparators, wastage was calculated for each cycle, using drug regimen, ToT and percentage relative dose intensity (RDI) to calculate whether a new drug packet was required. If so, the drug cost calculations assumed that a full packet was given upfront to all patients on treatment regardless of whether all of it was used. RDI for avelumab, axitinib and sunitinib was obtained from JAVELIN Renal 101 and calculated at 87%, 84%, and 81%, respectively. RDI for other TKIs was obtained from their respective clinical trials (see Appendix I).

B.3.5.1.2 Administration costs

Administration costs associated with the intervention and comparators are shown in Table B.3.46. Avelumab was assumed to be administered by a simple intravenous procedure in a hospital setting at each administration. For oral monotherapies, the first cycle administration cost included a consultant cost. However, for axitinib it was assumed that the consultation cost was already accounted for in the avelumab administration cost (with patients already visiting hospital), and therefore only pharmacist time was considered. Administration of oral therapy beyond the first cycle was costed as 12 minutes of hospital-based pharmacist staff time. Oral therapy administration was calculated in the same way as oral drug wastage, with drug regimen, ToT, and percentage RDI for each cycle used to calculate whether a new drug packet was required, and if so, an administration cost was applied.

Table B.3.46. Administration costs applied per treatment arm

Treatment	Administration cost		Administration type	Source
	First cycle	Subsequent cycles		
Avelumab	£174.00	£174.00	Intravenous (Simple)	NHS reference costs 2017/18 - Deliver Simple Parenteral Chemotherapy at First Attendance. Code SB13Z Outpatient[127]
Axitinib (in combination)	£9.60	£9.60	Oral (combination)	PSSRU 2018. Cost of 12 minutes pharmacist time (hospital-based staff: radiographer band 6)[128]
Sunitinib	£163.00	£9.60	Oral monotherapy	First cycle: NHS reference costs 2017/18 -Deliver exclusively oral chemotherapy. Code SB11Z Day and night[127] Subsequent cycles: PSSRU 2018. Cost of 12 minutes pharmacist time (hospital-based staff: radiographer band 6)[128]
Tivozanib	£163.00	£9.60	Oral monotherapy	
Pazopanib	£163.00	£9.60	Oral monotherapy	
Cabozantinib	£163.00	£9.60	Oral monotherapy	

Abbreviations: PSSRU = Personal Social Services Research Unit

B.3.5.2 Health-state resource use and unit costs

Resource use and cost estimates according to disease status (PFS/PPS) are shown in Table B.3.47. The base-case analysis reflected a micro-costing approach, which aligned with the recent NICE TA of nivolumab + ipilimumab for the first-line treatment of aRCC (TA581)[57] and consistent with other previous NICE TAs in aRCC.[60]

Table B.3.47. Resource use and costs associated with PFS and PPS health states

Resource	PFS		PPS		Cost per use	Source
	Weekly use	% patients	Weekly use	% patients		
GP visit	0.25	100%	0.25	100%	£31.00	PSSRU (2018) Section 10.3b p127, General practitioner unit costs. Patient contact lasting 9.2 minutes including direct staff costs excluding qualifications[128]
CT scan	0.08	100%	0	100%	£136.70	NHS ref costs 2017-18 "Computerised Tomography Scan of more than Three Areas", RD27Z[127]
Blood test	0.25	100%	0	100%	£2.51	NHS ref costs 2017-18 "Directly assessed pathological services - haematology", DAPS05[127]
Specialist community nurse visit	0	100%	0.38	100%	£67.99	PSSRU (2015) Section 10.4 p172. Nurse specialist (community), 1-hour patient time, excluding qualifications adjusted for inflation to 2018 prices[129, 130]
Pain medication	0	100%	7	100%	£9.65	BNF price morphine 10mg/1ml 10ml vial = £9.65[131]

Abbreviations: BNF = British National Formulary; CT = computerised tomography; GP = general practitioner; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit; TA = technology appraisal

B.3.5.3 Adverse reaction unit costs and resource use

Costs of management of Grade ≥3 AEs experienced by ≥5% of patients were included for the intervention and all comparators and were sourced from JAVELIN Renal 101 and NICE TAs (Table B.3.48). Costs of Grade ≥3 AEs are presented in Table B.3.49.

Table B.3.48. Incidence of Grade ≥3 TRAEs

AE	JAVELIN Renal 101		NICE TA512	NICE TA215	NICE TA542
	Avelumab + axitinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib
Diarrhoea	5.07	2.51	2.32	3.79	8.97
Hypertension	24.42	15.26	26.25	4.14	21.79
PPE syndrome	5.76	4.33	1.93	0.00	7.69
Thrombocytopenia	0.23	5.47	0.39	0.69	0.00
Anaemia	0.23	5.01	0.00	0.00	0.00
Platelet count decreased	0.00	5.01	0.00	0.00	1.28
Neutropenia	0.23	7.74	1.16	1.38	0.00
Neutrophil count decreased	0.00	5.69	0.00	0.00	0.00
Fatigue	3.00	3.64	5.41	1.72	5.13
Hypophosphatemia	0.00	0.00	4.25	0.00	8.97
Lipase increase	0.00	0.00	11.20	0.00	0.00
Stomatitis	1.84	0.91	0.39	0.00	5.13
Decreased appetite	1.61	0.91	0.39	0.00	5.13

Abbreviations: PPE = palmar-plantar erythrodysaesthesia; TRAE = treatment-related adverse event

Table B.3.49. Unit costs of adverse events

Adverse event	Unit cost	Reference
Diarrhoea	£1,248.34	FD10F Non-malignant Gastrointestinal Tract disorders with single intervention with CC score 5-8 Non-elective in patient short stay (NHS ref 17/18)
Hypertension	£843.60	Non-elective short stay unit cost of £615.76 (NHS ref 17/18) + Cost of Medical oncology visit WF01A; Non-admitted face-to-face attendance, follow up (£165.85, NHS ref 17/18) + 2 follow up GP visits (£31, PSSRU 2018)
Palmar-plantar erythrodysaesthesia syndrome	£615.76	Non-elective short stay unit cost of £615.76 (NHS ref 17/18)
Thrombocytopenia	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Anaemia	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Platelet count decrease	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Neutropenia	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Neutrophil count decrease	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Fatigue	£615.76	Non-elective short stay unit cost of £615.76 (NHS ref 17/18)
Hypophosphatemia	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Lipase increase	£357.13	Regular day and night admission SA04J Iron deficiency Anaemia with CC score 6-9, NHS Ref costs 17/18
Stomatitis	£1,248.34	FD10F Non-malignant Gastrointestinal Tract disorders with single intervention with CC score 5-8 Non-elective in patient short stay (NHS ref 17/18)
Decreased appetite	£615.76	Non-elective short stay unit cost of £615.76 (NHS ref 17/18)

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

The cost of each AE was multiplied by the proportion of patients in each treatment arm who experienced the AE, to produce a single value for AE costs per treatment arm (£358.65 for

avelumab + axitinib, £358.65 for sunitinib, £363.44 for tivozanib, £100.26 for pazopanib and £507.06 for cabozantinib). AE costs were applied independently of the selected subgroup and assigned as one-off costs in the first cycle of the model.

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Premedication

Patients received premedication with an antihistamine and paracetamol prior to the first four infusions of avelumab as per the avelumab SmPC.[23] The cost of £0.01 for paracetamol and £0.34 for chlorophenamine was added to the first four infusions of avelumab in the cost calculations.

B.3.5.4.2 Subsequent therapy costs

Subsequent therapies included in the base-case analysis are presented in Table B.3.50. Subsequent therapies were sourced from JAVELIN Renal 101 and were selected for inclusion if received by >10 patients in either treatment arm, given that subsequent therapies received by 10 or fewer patients are unlikely be used in UK clinical practice. JAVELIN Renal 101 data were used given that the subsequent therapies observed in the trial were broadly in line with what consulting oncologists would expect in a real-world UK setting.

Patients who received subsequent therapies administered to <10 patients in JAVELIN Renal 101 were proportionally distributed across the included subsequent therapies, resulting in reweighted patient numbers for each included therapy. From the whole trial population, 180 avelumab + axitinib patients and 216 sunitinib patients experienced a PFS event, therefore the number of patients receiving subsequent therapy (reweighted) was calculated as a proportion of those who had experienced a PFS event.

Table B.3.50. Subsequent therapies received by >10 patients in either treatment arm in JAVELIN Renal 101

Subsequent therapy	JAVELIN Renal 101 subsequent therapy received (number of patients)		JAVELIN Renal 101 subsequent therapy received (reweighted number of patients)		JAVELIN Renal 101 subsequent therapy received (% PFS event patients)	
	Avelumab + Axitinib	Sunitinib	Avelumab + Axitinib	Sunitinib	Avelumab + Axitinib	Sunitinib
Cabozantinib	42	28	45.8	34.2	25.4%	15.8%
Everolimus	8	3	8.7	3.7	4.9%	1.7%
Axitinib	15	17	16.3	20.8	9.1%	9.6%
Sunitinib	15	23	16.3	28.1	9.1%	13.0%
Nivolumab	14	107	15.3	130.6	8.5%	60.5%
Lenvatinib + everolimus*	11	16	12.0	19.5	6.7%	9.0%
Pazopanib	7	12	7.6	14.6	4.2%	6.8%

* Lenvatinib is only licensed for RCC in combination with everolimus. Because everolimus was received by more patients then lenvatinib, it was assumed that all patients who received lenvatinib received it in combination with everolimus and these patients were removed from the everolimus monotherapy group

The list prices of subsequent therapies that were not included as first-line comparators (Table B.3.45) are provided in Table B.3.51. The dosing regimens and ToT for the subsequent therapies in a second-line aRCC setting were sourced from the literature (Table B.3.52) to calculate an overall cost for a single full course of each subsequent therapy (Table

B.3.53), and reflect discounts associated with a non-confidential patient access schemes (PAS) for sunitinib and pazopanib only. Intravenous costs for subsequent therapies were calculated using existing cost per dose using method of moments whereas oral therapies were costed per mg. Administration costs used the values displayed in Table B.3.46, with the intravenous (simple) cost applied per administration for intravenous therapies, and the oral (first cycle - non-combination) cost applied as a one-off cost for oral therapies.

Table B.3.51. List prices of subsequent therapies not included as comparators (not reflective of confidential PAS)

Drug name	Available unit amounts	Units in packet	Price
Everolimus[132]	2.5 mg	30	£1,200
	5 mg	30	£2,250
	10 mg	30	£2,673
Lenvatinib[133]	4 mg	30	£1,437
	10 mg	30	£1,437
	2.5 mg	30	£1,200

Abbreviations: PAS = patient access scheme

Table B.3.52. Dosing of subsequent therapies

Subsequent therapy	Drug	Dose per administration	Administration route	Frequency of administration (days)	Units per dose	Time on treatment (days)	References
Cabozantinib	Cabozantinib	60 mg	Oral	1.00	60.00	231.70	TA542 Committee papers: Table 58[15]
Everolimus	Everolimus	10 mg	Oral	1.00	10.00	167.00	TA542 Committee papers: Table 58[15]
Axitinib	Axitinib	5 mg	Oral	1.00	5.00	220.50	TA542 Committee papers: Table 58[15]
Sunitinib	Sunitinib	50 mg	Oral	0.67	50.00	172.90	TA542 Committee papers: Table 58[15]
Nivolumab	Nivolumab	3 mg/kg	Intravenous	0.07	249.17	294.00	TA542 Committee papers: Table 58[15]
Lenvatinib + everolimus	Lenvatinib	18 mg	Oral	1.00	18.00	243.50	TA498 Committee papers: Table 40[15]
	Everolimus	5 mg	Oral	1.00	5.00		
Pazopanib	Pazopanib	800 mg	Oral	1.00	800.00	348.60	TA542 Committee papers: Table 58[15]

Abbreviations: PFS, progression-free survival; RCC, renal cell carcinoma; ToT, time on treatment.

Table B.3.53. Calculated total (one-off) costs of subsequent therapies

Subsequent therapy	Calculated cost
Cabozantinib	£39,883
Everolimus	£15,069
Axitinib	£14,011
Sunitinib	£13,084
Nivolumab	£63,367
Lenvatinib + everolimus	£32,168
Pazopanib	£22,958

The calculated subsequent therapy costs were weighted by the proportion of patients who experienced a PFS event and the estimated proportions receiving each subsequent therapy by first-line treatment arm (Table B.3.50), resulting in weighted subsequent therapy costs of £21,812 for avelumab + axitinib and £52,398 for sunitinib. A higher proportion of patients in the sunitinib arm received IO therapies in comparison to the avelumab + axitinib arm, which accounts for the higher cost. Subsequent treatment patterns for all other comparators were assumed equal to sunitinib given all comparators including sunitinib are TKIs. These assumptions were supported by UK consultant oncologists, who indicated that patients treated with a first-line IO therapy would not be treated subsequently with an IO.[107] The subsequent therapy costs were applied in the analysis to each patient upon disease progression and were assumed to be independent of risk subgroup. The subsequent therapy costs for each treatment arm are presented in Table B.3.54 as landmark undiscounted cumulative estimations using the base-case inputs.

Table B.3.54. Landmark cumulative undiscounted subsequent therapy costs

Time point	Avelumab + axitinib	Sunitinib	Tivozanib	Pazopanib
6 months	£6,531	£21,530	£20,870	£21,805
1 year	£10,270	£32,433	£31,141	£34,217
2 years	£13,953	£41,307	£39,857	£43,558
5 years	£17,776	£48,297	£47,254	£49,822
10 years	£19,637	£50,733	£50,107	£51,556

B.3.5.4.3 End-of-life costs

A one-off end-of-life cost was applied to patients at the point of dying to reflect the cost of terminal care, sourced from the King's Fund (Addicott et al. 2008).[134] The reported cost was £5,324.00, which was inflated to 2018 prices (£6,351.36) using the PSSRU 2018 hospital and community health services index.[128]

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

B.3.6.1 Base-case analysis inputs

A full list of parameter inputs, the associated distributions and scale of uncertainty are presented in Appendix J. Parameters were explored through probabilistic and deterministic sensitivity analyses as shown in Table B.3.55.

Table B.3.55. Summary of base case inputs

Component	Parameter bundle	Tested in OWSA	Tested in PSA	Tested in scenario analysis
Model settings	Time horizon	No	No	Yes
	Discount rates	No	No	Yes
	Cycle length	No	No	No
Patient characteristics	Mean age	No	No	No
	Proportion male	No	No	No
	Patient weight	No	No	No
Parametric survival parameters	OS	No	Yes	Yes
	PFS	No	Yes	Yes
	ToT	No	Yes	Yes
Adverse events	Frequencies	Yes	Yes	Yes
	Durations	Yes	Yes	No
	Costs	Yes	Yes	No
Drug costs	First-line drug costs	No	No	No
	Flat dose vs weight-based	No	No	Yes
	Wastage	No	No	Yes
	Relative dose intensity	Yes	Yes	Yes
	Stopping rule	No	No	Yes
	Treatment effect waning	Yes	Yes	Yes
Subsequent therapy costs	Duration of 2L treatment	No	No	No
	Treatment distribution in 2L	No	No	No
	Total costs of subsequent therapy by 1L treatment	Yes	Yes	No
Drug administration	Drug administration (IV & oral)	Yes	Yes	No
Monitoring	Health care resource use estimates per week by health state	Yes	Yes	Yes
	Terminal care costs	Yes	Yes	Yes
Utilities	PFS utility	Yes	Yes	Yes
	PPS survival utility	Yes	Yes	No
	AE disutility	No	No	Yes

Abbreviations: 1L = first-line; 2L = second-line; AE = adverse event; IV = intravenous; OS = overall survival; OWSA = one-way sensitivity analysis; PFS = progression-free survival; PPS = post-progression survival;

B.3.6.2 Assumptions

Table B.3.56. Summary of assumptions for base case analysis

Parameter	Base-case assumption		Justification
Model structure	A partitioned survival analysis incorporating PFS, PPS and death as health states is appropriate to most accurately measure outcomes of aRCC		In alignment with prior NICE submissions[12, 13, 15] Reflects the chronic nature of disease and care pathway in aRCC
Population	Patients with untreated aRCC		According to the NICE Final scope and in line with the anticipated licence of avelumab + axitinib
Survival curves	Avelumab + axitinib vs sunitinib	Application of stratified curves for avelumab + axitinib versus sunitinib	JAVELIN Renal 101 trial data was most appropriate to inform avelumab + axitinib versus sunitinib as it provides a direct comparison. Not applying the ITC, which contains other treatments within the network, reduces the risk of adding bias into the comparison. Given avelumab and sunitinib have different mechanisms of action, applying stratified curves for each arm was considered most appropriate.
		Generalised Gamma is the most appropriate PSM to estimate PFS of avelumab + axitinib	The generalised gamma was the best statistical and visual fit to the data and had long-term plausibility based on clinical feedback received at an advisory board of UK clinicians and health economists
		Log-logistic is the most appropriate PSM choice to estimate the OS of avelumab + axitinib	All PSMs had similar AIC/BIC statistics. The log-logistic curve was selected based on long-term plausibility in the shape of the curve.
		Log-logistic is the most appropriate PSM choice to estimate the PFS of sunitinib	Based on feedback at the advisory board, the Generalised F and Generalised Gamma distributions were considered too optimistic. The log-logistic curve was selected based on good visual representation to the data.
		Log-logistic is the most appropriate PSM choice to estimate the OS of sunitinib	The log-logistic curve was considered an appropriate fit based on the visual fit to the KM and the long-term plausibility of the curve. Based on the visual fit to the KM, the Weibull, Gompertz and generalised gamma curves were excluded based on lack of plausibility. The log-normal curve, despite being the best statistical fit was also considered to be an overestimate to the KM data. Of the remaining curves; the exponential and log-logistic projected similar survival until 10 years. The log-logistic was selected for sunitinib OS in the base-case analysis, as it had slightly higher

			long-term projections.
	Avelumab + axitinib versus pazopanib	Pazopanib is assumed equivalent to sunitinib	In line with previous NICE committee conclusions and clinical feedback, where sunitinib and pazopanib are considered to be equally effective, the base-case analysis assumes that pazopanib is equivalent to the stratified sunitinib curves.
	Avelumab + axitinib versus tivozanib	The non-PH ITC is the most appropriate way to compare avelumab + axitinib to tivozanib	It was not considered appropriate to assume tivozanib was equivalent to sunitinib (as is the case for pazopanib) based on prior appraisal committee conclusions. Therefore, an ITC was used to estimate tivozanib survival. Log-cumulative hazard plots from the TIVO-1 trial comparing sorafenib to tivozanib indicated that proportion hazards do not hold. Hence the non-PH ITC was considered the most appropriate option to compare avelumab + axitinib to tivozanib. For consistency this was applied to both PFS and OS. The benefit of ITC methods is that it allows all treatments to be compared within one cohesive analysis. To avoid the risk of bias by combining elements of different methods such as selecting stratified JAVELIN curves for avelumab and a curve for tivozanib derived from a non-PH ITC (which incorporates other comparators including sunitinib and avelumab + axitinib data from JAVELIN), the non-PH ITC output was also used to inform the avelumab + axitinib arm in this comparison.
		Generalised Gamma curves are used from the non-PH ITC to apply to PFS for avelumab + axitinib and tivozanib	The Generalised Gamma curves provided the best statistical fit to the non-PH ITC, and provided plausible survival estimates.
		Generalised Gamma curves are used from the non-PH ITC to apply to OS for avelumab + axitinib and tivozanib	The Generalised Gamma curves provided the best statistical fit to the non-PH ITC, and provided plausible survival estimates
	The studies used within the ITC were comparable to the JAVELIN Renal 101 population and appropriate for use in the ITC		Whilst there is heterogeneity between the studies, it was concluded that the baseline characteristics were sufficiently comparable.
ToT	ToT uses JAVELIN Renal ToT data for both avelumab + axitinib and sunitinib. A 2-year stopping rule for both avelumab and axitinib for 100% of patients for both, treatment waning starts immediately, lasts for 2 years and is applied to 33%	JAVELIN Renal 101 therapies ToT PLD data is used to extrapolate ToT curves to capture drugs costs	The available ToT data is appropriate to estimate time on treatment by extrapolating the PLD.
		Log-normal and log-logistic are the most appropriate distributions selected for extrapolating avelumab and	Both selected curves are within an acceptable range of the AIC/BIC values for the optimal fit. Both selected curves are similar to the base-case avelumab + axitinib PFS curve

	of patients. After 2 years, the same PFS & OS hazards as sunitinib are applied for these patients.	axitinib ToT respectively.	
		Log-normal is the most appropriate distribution for extrapolating sunitinib ToT.	The selected curve is within an acceptable range of the AIC/BIC values for the optimal fit. The fit is consistent with the selected avelumab ToT curve and is similar to the base-case sunitinib PFS curve.
		A two-year treatment stopping rule was applied for both avelumab and axitinib, based on the immune-modifying effect of avelumab.	In addition to supportive data in aRCC, data from IO therapies in other indications supports a two-year stopping rule for avelumab + axitinib. Prescribing oncologists would be receptive to a stopping rule and would be amenable to implementing it in their practice, and patients are also likely to benefit from the convenience, costs, and safety of a stopping rule.
		When patients stop treatment in pre-progression, a treatment waning effect is applied to adjust their PFS and OS hazards.	A treatment waning effect was incorporated in the base-case analysis, which assumed that, once avelumab + axitinib treatment is stopped at two years, 33% of patients (based on clinical feedback) gradually lose the treatment effect over two years after discontinuation, and instead follow the PFS and OS hazard associated with sunitinib.
		Pazopanib ToT is assumed equivalent to sunitinib.	Based on the assumption that sunitinib and pazopanib are considered to be equally effective, the base-case analysis assumes that ToT for pazopanib is the same as ToT for sunitinib.
		Tivozanib ToT uses PFS as a proxy for ToT.	Owing to the limited ToT data for tivozanib, it is assumed that ToT is the same as the PFS for tivozanib.
HRQoL	EQ-5D assessment is the most appropriate way to describe HRQoL in aRCC		Reported in NICE methods guidance[99] and in alignment to prior NICE submissions.[12, 13, 15]
	Pooled treatment utility between JAVELIN Renal 101 treatment arms is more representative than utility split by treatment		Clinical opinion confirmed that it was appropriate to pool treatment arms.[107]
	The utility for PFS: pooled (on-treatment) is more suitable than PFS: on-treatment and off treatment (pooled) for the PFS health state		Given similarity of ToT to PFS, it is appropriate to assume that the HRQoL of patients in the PFS state would be best represented by those still on treatment, associated with a utility value of 0.753.
	The utility for PPS: off-treatment is more suitable than PPS: pooled for the PPS health state		PPS off-treatment utility is expected to be more representative of the quality of life of patients in progression in the real-world, as validated by clinicians.[107]
	The calculated JAVELIN Renal 101 PFS and PPS base case utility values are appropriate to use for the intervention and all comparators		The calculated PFS and PPS values and percentage difference between the calculated PFS and PPS values are both centrally in the range of reported utility values from previous aRCC NICE TAs.
	Utility values applied in the base-case analysis are not dependent on selected subgroup		Analysis of JAVELIN Renal 101 HRQoL scores showed no significant difference in values between subgroups.
	It is appropriate to age-adjust utilities throughout the model		Ara and Brazier (2010)[120] found that age was a significant covariate in the

	time horizon	regression of HRQoL in the general population. As people age, they experience a natural decline in quality of life. It is therefore acceptable to assume that this would be the case in a patient population.
	Disutility should not be applied to patients to account for HRQoL decrements whilst experiencing adverse reactions	The use of the JAVELIN Renal 101 data to derive HRQL utilities inherently captures the disutilities which result from AEs. This may be a conservative estimate for other treatments outside of the trial.
Intervention and comparators' costs and resource use	Wastage is applied to all first-line drugs	It is appropriate to assume that there is no vial sharing within the NHS for intravenous drugs and that part-used packets are not recovered if unused
	Percentage RDI for each first-line therapy should be reflected	Given the availability of the percentage RDI values from JAVELIN Renal 101 and the use in previous NICE submissions[12, 15, 57] it was appropriate to reflect RDI
Medical resource use	The resource use values from NICE TA581 (nivolumab + ipilimumab submission) are the most appropriate values to use for monitoring	NICE TA581 is the most recent first-line aRCC NICE submission. Medical resource use inputs were accepted in the appraisal
	Monitoring costs are assumed not to differ between subgroups	Because modelled outcomes only reflect one subgroup setting at a time and there is no inter-subgroup analysis, there is no bias in assuming the same monitoring costs. NICE TA581 is an appraisal of an intermediate-/poor-risk aRCC population which resource use estimates were accepted
AE costs	The AEs sourced from the literature for the comparators were appropriate for the patient population	All treatment-related AEs for comparators were sourced from literature using populations not dissimilar to population of interest.
	Where AEs were not reported in the literature it is appropriate to assume AE as 0% for that treatment arm	All AE sources reported 'significant' treatment-related AEs. Whilst the definition of significant varied between sources, it can be assumed that if an AE was not reported, it was not significant and therefore can be assumed to not make a significant impact on results.
	It is appropriate to apply the AE cost as a one-off cost in the first cycle	There are no available data on the timing of AEs in the trial or literature sources. It is clinically plausible that most AEs would occur within the first year. Any discounting in the analysis would not affect AE costs.
Subsequent therapy costs	The subsequent therapy costs for all treatment arms are based on JAVELIN Renal 101 subsequent therapy administration proportions split by first-line therapies which are IO based (avelumab + axitinib arm assumed representative) or non-IO based (sunitinib arm used)	Because of the frequent changes to the aRCC treatment landscape, it is most appropriate to use the most recent subsequent treatment figures available alongside clinical opinion. JAVELIN Renal 101 data was used because the subsequent therapies observed were broadly in line with that which is stated in the nivolumab + ipilimumab submission
	It is appropriate to calculate the subsequent therapy as a cost applied upon patients experiencing PFS events	There are no available data on the timing or length of subsequent therapy administration in the trial data; therefore, PFS event is an appropriate proxy for subsequent therapy administration
End-of-life costs	The costs sourced from the King's Fund (2008) and adjusted for inflation are the most representative costs for end-of-life	These costs were used in the most recent aRCC submission (TA581) [nivolumab + ipilimumab].

Abbreviations: AE = adverse event; AIC = Akaike information criterion; aRCC = advanced renal cell carcinoma; BIC = Bayesian information criterion; DSU = Decision Support Unit; HRQoL = health-related quality of life; IO = immune-oncology; ITC = indirect treatment comparison; IV = intravenous; KM = Kaplan–Meier; NICE = National Institute for Health and Care Excellence; non-PH = non-proportional hazards; OS = overall survival; PFS = progression-free survival; PSM = parametric survival model; PH = proportional hazards; PPS = post-progression survival; TA = technology appraisal

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis

Base-case pairwise cost effectiveness results for avelumab + axitinib (inclusive of a commercial access agreement rebate [redacted] for avelumab and [redacted] for axitinib) versus sunitinib and pazopanib are presented in Table B.3.57. Avelumab + axitinib was estimated to generate an additional [redacted] life years and [redacted] QALYs compared with sunitinib and pazopanib (assuming similar efficacy between sunitinib and pazopanib). The base case ICER of [redacted] versus sunitinib and [redacted] versus pazopanib indicates that avelumab + axitinib is a cost-effective treatment at a cost-effectiveness threshold of £30,000.

Table B.3.57. Base-case pairwise cost-effectiveness results (with CAA/PAS for all treatments) versus sunitinib and pazopanib

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (AVE+AX vs)
Avelumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,542
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,242

Abbreviations: CAA = commercial access agreement; ICER = incremental cost-effectiveness ratio; LY = life year; PAS = patient access scheme; QALY = quality-adjusted life year

Base-case pairwise cost-effectiveness results for avelumab + axitinib versus tivozanib are presented in Table B.3.58, separately to the results versus sunitinib and pazopanib given that the approach to estimate the cost-effectiveness versus tivozanib utilised the ITC of parametric survival curves, whilst the comparison to sunitinib and pazopanib utilised stratified curves based directly on data from JAVELIN Renal 101. Therefore, pairwise results have been provided separately given the slight variation in the survival estimates generated between the two approaches. The base case ICER of [redacted] versus tivozanib indicates that avelumab + axitinib is a cost-effective treatment option at a cost-effectiveness threshold of £30,000.

Table B.3.58. Base case pairwise cost-effectiveness results (with CAA/PAS for avelumab + axitinib) versus tivozanib

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (AVE+AX vs)
Avelumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,220

Abbreviations: CAA = commercial access agreement; ICER = incremental cost-effectiveness ratio; LY = life year; PAS = patient access scheme; QALY = quality-adjusted life year

Disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix K.

B.3.8 Sensitivity analyses

Sensitivity analyses were undertaken through pairwise analysis between avelumab + axitinib and sunitinib. The parameters which were included in probabilistic sensitivity analysis (PSA) and deterministic analysis are presented in Table B.3.55.

B.3.8.1 Probabilistic sensitivity analysis

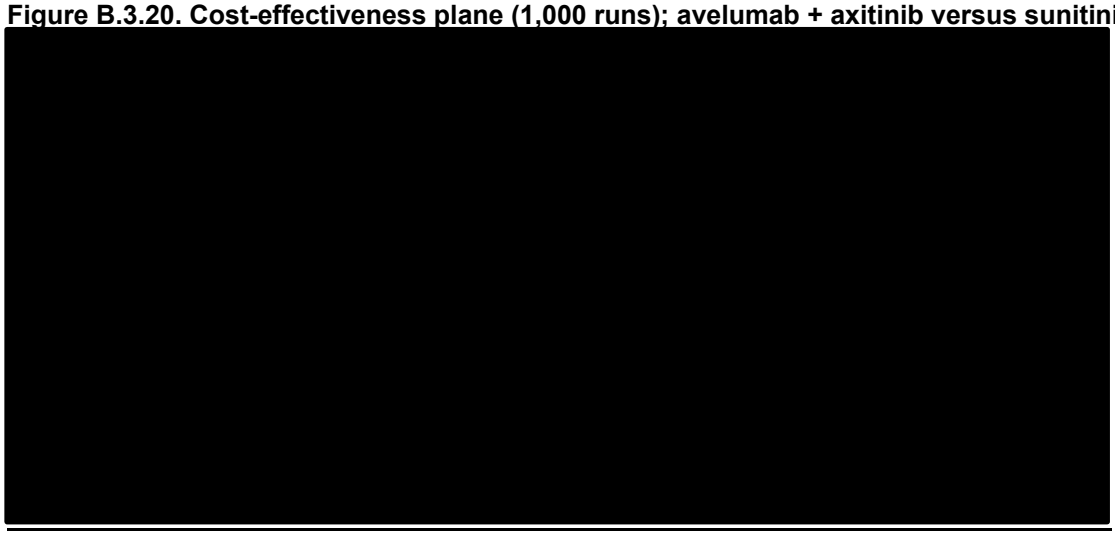
PSA was conducted for 1,000 iterations. The average incremental QALYs gained from avelumab + axitinib across the 1,000 iterations are presented in Table B.3.59 and Figure B.3.20. The results of the probabilistic analysis are similar to those of the deterministic analysis.

Table B.3.59. Mean results of PSA (1,000 runs) vs sunitinib and comparison with deterministic results

	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALYs)
Base case	[redacted]	[redacted]	[redacted]	26,242
Probabilistic analysis	[redacted]	[redacted]	[redacted]	24,961

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life years; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

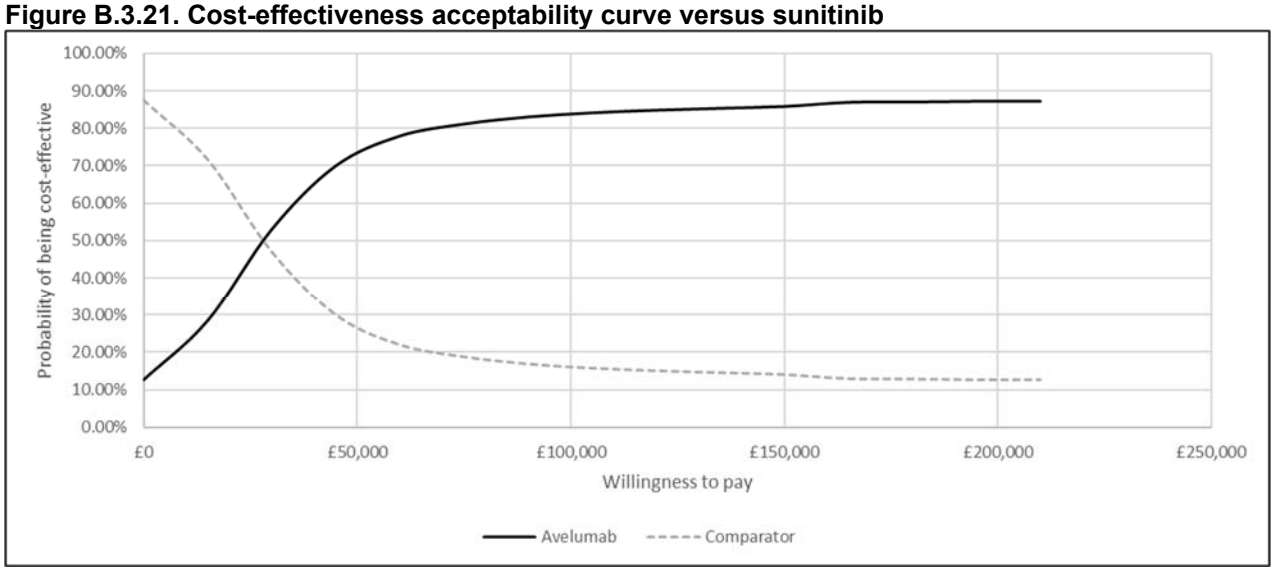
Figure B.3.20. Cost-effectiveness plane (1,000 runs); avelumab + axitinib versus sunitinib (ITT)



Abbreviations: PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure B.3.21 presents the cost-effectiveness acceptability curve for avelumab + axitinib compared with sunitinib, based on 1,000 PSA iterations at different willingness-to-pay (WTP) thresholds. At a WTP threshold of £30,000, avelumab + axitinib was cost effective against sunitinib in 55.5% of the PSA iterations.

Figure B.3.21. Cost-effectiveness acceptability curve versus sunitinib



B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was undertaken through one-way sensitivity analysis (OWSA), in which each base-case input was replaced with its lower and upper bound (see Table B.3.55), with all other inputs remaining unchanged from their base-case value.

Figure B.3.22 presents a tornado diagram showing the top 10 influential parameters with the greatest impact on the ICER. The percentage RDI of avelumab, axitinib and sunitinib were the most influential parameters for the ICER.

Figure B.3.22. Tornado diagram of the 10 most influential parameters on the ICER

[redacted]

Abbreviations: ICER = incremental cost-effectiveness ratio

B.3.8.3 Scenario analyses

The influence of specific model settings was explored through scenario analyses presented in Table B.3.60.

Table B.3.60. Scenario analyses

Category	Base case	Scenario description	Incremental results vs pairwise comparator		ICER vs sunitinib (£/QALY)
			Costs (£)	QALYs	
Base case			[redacted]	[redacted]	26,242
Model settings	Time horizon 40 years, discounting for costs and QALYs set to 3.5%	Time horizon: 5 years	[redacted]	[redacted]	101,644
		Time horizon: 25 years	[redacted]	[redacted]	27,858
		No outcome discounting (costs and QALYs)	[redacted]	[redacted]	16,294
PFS	JAVELIN stratified curves used: Gen gamma for avelumab + axitinib; Log-logistic for sunitinib	Avelumab: Stratified curves - Gompertz (best survival)	[redacted]	[redacted]	22,019
		Avelumab: Stratified curves - Weibull (worst survival)	[redacted]	[redacted]	41,288
		Avelumab: Stratified curves - Gen. gamma (best AIC)	[redacted]	[redacted]	26,242
		Avelumab: Stratified curves - Log-normal (best BIC)	[redacted]	[redacted]	32,287
		Sunitinib stratified curve as Gen F (best survival), avelumab stratified curve Gen Gamma	[redacted]	[redacted]	44,369
		Sunitinib stratified curve as Gen F (best survival), avelumab PH ITC, fixed effects	[redacted]	[redacted]	30,294
		Sunitinib stratified curve as Weibull (worst survival), avelumab stratified curve Gen Gamma	[redacted]	[redacted]	30,763
		Sunitinib stratified curve as Weibull (worst survival), avelumab PH ITC, fixed effects	[redacted]	[redacted]	36,917
OS	JAVELIN stratified curves used: Log logistic for avelumab + axitinib and for sunitinib	Avelumab: Stratified curves - Log-normal (best survival)	[redacted]	[redacted]	16,294
		Avelumab: Stratified curves - Gompertz (worst survival)	[redacted]	[redacted]	22,019
		Avelumab: Stratified curves - Exponential (best AIC/BIC)	[redacted]	[redacted]	41,288
		Sunitinib stratified curve as Gen Gamma (best survival), avelumab stratified curve Log-Logistic	[redacted]	[redacted]	26,242
		Sunitinib stratified curve as Gen Gamma (best survival), avelumab PH ITC fixed effects	[redacted]	[redacted]	32,287
		Sunitinib stratified curve as Gompertz (worst survival), avelumab stratified curve Log-Logistic	[redacted]	[redacted]	44,369
		Sunitinib stratified curve as Gompertz (worst survival), avelumab PH ITC fixed effects	[redacted]	[redacted]	30,294
ToT	Time on treatment is assumed to use JAVELIN Renal ToT for both avelumab + axitinib and sunitinib. A 2-year stopping rule for both	ToT: Assume ToT is equal to PFS	[redacted]	[redacted]	23,075
		ToT: Avelumab + axitinib - (Ave = Gompertz, Axi = Log-normal [highest])	[redacted]	[redacted]	26,935
		ToT: Avelumab + axitinib - (Ave = Exponential, Axi = Exponential [lowest])	[redacted]	[redacted]	24,686
		ToT: Sunitinib - Weibull (highest)	[redacted]	[redacted]	40,210
		ToT: Sunitinib - log-logistic (lowest)	[redacted]	[redacted]	23,994
		Apply stopping rule to avelumab: 24 months, 100% patients, no	[redacted]	[redacted]	21,000

	avelumab and axitinib for 100% of patients, treatment waning starts immediately, lasts for 2 years and is applied to 33% of patients. After 2 years, the same hazards as sunitinib is applied	waning			
		Apply stopping rule to avelumab: 24 months, 100% patients, waning applies to 33% of patients, takes full effect immediately after treatment stop	[redacted]	[redacted]	28,419
		Apply stopping rule to avelumab: 24 months, 100% patients, waning applies to 20% of patients, occurring gradually from treatment stop to 2 years post-treatment stop	[redacted]	[redacted]	24,021
		Apply stopping rule to avelumab: 24 months, 100% patients, waning applies to 50% of patients occurring gradually from treatment stop to 2 years post-treatment stop	[redacted]	[redacted]	29,537
Costs	Wastage applied to all therapies RDI included TA581 used for monitoring costs Kings Fund used as source for EOL costs	Avelumab dosing: weight based	[redacted]	[redacted]	37,007
		Wastage: Wastage not applied to IV drugs	[redacted]	[redacted]	27,712
		Wastage: Wastage not applied to any treatment arms	[redacted]	[redacted]	27,355
		RDI assumed to be 100% for all treatment arms	[redacted]	[redacted]	34,431
		TA542 (Cabozantinib submission) used for monitoring costs	[redacted]	[redacted]	31,481
		Round et al used for EOL costs	[redacted]	[redacted]	26,330
Utilities	Utilities use JAVELIN Renal 101 values, with on treatment for PFS, off treatment for PPS. Disutilities included	PFS utility: On-treatment and Off-Treatment Pooled	[redacted]	[redacted]	27,470
		AE disutilities applied	[redacted]	[redacted]	26,659

Abbreviations: AE = Adverse event; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; EOL = end of life; FE = fixed effects; ICER = incremental cost-effectiveness ratio; IO = immune-oncology; ITC = indirect treatment comparison; IV = intravenous; OS = overall survival; PFS = progression-free survival; PH = proportional hazard; QALY = quality-adjusted life-year; RDI = relative dose intensity; RE = random effects; ToT = time on treatment

Parameters that had a minimal impact on the ICER when varied in scenario analysis included reduction of the time horizon to 25 years, alternative utility values, and ToT extrapolations for all treatments except in the scenario when using the extrapolation for sunitinib ToT with the shortest ToT (Weibull). Modifying assumptions on the proportion of patients affected by treatment effect waning and the duration over which waning occurs had limited impact on the cost-effectiveness results. Modifying the base-case analysis to include the worst PFS estimates for avelumab + axitinib while keeping sunitinib PFS unchanged had the expected effect increasing the ICER.

Changes to base-case assumptions regarding OS had the highest impact: changing the selection of OS parametric survival for sunitinib to generalised gamma while leaving the base-case OS extrapolation for avelumab + axitinib unchanged led to sunitinib dominating. Selecting the parametric survival model with the worst OS for avelumab + axitinib while leaving sunitinib unchanged also led to sunitinib dominating. This scenario is considered to be highly unlikely given clinicians' expectations of long-term survival outcomes for IO-based treatment compared to TKIs.

For the comparison to tivozanib, an additional scenario analysis was performed to explore the impact of the uncertainty around the assumption of proportional hazards and the choice of ITC. The results obtained using the PH ITC did not show a large difference from the base-case results (see Table B.3.61).

Table B.3.61. Scenario analysis: pairwise cost-effectiveness results versus avelumab + axitinib vs tivozanib (with CAA for avelumab + axitinib):

	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base-case vs tivozanib (non-PH ITC)	[redacted]	[redacted]	[redacted]	£9,220
Scenario analysis vs tivozanib (PH ITC)	[redacted]	[redacted]	[redacted]	£13,330

Abbreviations: CAA = commercial access agreement; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life year; PH = proportional hazards; QALY = quality-adjusted life year

B.3.9 Subgroup analysis

Base-case pairwise cost effectiveness results for avelumab + axitinib versus cabozantinib in patients with IMDC intermediate- or poor-risk status are presented in Table B.3.62. Avelumab + axitinib is dominant versus cabozantinib, having higher incremental QALYs and lower costs.

Table B.3.62. Base-case pairwise cost-effectiveness results (with CAA for avelumab + axitinib only)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (AVE+AX vs)
Avelumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CAA = commercial access agreement; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix K.

B.3.9.1 Probabilistic sensitivity analysis

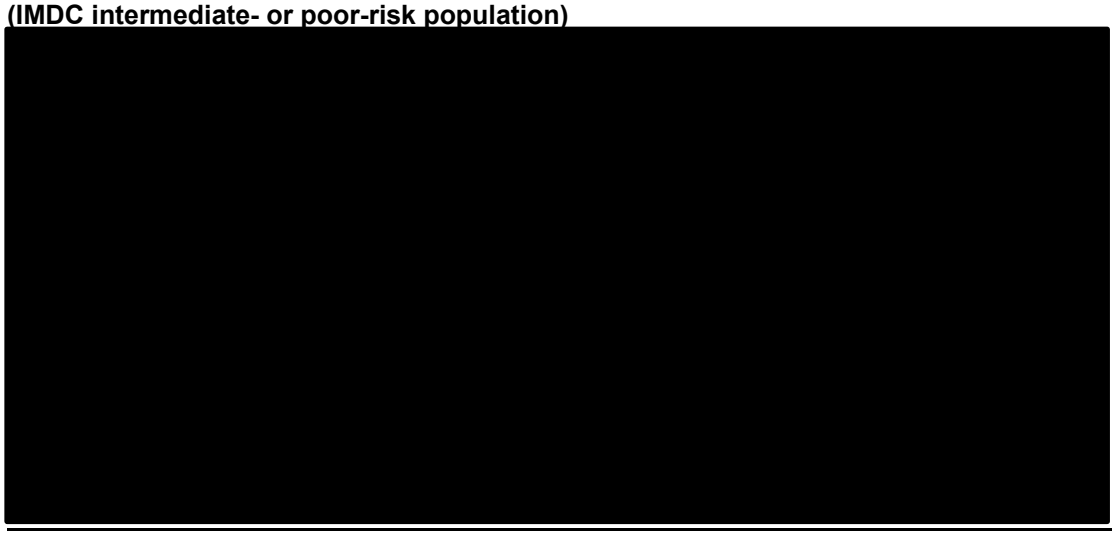
As was performed for the ITT population, PSA was conducted for 1,000 iterations. The mean incremental QALYs gained from avelumab + axitinib versus cabozantinib across the 1,000 iterations is presented in Table B.3.63 and Figure B.3.23. The results show that the results of the probabilistic analysis are similar to those of the deterministic analysis.

Table B.3.63. Mean results of PSA (1,000 runs) versus cabozantinib and comparison with deterministic results

	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic analysis	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure B.3.23. Cost-effectiveness plane (1,000 runs); avelumab + axitinib versus cabozantinib (IMDC intermediate- or poor-risk population)

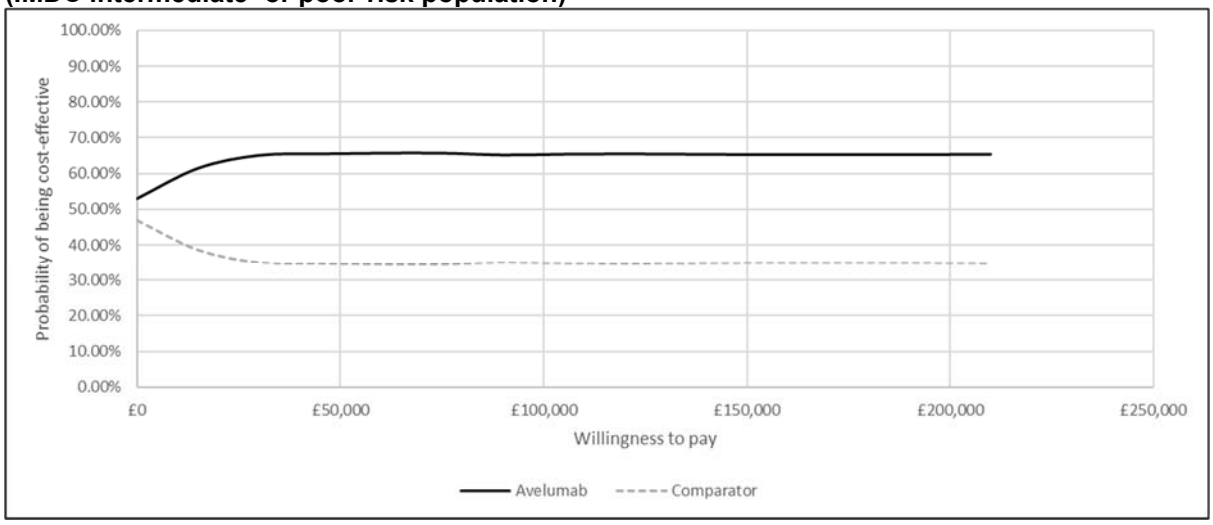


Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; QALY = quality-adjusted life year

Figure B.3.24 presents the cost-effectiveness acceptability curve for avelumab + axitinib compared with cabozantinib, based on 1,000 PSA iterations at different WTP thresholds. At

a WTP threshold of £30,000, avelumab + axitinib was cost effective against cabozantinib in 65.0% of the PSA iterations.

Figure B.3.24. Cost-effectiveness acceptability curve; avelumab + axitinib versus cabozantinib (IMDC intermediate- or poor-risk population)



Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium

B.3.9.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was undertaken through one-way sensitivity analysis (OWSA), in which each base-case input was replaced with its lower and upper bound (see Table B.3.55), with all other inputs remaining unchanged at their base-case value.

Figure B.3.25 presents a tornado diagram showing the top 10 influential parameters with the greatest impact on the ICER. The percentage RDI of avelumab, axitinib and sunitinib were the most influential parameters for the ICER when reflecting extreme upper and lower values.

Figure B.3.25. Tornado diagram of the 10 most influential parameters on the ICER

[redacted]

Abbreviations: ICER = incremental cost-effectiveness ratio

B.3.9.3 Scenario analysis

For the comparison to cabozantinib, additional scenario analyses were performed to explore potential uncertainty around the assumption of proportional hazards and the choice of ITC. As reported in Table B.3.64, results obtained for avelumab + axitinib versus cabozantinib using the PH ITC showed an increase in incremental costs and a reduction in the incremental QALY gain, resulting in cabozantinib dominating, although the negative incremental gain is marginal (-0.12 QALYs). These results are in line with what would be expected when assuming proportional hazards, given the PFS HR of cabozantinib of 0.48 vs. sunitinib in the Phase 2 CABOSUN trial. The small size of the CABOSUN trial was previously cited in the NICE TA of cabozantinib in 1L RCC as a source of uncertainty, as was the underperformance in terms of median PFS in the sunitinib arm in CABOSUN (5.3 months; see Table B.1.5) compared with the median PFS observed in the sunitinib arm (8.4 months) within the clinical trial assessing nivolumab + ipilimumab in 1L RCC intermediate- or poor-risk patients.[15] Median PFS in intermediate- or poor-risk status patients with the sunitinib arm of JAVELIN Renal 101 was [redacted].

For reasons described in Section B.2.9.3, the PH ITC does not appear to be an appropriate choice for the comparison to cabozantinib, especially given feedback received from clinical oncologists in the UK on the lack of plausibility for a long-term survival benefit of cabozantinib compared with avelumab + axitinib. Furthermore, it should be noted that sunitinib and pazopanib are the established TKIs with vastly greater usage among intermediate- or poor-risk status patients than cabozantinib in the NHS.

Table B.3.64. Scenario analysis: pairwise cost-effectiveness results avelumab + axitinib versus cabozantinib (with CAA for avelumab + axitinib): results using PH ITC for PFS and OS

	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALYs)
Base-case vs cabozantinib (non-PH ITC)	[redacted]	[redacted]	[redacted]	Dominant
Scenario analysis vs cabozantinib (PH ITC)	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: CAA = commercial access agreement; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life year; PH = proportional hazards; QALY = quality-adjusted life year

B.3.10 Validation

According to NICE DSU Technical Support Document 14, long-term extrapolated outcomes should be validated with the use of external data or clinical opinion.[135] Due to the novel combination treatment approach in aRCC, the data cannot be directly compared to external data sources with long-term follow-up. Thus, validation of clinical benefit observed with avelumab + axitinib depends upon comparison of outcomes between the model and clinical trials, whilst relying on expert opinion to confirm modelling assumptions. Predictions are reflective of clinical expectation and likely outcomes for aRCC patients in UK practice.

B.3.10.1 Comparison of outcomes – model and trial

As part of the validation process, results from the model were compared with survival outcomes in JAVELIN Renal 101. A summary of this comparison is presented in Table B.3.65.

Table B.3.65. Comparison survival outcomes reported in JAVELIN Renal 101 with modelled outcomes using stratified survival curves from JAVELIN Renal 101 for avelumab + axitinib (ITT population)

Outcome	Source	3 months (%)	6 months (%)	12 months (%)	18 months (%)	24 months (%)
PFS	JAVELIN Renal 101	81.8	69.2	53.5	45.2	NE
	Model	83.8	69.7	53.2	43.7	37.4
OS	JAVELIN Renal 101	97.0	94.4	86.3	79.6	70.3
	Model	97.2	93.6	86.2	79.2	72.8

Abbreviations: ITT = intention-to-treat; NE = not estimable

In JAVELIN 101 Renal, the avelumab + axitinib treatment arm was associated with a median PFS of 13.8 months, which aligns with the median PFS predicted by the model. Median OS has not yet been reached in JAVELIN Renal 101, however median OS predicted by the model is 53.36 months.

B.3.10.2 External validation

The modelling approach, assumptions and extrapolations beyond the follow-up period from JAVELIN Renal 101 were validated with clinical and health economic experts in group and one-to-one discussions.

B.3.10.2.1 During model development

In order to ensure the scientific rigour of this appraisal, Merck KGaA/Pfizer partnered with a number of health economic advisers. A modelling steering committee comprised of [redacted] were consulted early on at regular meetings over the course of several months in 2018 and early 2019 to advise on modelling methodologies used to inform the analysis. Additionally, [redacted] were consulted at a formal advisory board held by Merck KGaA/Pfizer on 21 March 2019.

As described in Section B.3.3.1, the parametric survival model options to extrapolate key outcomes such as PFS, OS and ToT were presented to clinicians at the March 2019 advisory board. The feedback received on the most plausible estimates based on clinical experience strongly influenced the choice of extrapolations to use for avelumab + axitinib and the comparators in the ITT population and intermediate- or poor-risk patients.

A key point of feedback provided by clinicians who participated in the advisory board was the agreement that patients would continue to receive benefit following discontinuation of IO treatment. The notion of 'the immune system remembers [the effect of IO treatment]' was described by the clinical advisors, based in part on observed outcomes of patients who have stopped various IO treatments due to AEs and continued to derive benefit.

B.3.10.2.2 Following model development

In order to ensure the technical rigour of the cost-effectiveness model and accuracy of the predicted outcomes, Merck KGaA/Pfizer sought external validation from an independent health economics and outcomes research consultancy who provided economic analysis and

insight into best modelling practices. The health economists who reviewed the model have extensive experience with HTA appraisals of IO therapies across a range of indications including aRCC and reviewed the model for errors, inconsistencies and plausibility of inputs alongside a checklist of questions.

In one-on-one discussions, clinical experts treating NHS patients with aRCC ([redacted]) provided critical feedback and validation of clinical assumptions and base-case settings of the cost-effectiveness analysis. These assumptions included best choices of parametric survival models for PFS, OS, and ToT, treatment stopping rule and potential treatment effect waning following discontinuation.

B.3.10.2.2.1 PFS extrapolations

Following the feedback received at the March 2019 advisory, the selected PFS extrapolations for avelumab + axitinib and comparators in the base case were presented to the advising clinicians in one-to-one discussions.

[redacted] stated that the base case PFS projections for avelumab + axitinib arm were slightly conservative, given that patients who are progression-free at 5 years would be at low risk of subsequent progression, and that we should see more of a flattening of the survival curve than seen with the generalised gamma PFS stratified curve.

[redacted] stated that in the first-line setting most patients progress within the first 2–5 years. Therefore, a long-term survival plateau should be observed beyond the inflection point with progression-free rate entirely stable beyond 10 years, similar to what has been observed in patients with melanoma treated with ipilimumab.[73] [redacted] agreed with the shape of the projected curve for the sunitinib arm and suggested realistic estimates would probably show 0% of patients progression-free beyond 10 years.

[redacted] indicated that the PFS extrapolations were in line with expectations of long-term outcomes associated with treatment with avelumab + axitinib and sunitinib.

B.3.10.2.2.2 OS extrapolations

Following the review of long-term PFS estimates, feedback was sought on the plausibility of base case OS extrapolations for avelumab + axitinib and comparators.

[redacted] suggested that OS estimates modelled for avelumab + axitinib arm were on the upper end of his expectations.

[redacted] discussed the inherent difficulty at present of estimating the OS outcomes following treatment with IO therapies beyond 5 years.

[redacted] gave feedback indicating that the extrapolated OS outcomes were in line with expectations for avelumab + axitinib, and that the estimates based on extrapolated OS for sunitinib was higher than those seen in his clinical experience.

B.3.10.2.2.3 Time on treatment estimates

Feedback was also sought on the ToT estimates included in the base case analysis.

[redacted] deemed the ToT estimates, with a third of patients still on avelumab treatment at 2 years, to be reasonable but indicated the unlikelihood of any patients remaining on axitinib treatment at 10 years, which the extrapolation of ToT data for axitinib shows in the absence of a stopping rule.

[redacted] said that most patients who are progression-free beyond 3 years would have derived ongoing benefit from avelumab rather than axitinib.

B.3.10.2.2.4 Clinical stopping rule and maintenance of treatment benefit

Clinical feedback was integral to developing the assumptions on treatment stopping and subsequent maintenance of treatment benefit. When asked about implementation of a stopping rule at a specific time point, both [redacted] and [redacted] agreed that the immune system "remembers" the treatment effect following treatment with IO therapies. Both clinicians expected treatment benefit to continue in most patients, supporting the rationale to stop treatment with avelumab. [redacted] stated, however, that he might feel nervous to stop axitinib at the same time as avelumab, for a small proportion of patients who may lose treatment benefit, and consequently would do so quickly. [redacted] believed that a 2-year stopping rule for avelumab would be acceptable, providing there was the possibility to re-challenge patients. Patients who are still receiving benefit a year after discontinuing the avelumab + axitinib combination would be likely to maintain benefit thereafter.

[redacted] believed that the majority of patients still on active treatment beyond one year would continue to benefit indefinitely with a low risk of relapse, and with benefit driven primarily by avelumab. Those patients whose disease is being controlled more by axitinib and rather than from avelumab would reveal themselves shortly (1-2 years) after stopping treatment. Dr Nathan expressed comfort with stopping both drugs at 2 years in the absence of contradictory data emerging and with access to restart the combination in patients who relapse.

[redacted] said that he would stop axitinib treatment but would keep patients on avelumab, as any patient responding to treatment beyond 2 years should tolerate long-term treatment with avelumab + axitinib. When asked at what point he may consider stopping axitinib, he was inclined to stop treatment at 2 years, with the rationale that the IO rather than the TKI is keeping the patient in remission. [redacted] did not believe that there would be a sudden loss of response for any patients stopping axitinib treatment, but that the treatment effect would wane gradually over time.

B.3.10.3 Summary

A summary of the validation processes conducted are provided in Table B.3.66.

Table B.3.66. Validation of the de novo cost-effectiveness analysis

Validation performed by	Nature of validation	Date(s)	Aspects covered
IO steering committee	Model development	Oct 2018–Jan 2019	Clinical data, economic model design and analyses
Advisory board which included a range of clinical and economic experts	Clinical overview	21st March 2019	Clinical data, treatment pathway, clinical assumptions, economic inputs, and modelling approach
Independent internal health economists	Quality-control checks	May 2019	Cost-effectiveness model calculations
[redacted]	Model projections, treatment duration and stopping rule	May–June 2019	PFS, OS and ToT extrapolations and landmark estimates, treatment duration assumptions, stopping rule and subsequent treatment effect waning assumptions

Abbreviations: IO = immuno-oncology

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Comparison with published economic literature

To our knowledge this is the first economic evaluation comparing avelumab + axitinib with approved TKIs in first-line treatment in patients with aRCC.

B.3.11.2 Relevance of the economic analysis to all patients who could potentially use the technology in the decision problem

This evaluation considers all patients identified in the decision problem.

B.3.11.3 Generalisability of the analysis

JAVELIN Renal 101 included patients with similar baseline characteristics to those expected in clinical practice, as validated by clinicians who treat aRCC in the UK across all risk groups. JAVELIN Renal 101 featured sunitinib as the direct comparator, a treatment which has a significant market share in the UK in the first-line treatment of aRCC. Subsequent treatments received by patients in the trial generally match what clinicians would expect based on recommendation for second-line in the UK, which consequently limits the uncertainty regarding the long-term survival outcomes projected in the analysis.

The cost-effectiveness analysis incorporated costs and resource usage from UK-based sources and from recent technology appraisals presented to NICE in aRCC. The necessary steps have been taken to produce a robust and conservative estimate of the clinical and cost-effectiveness of avelumab + axitinib reflective of UK clinical practice

B.3.11.4 Strength of the economic analysis

The key strengths of the economic analysis include the following:

- The partitioned survival approach utilises a simple model structure and has been used in previous aRCC appraisals, incorporates the available data from the pivotal trial and comparator trials and captures relevant outcomes in aRCC.

- An ITC of parametric survival curves was conducted to allow for comparisons of avelumab + axitinib compared with both tivozanib in the ITT population and cabozantinib in the intermediate- or poor-risk subgroup. This approach allows for a more robust comparison without the requirement of the PH assumption.
- EQ-5D data were collected in the JAVELIN Renal 101 study, aligning with the NICE reference case (EQ-5D; measured directly from patients; valued using UK general population tariff)
- Resource use and costs (administration, PFS and PPS disease management and terminal care costs) have been previously used and accepted in multiple previous aRCC appraisals, providing certainty in these values.
- Deterministic sensitivity analysis and scenario analysis demonstrated that the results are not highly sensitive to the majority of parameters and assumptions.

B.3.11.5 Limitation of the economic analysis

The analysis was limited due to both PFS and OS data having to be extrapolated as neither were complete (i.e. not all patients had experienced the corresponding event) from JAVELIN Renal 101, nor had median OS been reached in either treatment arm. By extrapolating based on the observed data in JAVELIN Renal 101, however, the best available evidence has been taken into account. The curves fitted to survival data varied in their extrapolations, indicating that there is uncertainty in the long-term outcomes for these patients. However, any uncertainty around the long-term extrapolation was addressed by the use of:

- Long-term data from previous aRCC trials with median follow-up greater than JAVELIN Renal 101 to provide expected landmark survival rates
- UK clinical expert opinion to select the most appropriate survival curves and inform and validate assumptions
- Scenario analysis to demonstrate the impact of assuming alternative survival curves and assumptions

The current lack of long-term follow-up of patients who are progression-free at 2-years and stop treatment is also a limitation of the economic analysis which contributes to uncertainty. However, long-term outcomes associated with other IO treatments used in aRCC as well as in other indications provides supportive evidence for the assumption of continued benefit following treatment stop.

B.3.11.6 Conclusions

Avelumab + axitinib is a novel, innovative treatment demonstrating improvements for key outcomes in the first-line treatment of aRCC. This combination, in its Phase 3 study against an active comparator, was the first IO + TKI to show a doubling of the response rates and a significant increase in PFS (see Section B.2.6.1.2). When compared to currently approved 1L treatments, avelumab + axitinib results in the longest median PFS, in turn delaying the onset of disease symptoms and the need for subsequent treatments. As such, avelumab + axitinib is a suitable treatment option for physicians and patients alongside the three-current standard-of-care TKIs.

The base-case economic analysis shows that avelumab + axitinib is a cost-effective treatment, with ICERs versus sunitinib, pazopanib and tivozanib of [redacted], [redacted] and [redacted], respectively. Avelumab + axitinib dominated cabozantinib in the subgroup analysis of

intermediate- or poor-risk status patients. The economic analysis had a number of strengths, including use of a simple and well-accepted model structure, indirect comparisons that allowed for the exploration of non-proportional hazards assumption on survival, utilities that were derived directly from patients and resource usage that had been utilised and accepted in previous appraisals. The main limitation of the analysis is the immaturity of the survival data, which is not yet substantial enough to demonstrate an immune response, visible through a flattening of the KM curve. The model projections, however, are consistent with the clinical data and were validated by comparison to clinical trial data and previous economic analyses. We also acknowledged the uncertainty around long-term PFS and OS estimates following the implementation of a treatment stopping rule. However, given the well-established immune-modifying effects of IOs that are known to drive benefit beyond treatment discontinuation, along with clinical feedback from UK oncologists, a reasonable assumption of long-term benefit can be assumed.

With a comprehensive view of both the JAVELIN Renal 101 data and a wider understanding of the long-term benefits of IO therapy, Merck and Pfizer are seeking funding for avelumab + axitinib through the Cancer Drugs Fund. It is anticipated that JAVELIN Renal 101 data will be sufficiently mature for reassessment following the final analysis, which is currently expected by [redacted]. In the interim, inclusion in the Cancer Drugs Fund will allow patients access to this promising and innovative treatment (as recognised by its PIM designation and positive EAMS scientific opinion from the MHRA) while clinical trial data matures.

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B.5. Appendices

Appendix C. Summary of product characteristics (SmPC) and European public assessment report (EPAR)

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. Summary of parameters included within the base-case economic model

Appendix K. Clinical outcomes and disaggregated results from the model

Appendix L. Checklist of confidential information

Appendix M. Clinical effectiveness – supplementary information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]

Clarification questions

August 2019

File name	Version	Contains confidential information	Date
ID1547 AVE+AXI aRCC ERG clarification questions Responses Fully Redacted	1.0	No	19 August 2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Data included in the network meta-analysis

A1. Priority request: Progression-free survival (PFS) and overall survival (OS) data. Table B.5.10 of Appendix D.2 summarises the survival outcomes (PFS and OS) for the trials included in the network meta-analyses (NMAs):

a. Please clarify, for each trial, which rows of data specifically from Table B.5.10 are used within the NMAs for PFS and OS.

b. Please also clarify how data included in the NMAs were extracted. For example, was digitisation software used to extract participant level data from Kaplan-Meier curves?

a. A copy of Table B.5.10 from the CS is presented below (Table 1) and has been updated to include an additional column detailing which data are used within the ITCs (rows highlighted in green). In some cases, analyses have been updated for minor corrections (rows highlighted in yellow). These errors resulted from the following: inadvertent use of investigator assessed PFS rather than from BICR [Motzer 2013], entering an incorrect value for confidence interval for cabozantinib OS due to typographical error [CABOSUN], and excluding a confidence interval in from the PH ITC for OS [COMPARZ]. All relevant details on these errors specified are in the table. These corrections result in minimal differences to the ITC results.

Table 1. Summary of survival outcomes of studies included in the mixed treatment comparisons

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
ITT population network										
Motzer 2019[11] (JAVELIN Renal 101)	AVE 10 mg/ kg q2w + AXI 5 mg BD	Overall	442	NR	Not Reached	0.78 (0.554-1.084)	NR	12.5 (11.1-15.2)	0.64 (0.625-0.775)	• OS HR and associated variability incorporated into the PH ITC • OS PLD incorporated into the non-PH ITC analyses.
	SUN 50 mg/d 4/2 schedule	Overall	444	NR	Not Reached	NR	NR	8.4 (8.2-9.7)	-	
	AVE 10 mg/ kg q2w + AXI 5 mg BD	Overall, IRC-assessed	442	NR	NR	NR	NR	13.8 (11.1-NE)	0.69 (0.56-0.84)	• PFS HR and associated variability incorporated into the PH ITC • PFS PLD incorporated into the non-PH ITC analyses.
	SUN 50 mg/d 4/2 schedule	Overall, IRC-assessed	444	NR	NR	NR	NR	8.4(6.9-11.1)	-	
	AVE 10 mg/ kg q2w + AXI 5 mg BD	IMDC risk group: Favourable	94	NR	NR	NR	NR	NE (16.1-NE)	0.54 (0.321-0.907)	
	SUN 50 mg/d 4/2 schedule	IMDC risk group: Favourable	96	NR	NR	NR	NR	13.8 (11.1-18.6)	-	
	AVE 10 mg/ kg q2w + AXI 5 mg BD	MSKCC risk group: Favourable	96	NR	NR	NR	NR	NE (12.6-NE)	0.65 (0.397-1.072)	
	SUN 50 mg/d 4/2 schedule	MSKCC risk group: Favourable	100	NR	NR	NR	NR	16.7 (11.1-18.6)	-	
	AVE 10 mg/ kg q2w + AXI 5 mg BD	MSKCC risk group: intermediate	283	NR	NR	NR	NR	13.3 (8.5-NE)	0.72 (0.559-0.915)	
	SUN 50 mg/d 4/2 schedule	MSKCC risk group: intermediate	293	NR	NR	NR	NR	7.9 (6.7-9.8)	-	

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
	AVE 10 mg/ kg q2w + AXI 5 mg BD	MSKCC risk group: Poor	51	NR	NR	NR	NR	5.6 (2.6-11.2)	0.5 (0.296-0.827)	
	SUN 50 mg/d 4/2 schedule	MSKCC risk group: Poor	45	NR	NR	NR	NR	2.8 (1.5-2.9)		
Eichelberg 2015[5] (SWITCH/ NCT00732914)	SOR 400 mg BD - SUN 50 mg/d 4/2 schedule	Overall	182	NR	NR	NR	NR	5.9	1.19	Published HRs (and KMs) and associated variability for OS and 1L progression-free survival incorporated into the ITCs
	SUN 50 mg/d 4/2 schedule - SOR 400 mg BD	Overall	183	NR	NR	NR	NR	8.5	NR	
	SOR 400 mg BD - SUN 50 mg/d 4/2 schedule	MSKCC risk group: Poor	NR	NR	NR	NR	NR	NR	1.3	
	SUN 50 mg/d 4/2 schedule - SOR 400 mg BD	MSKCC risk group: Poor	NR	NR	NR	NR	NR	NR	NR	
	SOR 400 mg BD - SUN 50 mg/d 4/2 schedule	MSKCC risk group: Intermediate	NR	NR	NR	NR	NR	NR	1.14	
	SUN 50 mg/d 4/2 schedule - SOR 400 mg BD	MSKCC risk group: Intermediate	NR	NR	NR	NR	NR	NR	NR	
Hutson 2013[8] (NCT009208	AXI 5 mg BD	Overall	192	NR	NR	NR	NR	10.1 (7.2-12.1)	0.77 (0.56-1.05)	KM data used within non-PH ITC (PH ITC using independent review HR is presented in Table

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
16)	SOR 400 mg BD	Overall	96	NR	NR	NR	NR	6.5 (4.7-8.3)	NR	2)
	AXI 5 mg BD	Overall	NR	NR	NR	NR	NR	11.1	0.77 (0.57-1.04)	Data used within the PH ITC
	SOR 400 mg BD	Overall	NR	NR	NR	NR	NR	7.4	NR	
	AXI 5 mg BD	MSKCC risk group: favourable	NR	NR	NR	NR	NR	NR	0.64 (0.4-1.02)	
	SOR 400 mg BD	MSKCC risk group: favourable	NR	NR	NR	NR	NR	NR	NR	
	AXI 5 mg BD	MSKCC risk group: intermediate/poor	NR	NR	NR	NR	NR	NR	0.83 (0.54-1.28)	
	SOR 400 mg BD	MSKCC risk group: intermediate/poor	NR	NR	NR	NR	NR	NR	NR	
	AXI 5 mg BD	Overall	192	NR	21.7 (18-31.7)	0.995 (0.731-1.356)	NR	NR	NR	Data used within the ITC
	SOR 400 mg BD	Overall	96	NR	23.3 (18.1-33.2)	NR	NR	NR	NR	
Motzer 2013[9] COMPARZ/	PAZ 800 mg/d	Overall	557	NR	28.4 (26.2-35.6)	0.91 (0.76-1.08)	NR	10.5 (8.3-11.1)	1 (0.86-1.15)	OS data used within the PH ITC

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
NCT00720941)	SUN 50 mg/d 4/2 schedule	Overall	553	NR	29.3 (25.3-32.5)	NR	NR	10.2 (8.3-11.1)	NR	
	PAZ 800 mg/d	Overall	557	NR	NR	NR	NR	8.4 (8.3-10.9)	1.05 (0.9-1.22)	PFS data used within the ITCs
	SUN 50 mg/d 4/2 schedule	Overall	553	NR	NR	NR	NR	9.5 (8.3-11.1)	NR	
	PAZ 800 mg/d	Overall	557	NR	28.3 (26-35.5)	0.92 (0.79-1.06)	NR	NR	NR	KM data used within the non-PH ITC – (more recent HR in this row for OS had incorrectly been excluded from PH ITC analyses – updated results are presented in Table 3 below)
	SUN 50 mg/d 4/2 schedule	Overall	553	NR	29.1 (25.4-33.1)	NR	NR	NR	NR	
	PAZ 800 mg/d	MSKCC risk group: Favourable	557	NR	42.5 (37.9-not reached)	0.88 (0.63-1.21)	NR	NR	NR	
	SUN 50 mg/d 4/2 schedule	MSKCC risk group: Favourable	553	NR	43.6 (37.1-47.4)	NR	NR	NR	NR	
	PAZ 800 mg/d	MSKCC risk group: Intermediate	557	NR	26.9 (23.1-35.6)	0.9 (0.74-1.09)	NR	NR	NR	
	SUN 50 mg/d 4/2 schedule	MSKCC risk group: Intermediate	553	NR	26.1 (20.7-31.6)	NR	NR	NR	NR	
	PAZ 800 mg/d	MSKCC risk group: Poor	557	NR	9.9 (7.3-12.3)	0.85 (0.56-1.28)	NR	NR	NR	
	SUN 50 mg/d 4/2 schedule	MSKCC risk group: Poor	553	NR	7.7 (5.4-11.9)	NR	NR	NR	NR	

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
Motzer 2013[7] (TIVO-1/NCT01030783)	TIV 1.5 mg OD	Overall	260	NR	NR	NR	NR	12.7	0.756 (0.58-0.985)	• PFS data used in ITCs • OS data published in NICE TA512 incorporated for OS The HR for PFS presented here corresponds to the treatment-naïve patient subgroup (and has a corresponding sample size of 181 in each arm)
	SOR 400 mg BD	Overall	257	NR	NR	NR	NR	9.1	NR	
Tomita 2017[6] (CROSS-J-RCC/ NCT01481870)	SUN 50 mg/d 4/2 schedule → SOR 400 mg BD	Overall	60	NR	38.4	0.934 (0.588-1.485)	NR	8.7	0.67 (0.42-1.08)	Data used within the ITCs
	SOR 400 mg BD → SUN 50 mg/d 4/2 schedule	Overall	60	NR	30.9	NR	NR	7	NR	
IMDC intermediate- or poor-risk network										
Motzer 2019[11] (JAVELIN Renal 101)	AVE 10 mg/ kg q2w + AXI 5 mg BD	IMDC risk group: Intermediate	271	NR	NR	NR	NR	13.8 (9.7-NE)	0.74 (0.57-0.95)	Pooled poor-intermediate IMDC risk population IPD from JAVELIN Renal 101 used to inform: • OS HR and associated variability incorporated into the PH ITC • OS PLD incorporated into
	SUN 50 mg/d 4/2 schedule	IMDC risk group: Intermediate	276	NR	NR	NR	NR	8.4 (7-11.2)	-	
	AVE 10 mg/ kg q2w + AXI 5 mg BD	IMDC risk group: Poor	72	NR	NR	NR	NR	6 (3.6-8.7)	0.57 (0.375-0.88)	

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
	SUN 50 mg/d 4/2 schedule	IMDC risk group: Poor	71	NR	NR	NR	NR	2.9 (2.7-5.5)	-	the non-PH ITC analyses • PFS IRC HR and associated variability incorporated into the PH ITC • PFS ICR PLD incorporated into the non-PH ITC analyses.
Choueiri 2018[10] (Alliance A031203 CABOSUN /NCT01835158)	CAB 60 mg/d	Overall	79	NR	26.6 (14.6-Not estimable)	0.8 (0.53-1.21)	NR	8.6 (6.8-14)	0.48 (0.31-0.74)	OS and PFS data used within ITCs Error identified in ITC input (1.12 instead of 1.21 for the upper 95% CI for OS), updated results presented below in Table 4.
	SUN 37.5 mg/d	Overall	78	NR	21.2 (16.3-27.4)	NR	NR	5.3 (3.0-8.2)	NR	
	CAB 60 mg/d	Overall	NR	NR	NR	NR	NR	8.3 (6.5-12.4)	0.56 (0.37-0.83)	
	SUN 37.5 mg/d	Overall	NR	NR	NR	NR	NR	5.4 (3.4-8.2)	NR	
	CAB 60 mg/d	Overall	79	NR	30.3 (14.6-35)	0.8 (0.5-1.26)	NR	NR	NR	
	SUN 37.5 mg/d	Overall	78	NR	21.8 (16.3-27)	NR	NR	NR	NR	
	CAB 60 mg/d	Overall	79	NR	26.4	0.87 (0.55-1.4)	NR	8.2 (6.2-8.8)	0.66 (0.46-0.95)	
	SUN 37.5 mg/d	Overall	78	NR	23.5	NR	NR	5.6 (3.4-8.1)	NR	

Study	Treatments	Population	N	OS (months)			PFS (months)			
				n (%)	Median (95% CI)	HR (95% CI)	n (%)	Median (95% CI)	HR (95% CI)	
	CAB 60 mg/d	IMDC risk group: Intermediate	NR	NR	NR	NR	NR	8.31	0.64 (0.43-0.96)	
	SUN 37.5 mg/d	IMDC risk group: Intermediate	NR	NR	NR	NR	NR	6.4	NR	
	CAB 60 mg/d	IMDC risk group: Poor	NR	NR	NR	NR	NR	6.14	0.75 (0.35-1.65)	
	SUN 37.5 mg/d	IMDC risk group: Poor	NR	NR	NR	NR	NR	2.77	NR	
	CAB 60 mg/d	IMDC risk group: Intermediate	NR	NR	NR	NR	NR	11.4	0.52 (0.32-0.82)	
	SUN 37.5 mg/d	IMDC risk group: Intermediate	NR	NR	NR	NR	NR	6.1	NR	
	CAB 60 mg/d	IMDC risk group: Poor	NR	NR	NR	NR	NR	6.8	0.31 (0.11-0.92)	
	SUN 37.5 mg/d	IMDC risk group: Poor	NR	NR	NR	NR	NR	2.7	NR	

Abbreviations: AVE = avelumab; AXI = axitinib; BD = twice daily; CAB = cabozantinib; CI = confidence interval; d = day; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent review committee; ITT = intention-to-treat; kg = kilogram; mg = milligram; MSKCC = Memorial Sloan Kettering Cancer Center; n = number of patients in each category; N = number of patients evaluable; NE = not estimable; NR = not reported; OD = once daily; OS = overall survival; PAZ = pazopanib; PFS = progression-free survival; Q2W = every 2 weeks; RCC= renal cell carcinoma; SOR = sorafenib; SUN = sunitinib; TIV = tivozanib
Source: Pfizer Data on File, 2019[1]

Table 2: Updated PFS Fixed effects ITC ITT population (using Independent review PFS data for Hutson 2013)

Reference	Treatment	Initial	Updated
		HR (95% CrI)	HR (95% CrI)
Sunitinib	Avelumab + Axitinib	0.69 (0.57 to 0.84)	0.69 (0.57 to 0.84)
	Tivozanib	0.95 (0.67 to 1.33)	0.94 (0.67 to 1.33)
	Pazopanib	1.05 (0.90 to 1.22)	1.05 (0.90 to 1.22)
	Sorafenib	1.25 (1.00 to 1.56)	1.25 (1.00 to 1.55)
	Axitinib	0.96 (0.66 to 1.40)	0.96 (0.66 to 1.41)
Treatment	**Reference**	**HR (95% CrI)**)	**HR (95% CrI)**
Avelumab + Axitinib	Tivozanib	0.73 (0.49 to 1.09)	0.73 (0.49 to 1.09)
	Pazopanib	0.66 (0.51 to 0.85)	0.66 (0.51 to 0.85)
	Sunitinib	0.69 (0.57 to 0.84)	0.69 (0.57 to 0.84)
	Sorafenib	0.55 (0.41 to 0.74)	0.55 (0.41 to 0.74)
	Axitinib	0.72 (0.47 to 1.09)	0.72 (0.47 to 1.10)

Table 3: Updated OS Fixed effects ITC ITT population (using COMPARZ study data – data cut off 30 September 2013)

Reference	Treatment	Initial	Updated
		HR (95% CrI)	HR (95% CrI)
Sunitinib	Avelumab + Axitinib	0.78 (0.56 to 1.09)	0.78 (0.56 to 1.09)
	Tivozanib	1.26 (0.84 to 1.88)	1.25 (0.84 to 1.88)
	Pazopanib	0.91 (0.76 to 1.08)	0.92 (0.79 to 1.06)
	Sorafenib	1.02 (0.79 to 1.32)	1.02 (0.79 to 1.32)
	Axitinib	1.02 (0.68 to 1.52)	1.02 (0.68 to 1.52)
Treatment	**Reference**	**HR (95% CrI)**)	**HR (95% CrI)**
Avelumab + Axitinib	Tivozanib	0.62 (0.37 to 1.05)	0.62 (0.37 to 1.05)
	Pazopanib	0.86 (0.59 to 1.25)	0.85 (0.59 to 1.22)
	Sunitinib	0.78 (0.56 to 1.09)	0.78 (0.56 to 1.09)
	Sorafenib	0.76 (0.50 to 1.17)	0.76 (0.50 to 1.17)
	Axitinib	0.77 (0.46 to 1.30)	0.77 (0.45 to 1.30)

Table 4: Updated OS Fixed effects ITC in poor-intermediate risk patients for the comparison of the JAVELIN and CABOSUN trials

Reference	Treatment	Initial	Updated
		HR (95% CrI)	HR (95% CrI)
Sunitinib	Avelumab + Axitinib	0.76 (0.54 to 1.08)	0.76 (0.54 to 1.08)
	Cabozantinib	0.80 (0.55 to 1.16)	0.80 (0.53 to 1.21)
Treatment	**Reference**	**HR (95% CrI)**)	**HR (95% CrI)**
Avelumab + Axitinib	Sunitinib	0.76 (0.54 to 1.08)	0.76 (0.54 to 1.08)
	Cabozantinib	0.95 (0.57 to 1.59)	0.95 (0.56 to 1.64)

b. Comparator data have been included in the non-PH ITCs based on pseudo-PLD produced by digitisation using GetData Graph Digitizer[1] and the algorithm of Guyot.[2]

A2. Priority request: non-proportional hazards:

a. Please provide log cumulative hazard plots for PFS and OS data for all trials included in the NMAs (Motzer 2013 [COMPARZ], Motzer 2013 [TIVO-1], Tomita 2017 [CROSS-J-RCC], Eichelberg 2015 [SWITCH], Hutson 2013, Choueiri 2018 [CABOSUN]).

b. Please test proportional hazards for both PFS and OS in all trials included in the NMAs using a statistical significance test (e.g. by testing Schoenfeld residuals or testing the significance of a time-varying covariate in a Cox proportional hazards model).

a. and b. Log-cumulative hazard plots and corresponding Schoenfeld residual plots are provided below for PFS (Figure 1 - Figure 12) and OS (Figure 13 - Figure 21).

Despite the variation in shape seen in the Schoenfeld residual (SR) plots for PFS, the majority of SR plots show no clear violation of the PH assumption. However, two studies are considered to be exceptions to this:

- *Motzer 2013[3] (TIVO-1; assessing tivozanib versus sunitinib): suggests potential non-proportionality based on the bow shown in the SR plot which corresponds to the crossing point shown in the LCH plot (although this is not shown to be significant).*
- *Tomita 2017[4] (CROSS-J-RCC; assessing sorafenib versus sunitinib): the SR plot in this case shows more variability and suggests potentially significant non-proportionality. However, based on the LCH plot this is considered likely to be partially due to the similarity of curves (in this case supported by a smaller sample size).*

For OS, although the SR plots do not suggest any significant indication of non-proportionality, a number of the LCH curves do show curves crossing in a number of cases. For the majority, this is considered likely due to the approximate equivalence of curves, however, as above, Choueiri 2018[5] does show a bow in the SR plot, and the LCH plot for Motzer 2013 (TIVO-1) does indicate the potential convergence of curves towards the end of the trial period.

PFS

Figure 1: Choueiri 2018 PFS Log-cumulative hazard plot

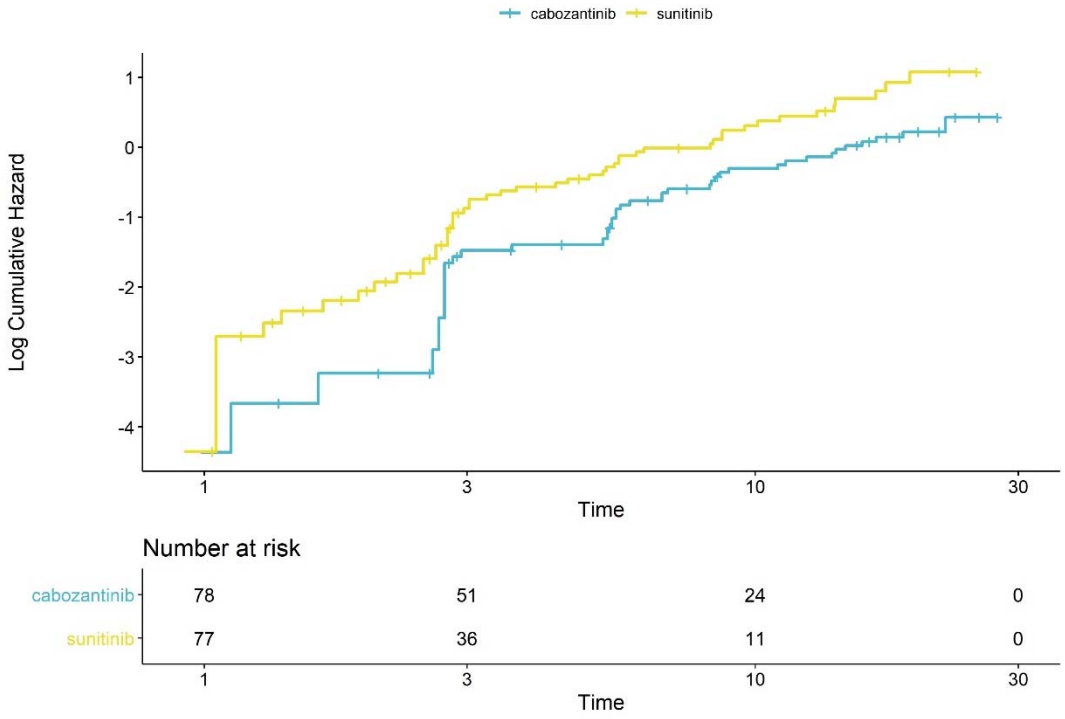


Figure 2: Choueiri 2018 PFS Schoenfeld residual plot

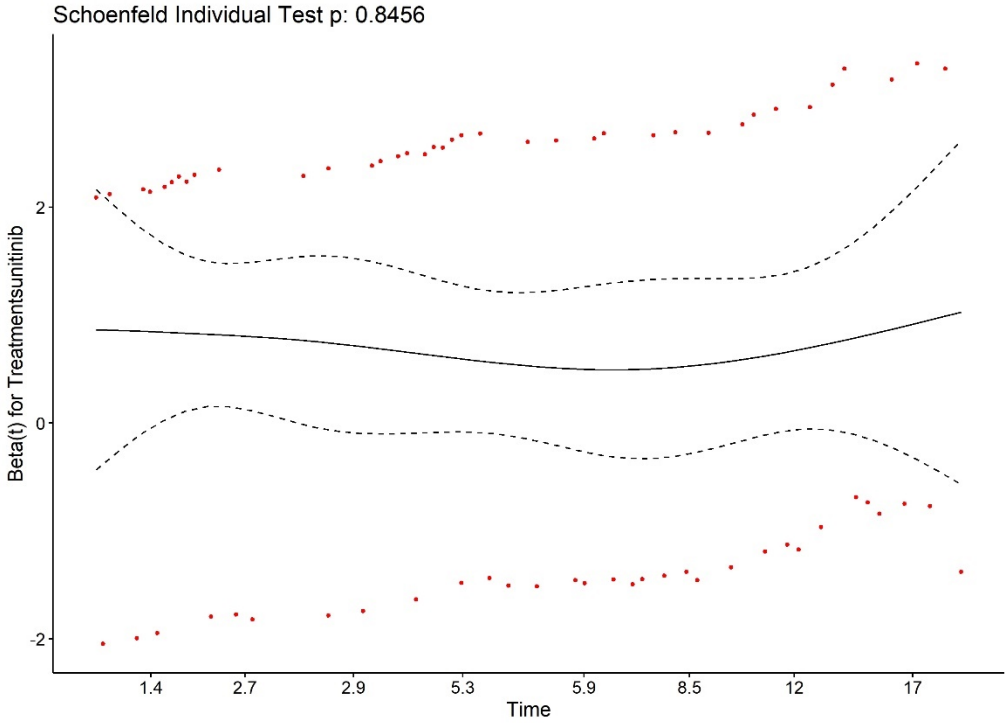


Figure 3: Eichelberg 2015 PFS Log-cumulative hazard plot

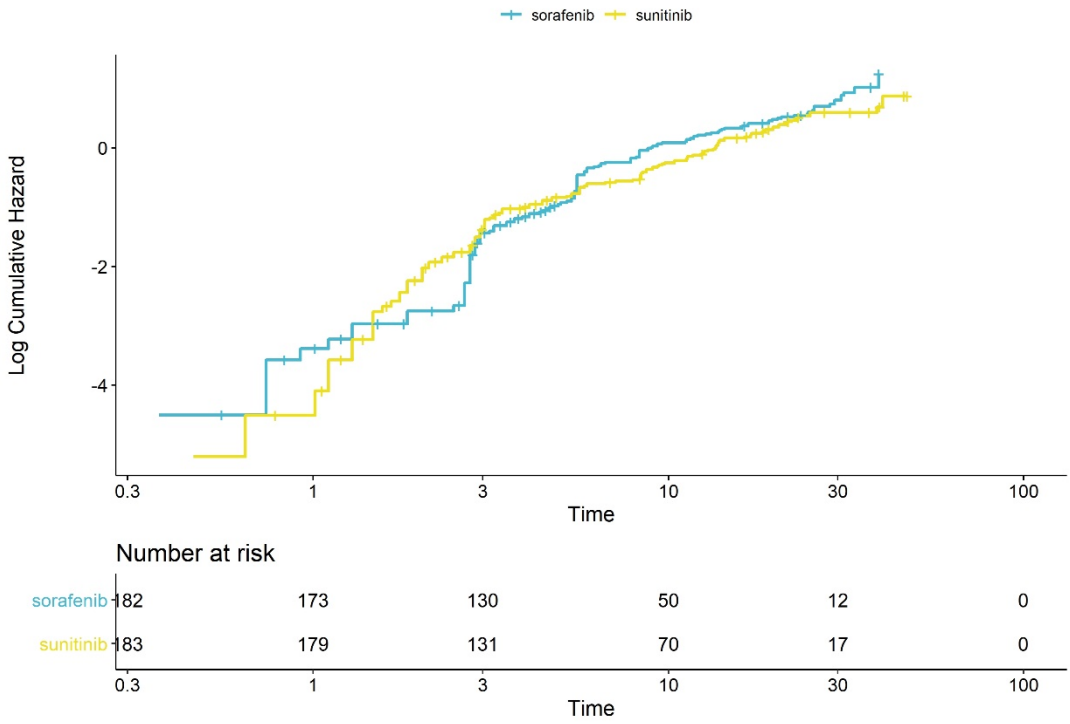


Figure 4: Eichelberg 2015 PFS Schoenfeld residual plot

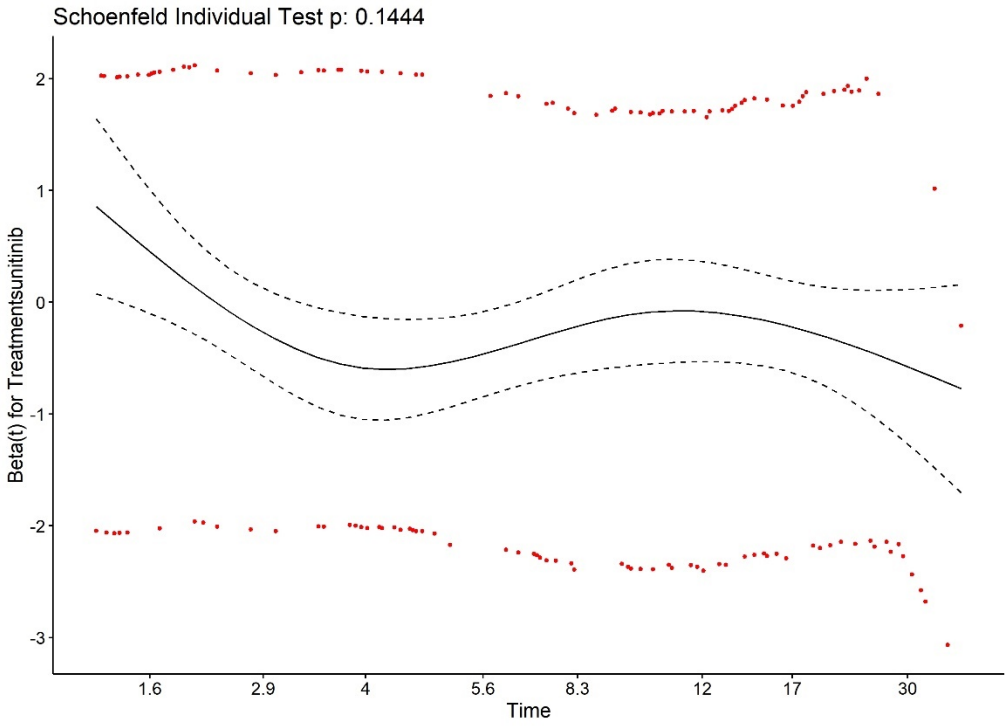


Figure 5: Hutson 2013 PFS Log-cumulative hazard plot

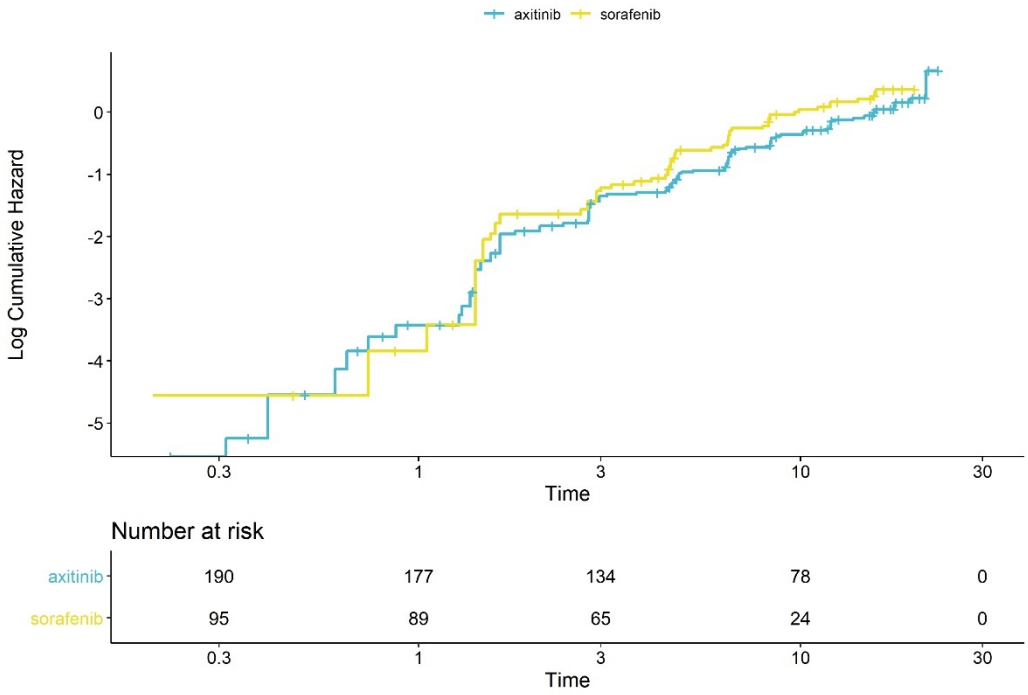


Figure 6: Hutson 2013 PFS Schoenfeld residual plot

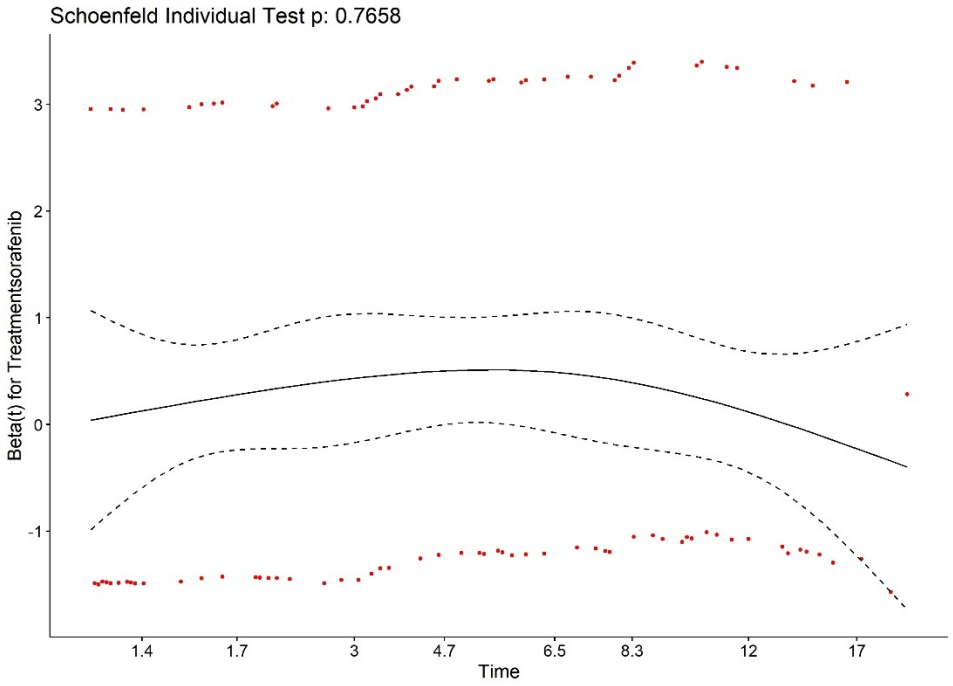


Figure 7: Motzer 2013 (COMPARZ) PFS Log-cumulative hazard plot

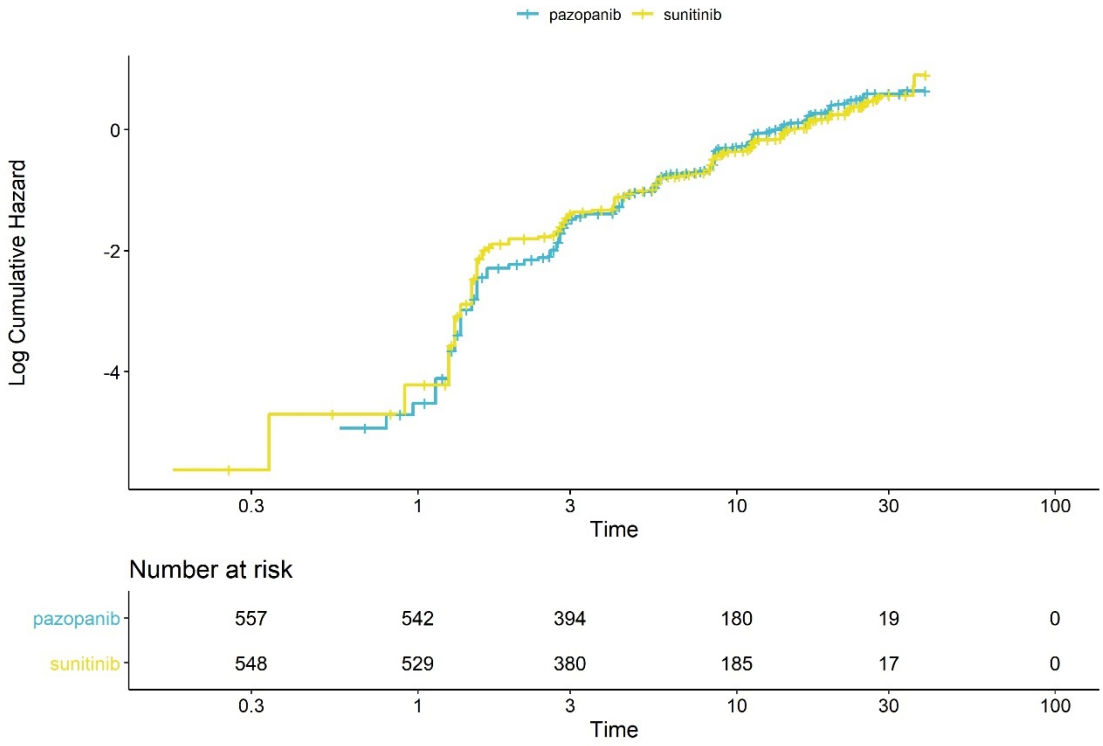


Figure 8: Motzer 2013 (COMPARZ) PFS Schoenfeld residual plot

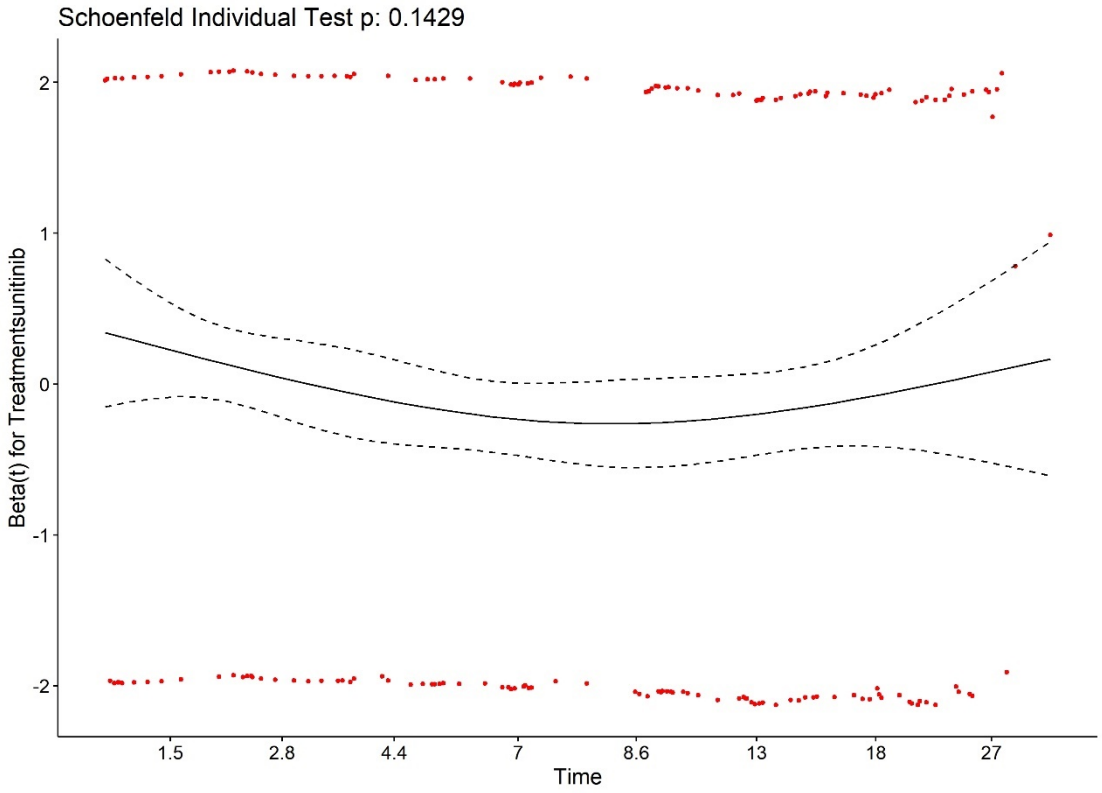


Figure 9: Motzer 2013 (TIVO-1) PFS Log-cumulative hazard plot

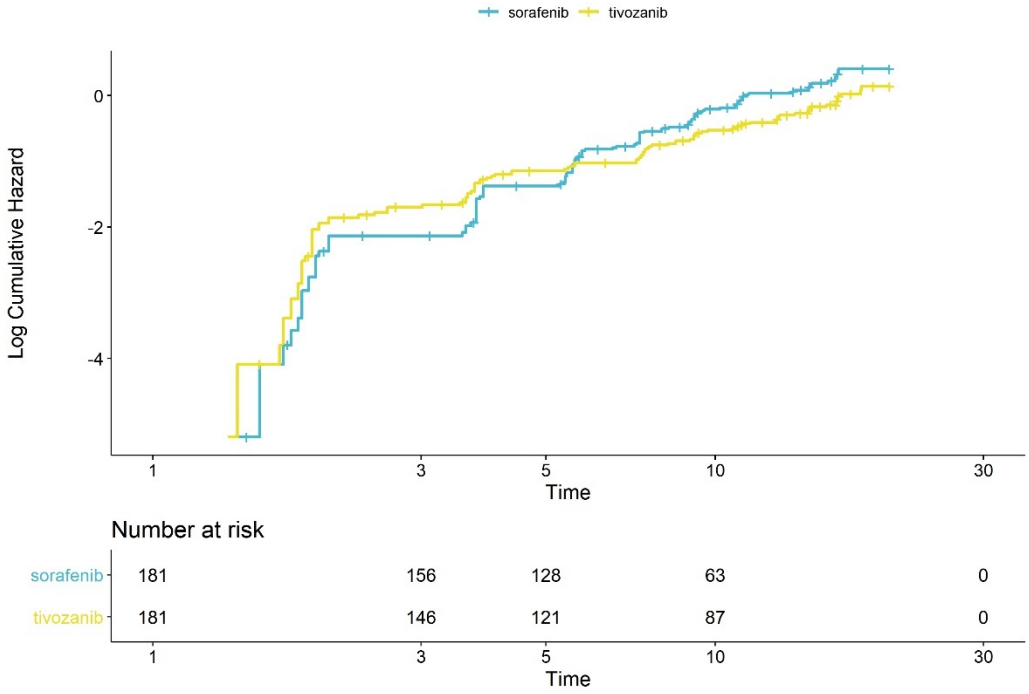


Figure 10: Motzer 2013 (TIVO-1) PFS Schoenfeld residual plot

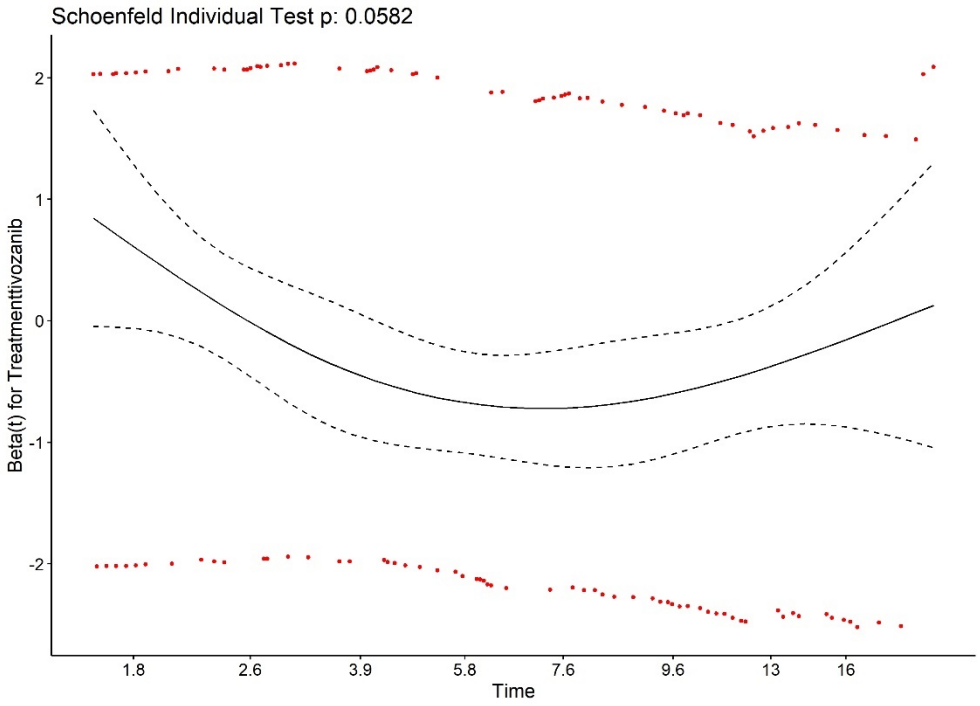


Figure 11: Tomita 2017 PFS Log-cumulative hazard plot

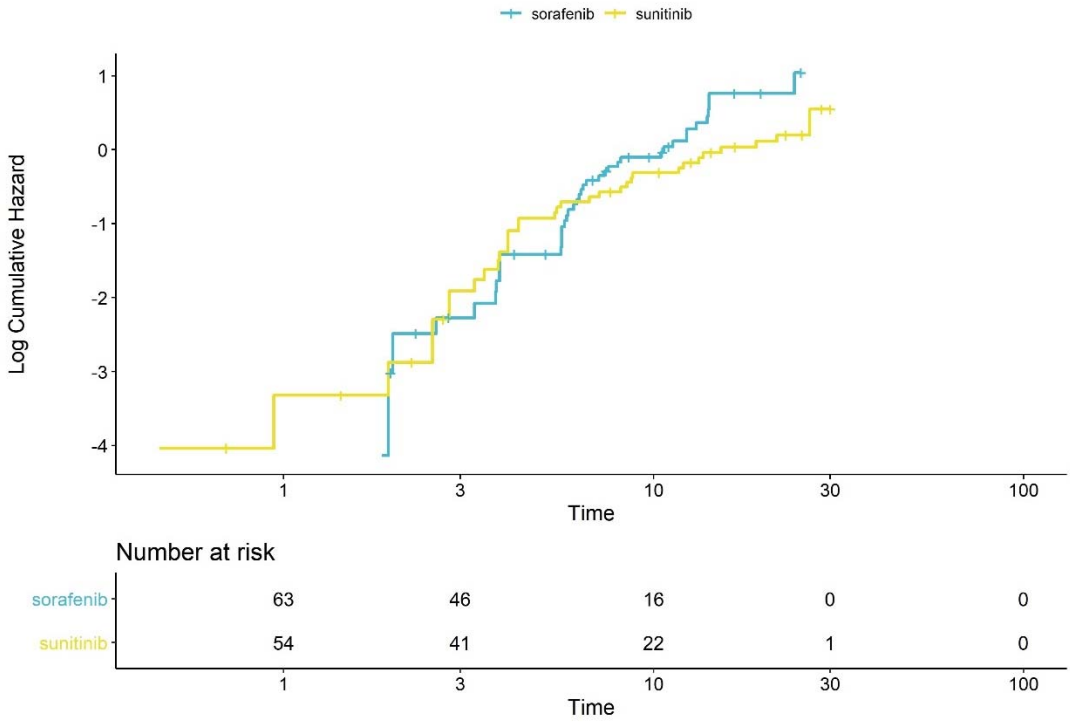
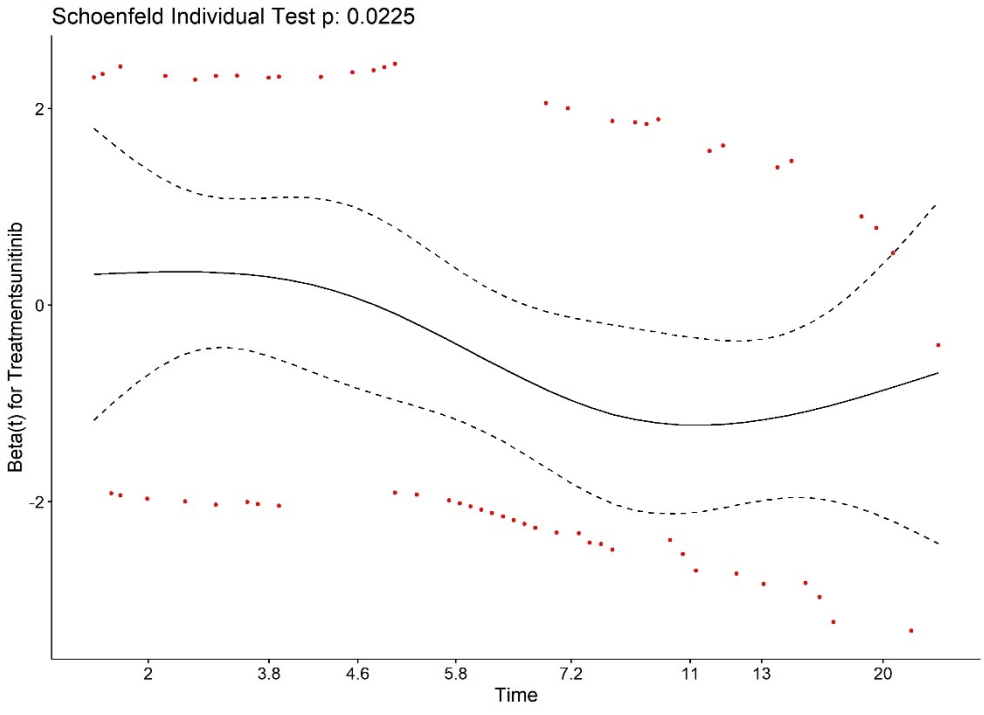


Figure 12: Tomita 2017 PFS Schoenfeld residual plot



OS

Figure 13: Choueiri 2018 OS Log-cumulative hazard plot

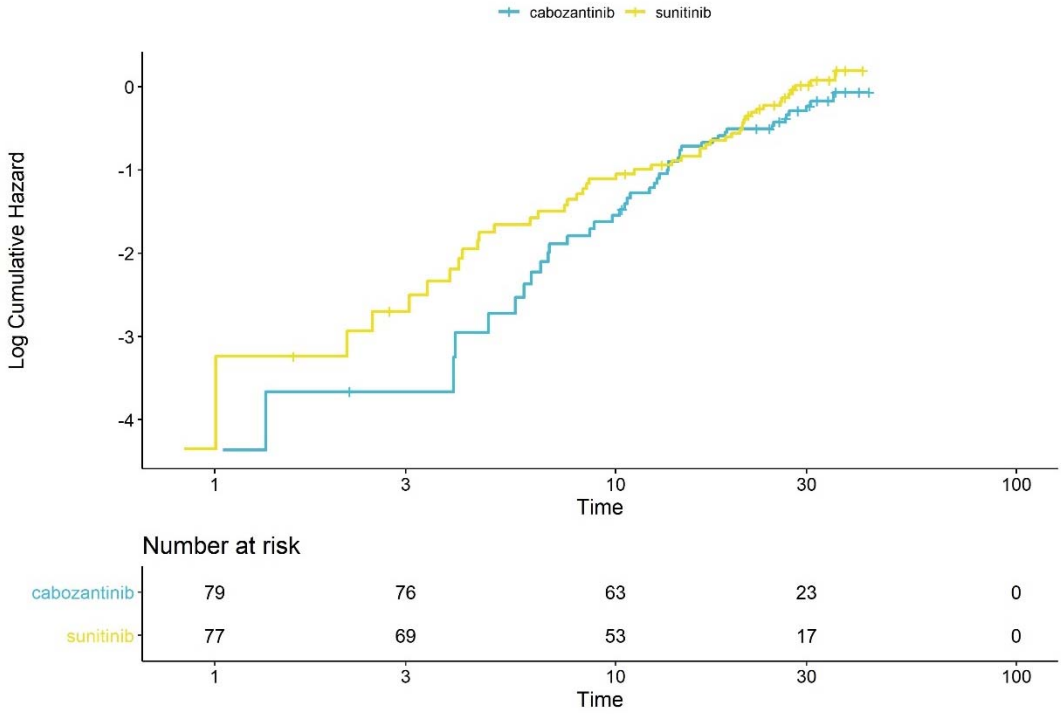


Figure 14: Choueiri 2018 OS Schoenfeld residual plot

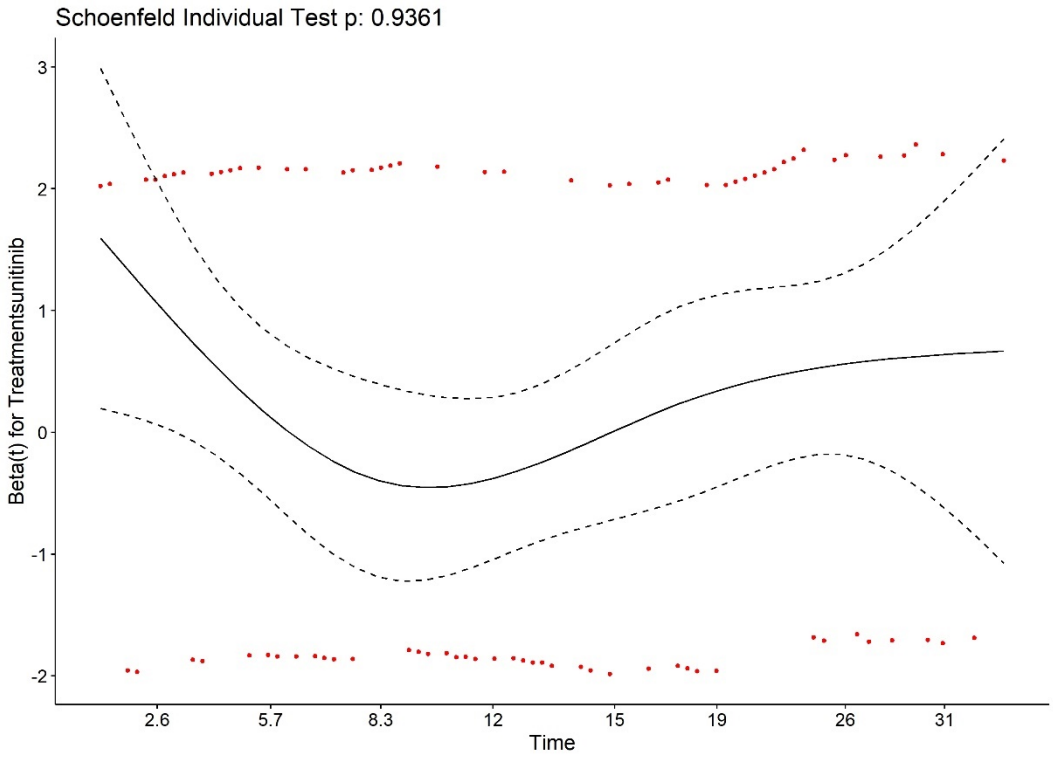


Figure 15: Eichelberg 2015 OS Log-cumulative hazard plot

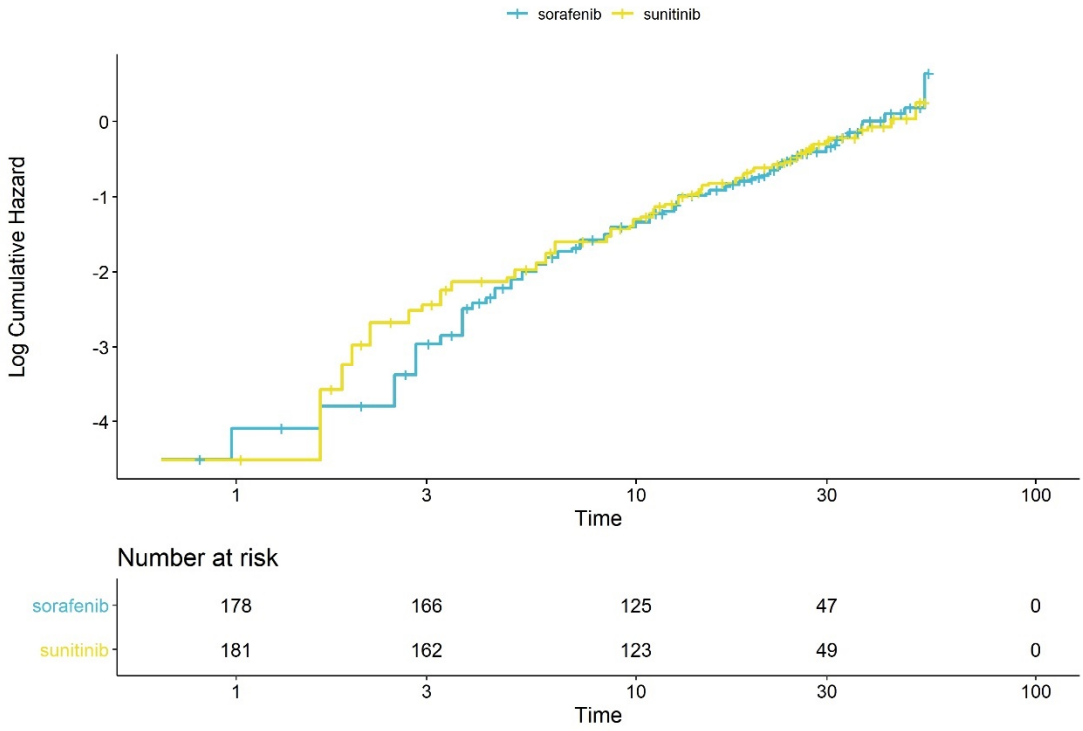


Figure 16: Eichelberg 2015 OS Schoenfeld residual plot

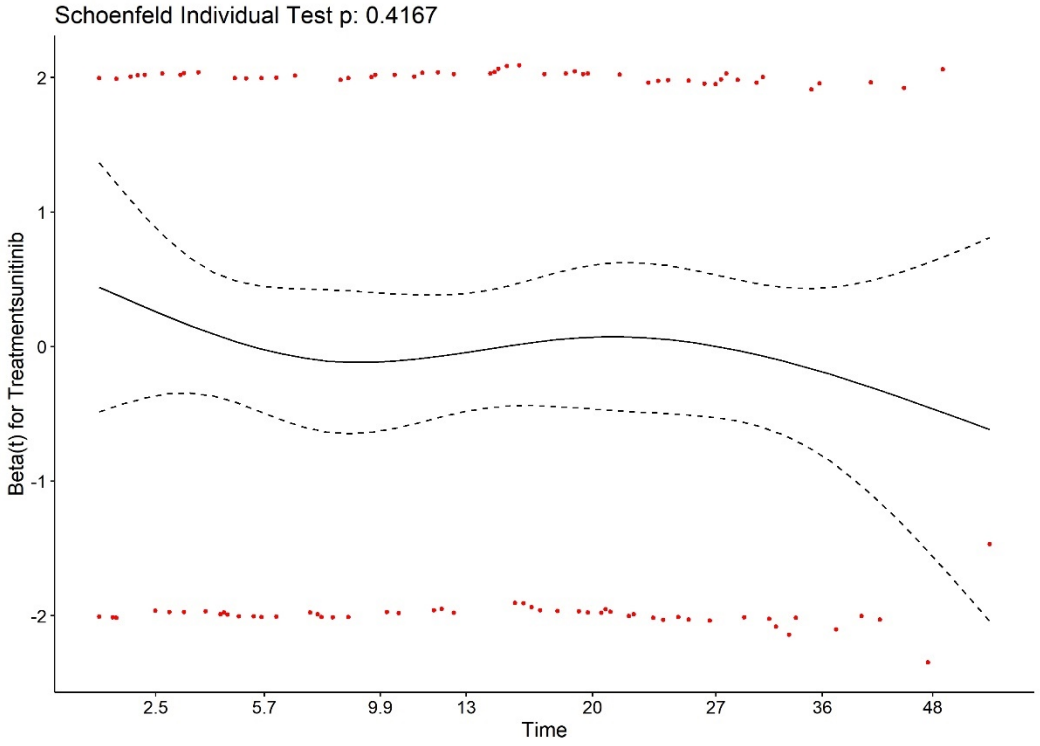


Figure 17: Hutson 2013 OS Log-cumulative hazard plot

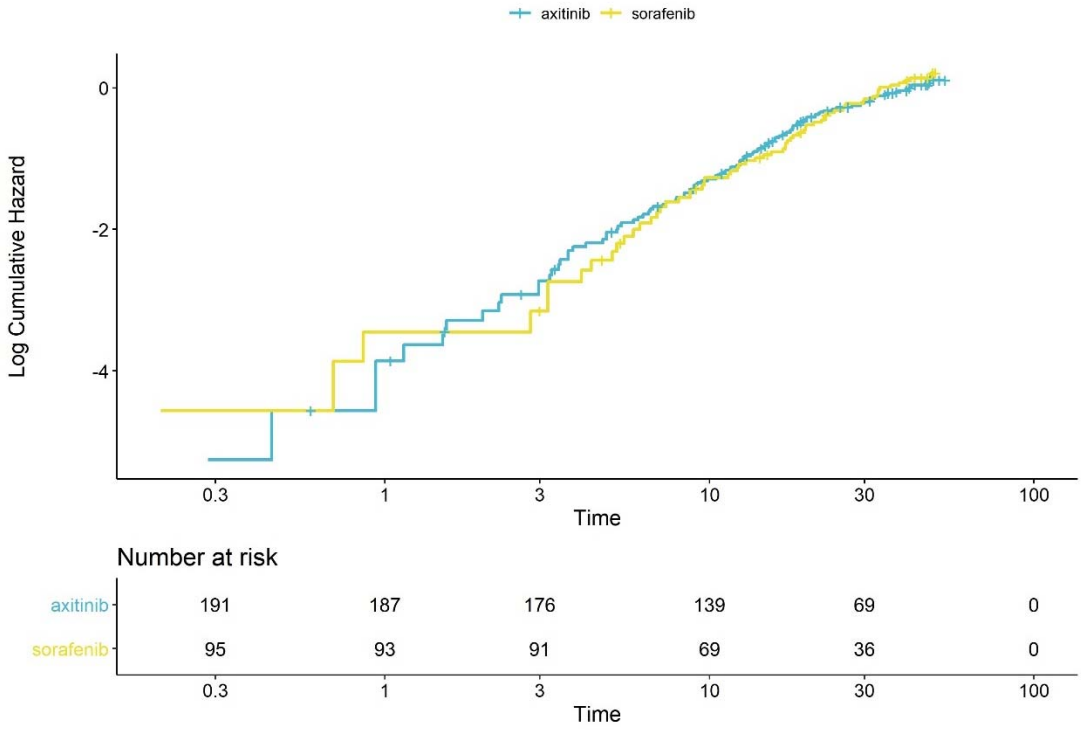


Figure 18: Hutson 2013 OS Schoenfeld residual plot

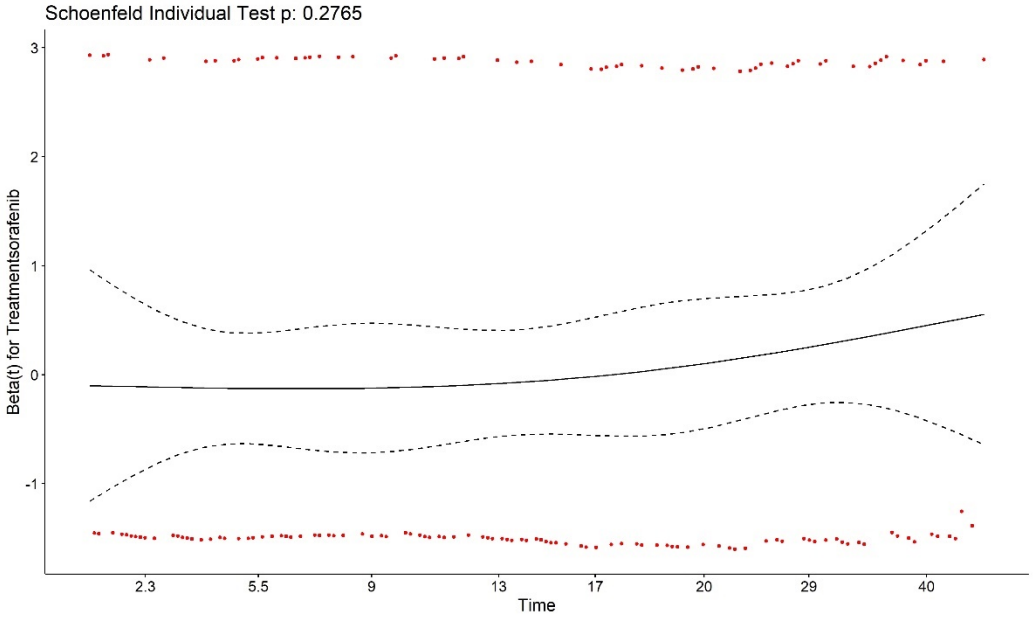


Figure 19: Motzer 2013 (COMPARZ) OS Log-cumulative hazard plot

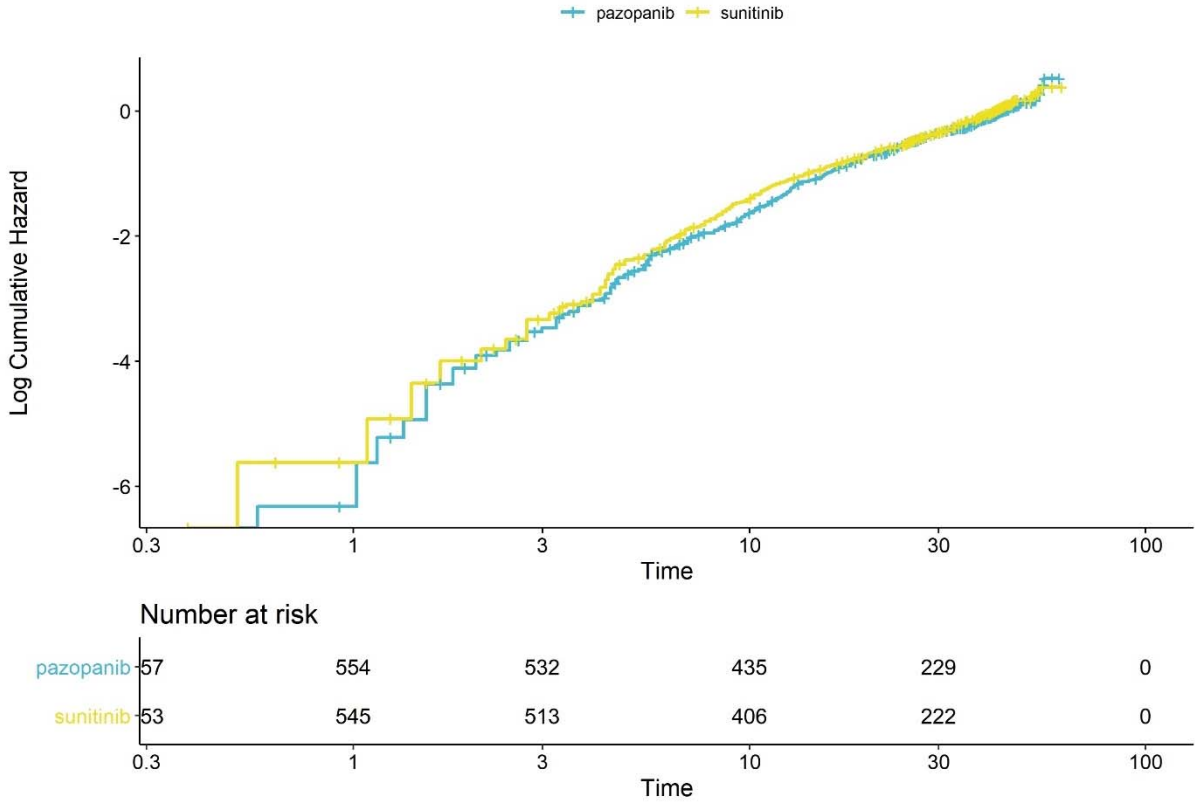


Figure 20: Motzer 2013 (COMPARZ) OS Schoenfeld residual plot

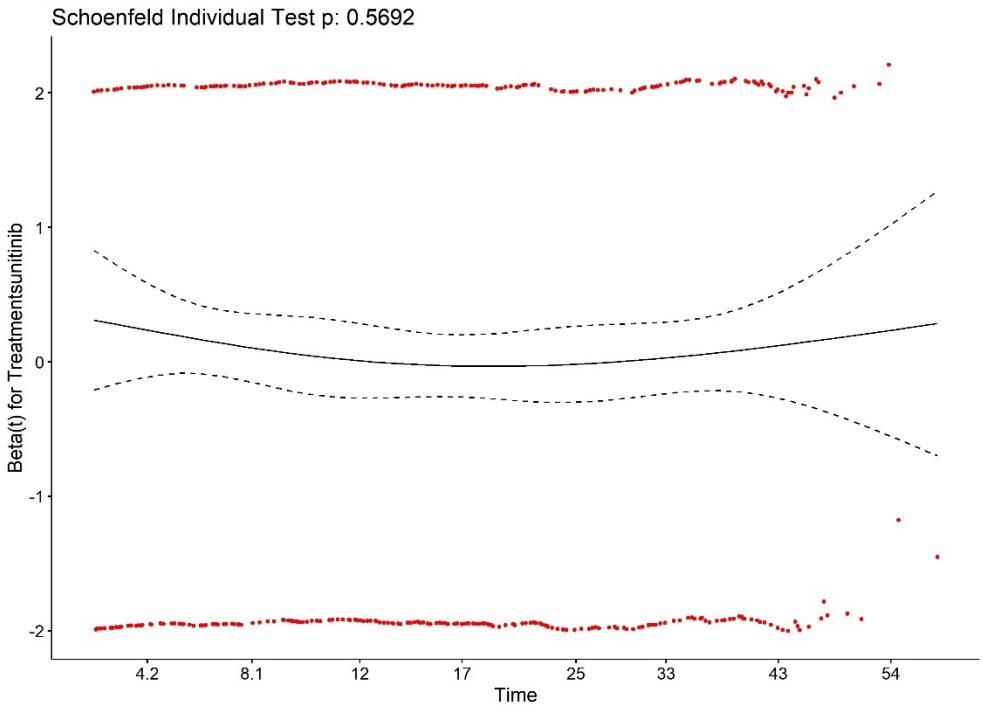


Figure 21: Motzer 2013 (TIVO-1) OS Log-cumulative hazard plot

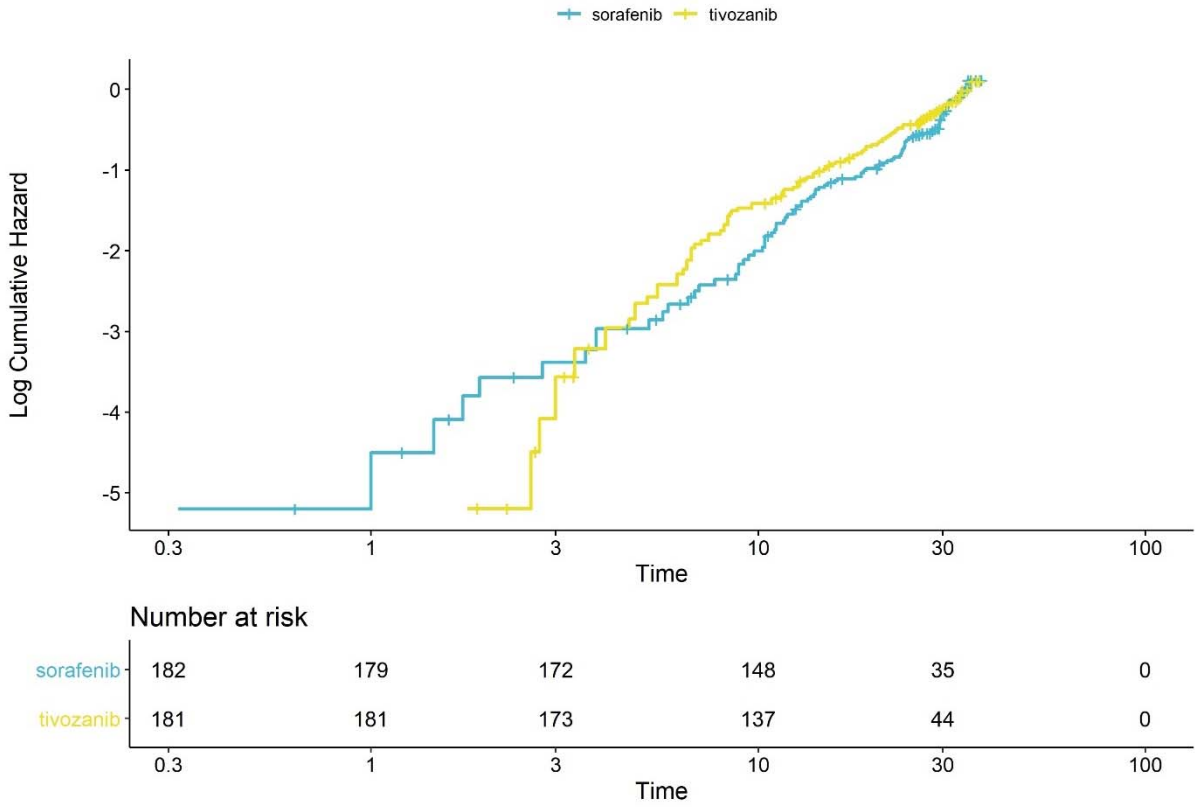
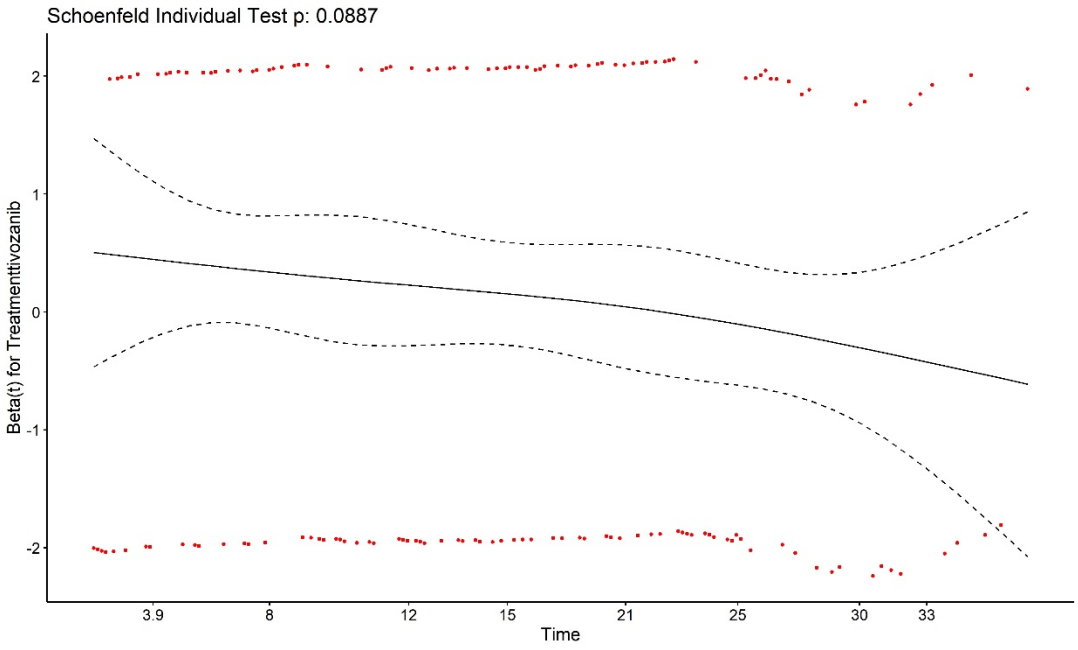


Figure 22: Motzer 2013 (TIVO-1) OS Schoenfeld residual plot



A3. Priority request: NMAs of parametric survival curves. Please clarify the following with regard to the approach employed for the NMAs of parametric survival curves (Appendix D.3.2 and Appendix D.4):

a. Were fixed-effects or random-effects used when performing NMAs of parametric survival curves? If random-effects were used, please provide a measure of heterogeneity for each model presented in Tables B.5.15 to B.5.18 (e.g. a between-trials standard deviation).

b. Please clarify whether the intervals presented within Tables B.5.15 to B.5.18 confidence intervals.

c. Please provide example statistical code for performing NMAs of parametric survival curves using the 'flexsurv' package in R software. For example, code for the best fitting model for PFS and for OS.

a. As previously clarified with NICE and the ERG during the teleconference held 8 August 2019, the CS (p44 of section B.2.9) states that the NMA of parametric survival curves uses fixed effects, and as such, no measure of between-study heterogeneity is produced.

b. The intervals presented in these tables do correspond to 95% confidence intervals (estimated within the summary.flexsurvreg function).

c. Example R code to fit all models considered is presented below:

tte.data is a data frame which includes PLD for the JAVELIN study and pseudo PLD for all included comparator studies with variables for Time (Time.days), Event, Treatment (TRT) and Study.

```
tte.mods <- list(  weibull = list(modname = "weibull",  dist = "weibull", model =
flexsurvreg(Surv(Time.days, Event) ~ TRT + Study + shape(TRT) + shape(Study), data =
tte.data, dist = 'weibull')),

  gompertz = list(modname = "gompertz",dist = "gompertz", model =
flexsurvreg(Surv(Time.days, Event) ~ TRT + Study + shape(TRT) + shape(Study), data =
tte.data, dist = 'gompertz')),
```

lnorm = list(modname = "lnorm",dist = "lnorm", model = flexsurvreg(Surv(Time.days, Event) ~ TRT + Study + sdlog(TRT) + sdlog(Study), data = tte.data, dist = 'lnorm')),

llogis = list(modname = "llogis",dist = "llogis", model = flexsurvreg(Surv(Time.days, Event) ~ TRT + Study + shape(TRT) + shape(Study), data = tte.data, dist = 'llogis')),

gengamma = list(modname = "gengamma",dist = "gengamma", model = flexsurvreg(Surv(Time.days, Event) ~ TRT + Study + sigma(TRT) + sigma(Study), data = tte.data, dist = 'gengamma')),

genf = list(modname = "genf", dist = "genf", model = flexsurvreg(Surv(Time.days, Event) ~ TRT + Study + sigma(TRT) + sigma(Study), data = tte.data, dist = 'genf')),

Additional results from the JAVELIN Renal 101 trial

A4. Please provide the following results which are not available within the CS:

a. **Priority request: Median follow-up time for PFS by BICR assessment at IA2 (Document B Table B.2.12 of the CS).**

The referenced text includes both IA1 and IA2, therefore the company have submitted the requested data for both data cuts. Table 5 and Table 6 report the follow-up time for PFS by BICR assessment from IA1 and IA2 respectively.

Table 5: Summary of Time of Follow-up for Progression-Free Survival Based on BICR Assessment (RECIST v1.1) – Full Analysis Set (IA1)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Follow-up probability (95% CI)*		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Duration of Follow-up (months)**		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]

Summary based on reverse Kaplan-Meier method reversing the event/censoring flag used in the primary analysis as specified in Schemper and Smith (1996)
*CIs are derived using the log-log transformation with back transformation to untransformed scale.
**CIs are calculated using Brookmeyer and Crowley method
PFIZER CONFIDENTIAL SDTM Creation: 06AUG2018 (14:26) Source Data: ADTTEB Output File:

./B9991003/B9991003_BDR1/adtteb_pfs_s002 Date of Generation: 20SEP2018 (06:52)

Table 6: Summary of Time of Follow-up for Progression-Free Survival Based on BICR Assessment (RECIST v1.1) – Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Follow-up probability (95% CI)*		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
at 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Duration of Follow-up (months)**		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]

Summary based on reverse Kaplan-Meier method reversing the event/censoring flag used in the primary analysis as specified in Schemper and Smith (1996)
*CIs are derived using the log-log transformation with back transformation to untransformed scale.
**CIs are calculated using Brookmeyer and Crowley method
PFIZER CONFIDENTIAL SDTM Creation: 16FEB2019 (00:52) Source Data: ADTTEB Output File: ./b9991003_Day120/B9991003_Day120/adtteb_pfs_s002 Date of Generation: 18FEB2019 (08:41)

b. Numerical results for sensitivity analyses performed for PFS (p44 of Document B Section B.2.6.1.2 of the CS and Appendix L of the CS).

- Considering all progressive disease (PD) and deaths as events regardless of missing assessments or timing of the event
- On the per protocol (PP) analysis set for PFS
- Using an unstratified analysis
- Considering all deaths as events
- Not censoring initiation of subsequent anti-cancer therapies.

Tables containing numeric results for sensitivity analyses performed for PFS are presented below for both IA1 and IA2 in the following tables:

- *Considering all progressive disease (PD) and deaths as events regardless of missing assessments or timing of the event: IA1 - Table 7; IA2 - Table 8*
- *On the per protocol (PP) analysis set for PFS: IA1 - Table 9; IA2 - Table 10*
- *Using an unstratified analysis: IA1 -Table 11; IA2 - Table 12*
- *Considering all deaths as events: IA1 - Table 13; IA2 - Table 14*

- *Not censoring initiation of subsequent anti-cancer therapies: IA1 - Table 15; IA2 - Table 16*

Table 7 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Sensitivity Analysis Counting all PD and Deaths as Events - Full Analysis Set (IA1)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI)*		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI)**		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis [3] Comparison vs Sunitinib		
Hazard Ratio†	[redacted]	
95% CI‡	[redacted]	
1-sided p-value††	[redacted]	
2-sided p-value††	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
*CIs are derived using the log-log transformation with back transformation to untransformed scale.
**CIs are calculated using Brookmeyer and Crowley method.
†Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
‡ Cox proportional hazard model used.
†† Log-rank test is used.

Table 8 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Sensitivity Analysis Counting all PD and Deaths as Events - Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		

No adequate baseline assessment	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI)*		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
at 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI)**		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis† Comparison vs Sunitinib		
Hazard Ratio‡	[redacted]	
95% CI‡	[redacted]	
1-sided p-value‡	[redacted]	
2-sided p-value‡	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group. *CIs are derived using the log-log transformation with back transformation to untransformed scale.**CIs are calculated using Brookmeyer and Crowley method. †Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. ‡Cox proportional hazard model used. †† Log-rank test is used.

Table 9 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Per Protocol Analysis Set for PFS by BICR (IA1)

	Avelumab + Axitinib (N=405)	Sunitinib (N=405)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]

at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis [3] Comparison vs Sunitinib		
Hazard Ratio [4]	[redacted]	
95% CI [4]	[redacted]	
1-sided p-value [5]	[redacted]	
2-sided p-value [5]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale. [2] CIs are calculated using Brookmeyer and Crowley method.[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. [4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 10 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Per Protocol Analysis Set for PFS by BICR (IA2)

	Avelumab + Axitinib (N=407)	**Sunitinib (N=409)**
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis [3] Comparison vs Sunitinib		
Hazard Ratio [4]	[redacted]	
95% CI [4]	[redacted]	
1-sided p-value [5]	[redacted]	

2-sided p-value [5]	[redacted]

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. [4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 11 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Unstratified Sensitivity Analysis - Full Analysis Set (IA1)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Unstratified analysis Comparison vs Sunitinib		
Hazard Ratio [3]	[redacted]	
95% CI [3]	[redacted]	
1-sided p-value [4]	[redacted]	
2-sided p-value [4]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. [4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 12 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Unstratified Sensitivity Analysis - Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
at 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Unstratified analysis Comparison vs Sunitinib		
Hazard Ratio [3]	[redacted]	
95% CI [3]	[redacted]	
1-sided p-value [4]	[redacted]	
2-sided p-value [4]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method. [3] Cox proportional hazard model used.
[4] Log-rank test is used.

Table 13 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Sensitivity Analysis Counting all Deaths as Events - Full Analysis Set (IA1)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]

Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis Comparison vs Sunitinib [3]		
Hazard Ratio [4]	[redacted]	
95% CI [4]	[redacted]	
1-sided p-value [5]	[redacted]	
2-sided p-value [5]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 14 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Sensitivity Analysis Counting all Deaths as Events - Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Start of new anti-cancer therapy	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]

No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis Comparison vs Sunitinib [3]		
Hazard Ratio [4]	[redacted]	
95% CI [4]	[redacted]	
1-sided p-value [5]	[redacted]	
2-sided p-value [5]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 15 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Sensitivity Analysis Not Using Start of Subsequent Anti-Cancer Therapy as a Censoring Reason - Full Analysis Set (IA1)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]

at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis Comparison vs Sunitinib [3]		
Hazard Ratio [4]	[redacted]	
95% CI [4]	[redacted]	
1-sided p-value [5]	[redacted]	
2-sided p-value [5]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 16 Summary of Progression-Free Survival Based on BICR Assessment (RECIST v1.1): Sensitivity Analysis Not Using Start of Subsequent Anti-Cancer Therapy as a Censoring Reason - Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Type of event, n (%)		
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
No adequate baseline assessment	[redacted]	[redacted]
Event after ≥ 2 missing or inadequate post-baseline assessments	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
No adequate post-baseline tumor assessment	[redacted]	[redacted]
Ongoing without an event	[redacted]	[redacted]
Probability of being event-free (95% CI) [1]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis Comparison vs Sunitinib [3]		

Hazard Ratio [4]	[redacted]
95% CI [4]	[redacted]
1-sided p-value [5]	[redacted]
2-sided p-value [5]	[redacted]

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for progression-free survival by BICR within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.

c. Numerical results for sensitivity analysis performed for OS (p51 of Document B Section B.2.6.1.5 of the CS and Appendix L of the CS).

- On the PP analysis set for PFS

*As clarified with NICE following receipt of the clarification questions, this clarification question should refer to **OS**, not PFS. The PP analysis for PFS for IA1 is reported in Table 17 and in Table 18 for IA2.*

- Using an unstratified analysis.

The numerical results for the unstratified sensitivity analysis performed for OS are presented below for IA1 in Table 19 and for IA2 in Table 20.

Table 17 Summary of Overall Survival - Per Protocol Analysis Set for OS (IA1)

	Avelumab + Axitinib (N=434)	Sunitinib (N=439)
Subjects with event, n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up [1]	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Probability of being event-free (95% CI) [2]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]

Stratified analysis Comparison vs Sunitinib [4]	
Hazard Ratio [5]	[redacted]
95% CI [5]	[redacted]
1-sided p-value [6]	[redacted]
2-sided p-value [6]	[redacted]

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for overall survival within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the investigator and subjects with last follow-up > 16 weeks prior to data cutoff (20JUN2018).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
[5] Cox proportional hazard model used.
[6] Log-rank test is used.

Table 18 Summary of Overall Survival - Per Protocol Analysis Set for OS (IA2)

	Avelumab + Axitinib (N=434)	Sunitinib (N=439)
Subjects with event, n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up [1]	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Probability of being event-free (95% CI) [2]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis Comparison vs Sunitinib [4]		
Hazard Ratio [5]	[redacted]	
95% CI [5]	[redacted]	
1-sided p-value [6]	[redacted]	
2-sided p-value [6]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for overall survival within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the investigator and subjects with last follow-up > 16 weeks prior to data cutoff (28JAN2018).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Stratified by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used.
[5] Cox proportional hazard model used.
[6] Log-rank test is used.

Table 19 Summary of Overall Survival: Unstratified Sensitivity Analysis – Full Analysis Set (IA1)

	Avelumab + Axitinib (N=434)	Sunitinib (N=439)
Subjects with event, n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up [1]	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Probability of being event-free (95% CI) [2]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Stratified analysis Comparison vs Sunitinib [4]		
Hazard Ratio [5]	[redacted]	
95% CI [5]	[redacted]	
1-sided p-value [6]	[redacted]	
2-sided p-value [6]	[redacted]	

The denominator to calculate percentages is N, the number of subjects in the per protocol analysis set for overall survival within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the investigator and subjects with last follow-up > 16 weeks prior to data cutoff (20JUN2018).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.

Table 20 Summary of Overall Survival: Unstratified Sensitivity Analysis - Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
Subjects with event, n (%)	[redacted]	[redacted]
Subjects censored, n (%)	[redacted]	[redacted]
Reason for censoring, n (%)		
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up [1]	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Probability of being event-free (95% CI) [2]		
at 6 months	[redacted]	[redacted]
at 12 months	[redacted]	[redacted]
at 18 months	[redacted]	[redacted]
at 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		

Q1	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q3	[redacted]	[redacted]
Unstratified analysis Comparison vs Sunitinib		
Hazard Ratio [4]	[redacted]	
95% CI [4]	[redacted]	
1-sided p-value [5]	[redacted]	
2-sided p-value [5]	[redacted]	

The denominator to calculate percentages is N, the number of the full analysis set within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the Investigator and subjects with last follow-up > 16 weeks prior to data cutoff (28JAN019).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.

d. Results for all pre-specified subgroup analyses for PFS, objective response, DOR and OS listed within Document B Section B2.7 and Appendix E of the CS.

Results for all pre-specified subgroup analyses are reported below for:

- *PFS: see Table 21 and*

Subgroup	Avelumab + Axitinib (N=442)			Sunitinib (N=444)			Avelumab + Axitinib vs Sunitinib	
	n (%) [1]	# Events (%) [2]	Median PFS (95% CI) (Months) [3]	n (%) [1]	# Events (%) [2]	Median PFS (95% CI) (Months) [3]	HR [4]	95% CI [4]
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]							
ECOG PS = 1 (per IRT)	[redacted]							
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]							
Canada/W. Europe (per IRT)	[redacted]							
Rest of the World (per IRT)	[redacted]							
Age:								
< 65 years	[redacted]							
≥ 65 years	[redacted]							
Gender:								
Male	[redacted]							
Female	[redacted]							
Race:								
Caucasian / White	[redacted]							
Asian	[redacted]							
Other	[redacted]							
Pooled Geographic Region:								

North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC prognostic criteria at baseline:								
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:								
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status:								
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] The denominator to calculate percentages is N, the number of patients in the full analysis set in each treatment group. [2] The denominator to calculate percentages is the number of patients in the full analysis set in each treatment group and subgroup. [3] Based on the Brookmeyer and Crowley method.[4] Unstratified Cox proportional hazard model used. Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

- Figure 23 *for IA1, see Table 22 and Figure 24 for IA2*

- *Objective response: see Table 23 and Figure 25 for IA1,*

- *Table* 24 *and for IA2*
- *DOR: see Table 25 for IA1 and Table 26 for IA2*
- *OS: see Table 27 and Figure 27 for IA1,*

- *Table* 28 *and Figure 28 for IA2*

Table 21 Subgroup Analysis of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Full Analysis Set (IA1)

Subgroup	Avelumab + Axitinib (N=442)			Sunitinib (N=444)			Avelumab + Axitinib vs Sunitinib	
	n (%) [1]	# Events (%) [2]	Median PFS (95% CI) (Months) [3]	n (%) [1]	# Events (%) [2]	Median PFS (95% CI) (Months) [3]	HR [4]	95% CI [4]
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]							
ECOG PS = 1 (per IRT)	[redacted]							
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]							
Canada/W. Europe (per IRT)	[redacted]							
Rest of the World (per IRT)	[redacted]							
Age:								
< 65 years	[redacted]							
≥ 65 years	[redacted]							
Gender:								
Male	[redacted]							
Female	[redacted]							
Race:								
Caucasian / White	[redacted]							
Asian	[redacted]							
Other	[redacted]							
Pooled Geographic Region:								
North America	[redacted]							
Europe	[redacted]							
Asia	[redacted]							
Rest of the World	[redacted]							

Nephrectomy at baseline:								
Yes	[redacted]							
No	[redacted]							
MSKCC prognostic criteria at baseline:								
MSKCC: Favorable	[redacted]							
MSKCC: Intermediate	[redacted]							
MSKCC: Poor	[redacted]							
Heng prognostic criteria at baseline:								
HENG: Favorable	[redacted]							
HENG: Intermediate	[redacted]							
HENG: Poor	[redacted]							
PD-L1 Status:								
Positive	[redacted]							
Negative	[redacted]							
Unknown	[redacted]							

[1] The denominator to calculate percentages is N, the number of patients in the full analysis set in each treatment group. [2] The denominator to calculate percentages is the number of patients in the full analysis set in each treatment group and subgroup. [3] Based on the Brookmeyer and Crowley method.[4] Unstratified Cox proportional hazard [redacted] d (Ethnicity since only two subgroups and

[redacted]

ll Analysis Set (IA1)

[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratification is by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

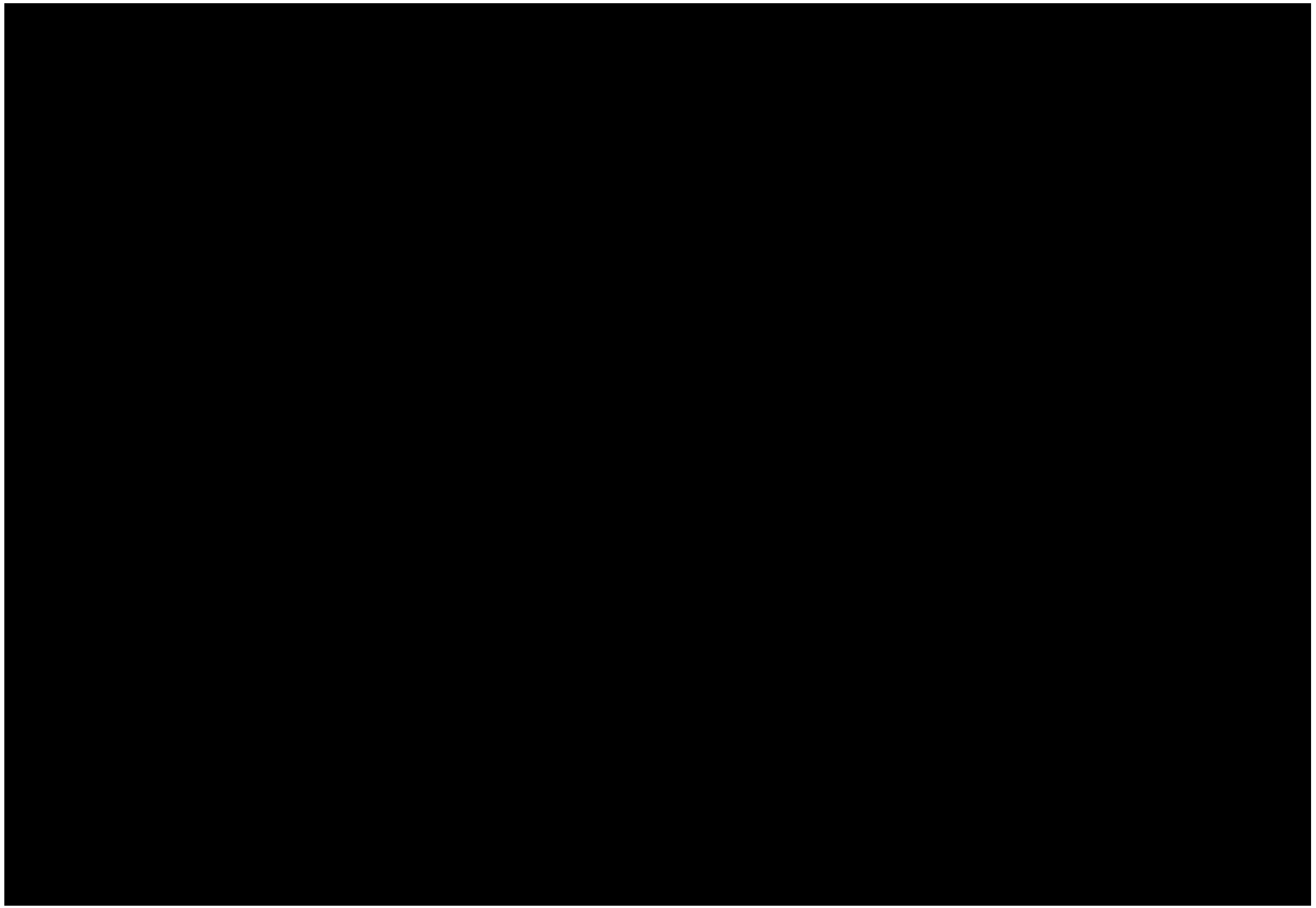
Table 22 Subgroup Analysis of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Full Analysis Set (IA2)

Subgroup	Avelumab + Axitinib (N=442)			Sunitinib (N=444)			Avelumab + Axitinib vs Sunitinib	
	n (%) [1]	# Events (%) [2]	Median PFS (95% CI) (Months) [3]	n (%) [1]	# Events (%) [2]	Median PFS (95% CI) (Months) [3]	HR [4]	95% CI [4]
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada/W. Europe (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age:								
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender:								
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race:								
Caucasian / White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Geographic Region:								
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MSKCC prognostic criteria at baseline:								
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:								
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status:								
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] The denominator to calculate percentages is N, the number of patients in the full analysis set in each treatment group.
[2] The denominator to calculate percentages is the number of patients in the full analysis set in each treatment group and subgroup.
[3] Based on the Brookmeyer and Crowley method.
[4] Unstratified Cox proportional hazard model used.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Figure 24 Forest Plot of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) by Subgroups - Full Analysis Set (IA2)



N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratification is by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Table 23 Subgroup Analysis of Objective Response Based on BICR Assessment (RECIST v1.1) - Full Analysis Set (IA1)

Subgroup	Avelumab + Axitinib (N=442)			Sunitinib (N=444)			Avelumab + Axitinib vs Sunitinib	
	n (%) [1]	Responders (CR+PR) n (%) [2]	95% CI [3]	n (%) [1]	Responders (CR+PR) n (%) [2]	95% CI [3]	Odds ratio [4]	95% CI [4]
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]							
ECOG PS = 1 (per IRT)	[redacted]							
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]							
Canada/W. Europe (per IRT)	[redacted]							
Rest of the World (per IRT)	[redacted]							
Age:								
< 65 years	[redacted]							
≥ 65 years	[redacted]							
Gender:								
Male	[redacted]							
Female	[redacted]							
Race:								
Caucasian / White	[redacted]							
Asian	[redacted]							
Other	[redacted]							
Pooled Geographic Region:								
North America	[redacted]							
Europe	[redacted]							
Asia	[redacted]							
Rest of the World	[redacted]							
Nephrectomy at baseline:								
Yes	[redacted]							
No	[redacted]							

MSKCC prognostic criteria at baseline:								
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:								
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status:								
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR=complete response; PR=partial response.
[1] The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[2] Percentage is objective response rate, the denominator to calculate percentages is n, the number of subjects in the full analysis set within each treatment group and subgroup.
[3] Clopper-Pearson method used.
[4] Odds ratio is estimated using Mantel-Haenszel method. Odds Ratio > 1 indicates better outcome for Avelumab + Axitinib compared to Sunitinib; exact CI is calculated.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Figure 25 Forest Plot of Confirmed Objective Response Based on BICR Assessment (RECIST v1.1) by Subgroups - Full Analysis Set (IA1)

N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Odds ratio is estimated using Mantel-Haenszel method. Exact CI is calculated.
[2] Stratification is by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 06AUG2018 (14:26) Source Data: ADRSB Output File: ./B9991003/B9991003_BDR1/adrsb_or_f001_subgrp Date of Generation: 08OCT2018 (16:11)

Table 24 Subgroup Analysis of Objective Response Based on BICR Assessment (RECIST v1.1) - Full Analysis Set (IA2)

Subgroup	Avelumab + Axitinib (N=442)			Sunitinib (N=444)			Avelumab + Axitinib vs Sunitinib	
	n (%) [1]	Responders (CR+PR) n (%) [2]	95% CI [3]	n (%) [1]	Responders (CR+PR) n (%) [2]	95% CI [3]	Odds ratio [4]	95% CI [4]
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada/W. Europe (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age:								
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender:								
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race:								
Caucasian / White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Geographic Region:								
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MSKCC prognostic criteria at baseline:								
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:								
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status:								
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CR=complete response; PR=partial response.
[1] The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[2] Percentage is objective response rate, the denominator to calculate percentages is n, the number of subjects in the full analysis set within each treatment group and subgroup.
[3] Clopper-Pearson method used.
[4] Odds ratio is estimated using Mantel-Haenszel method. Odds Ratio > 1 indicates better outcome for Avelumab + Axitinib compared to Sunitinib; exact CI is calculated.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Figure 26 Forest Plot of Confirmed Objective Response Based on BICR Assessment (RECIST v1.1) by Subgroups - Full Analysis Set (IA2)

N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Odds ratio is estimated using Mantel-Haenszel method. Exact CI is calculated.
[2] Stratification is by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Table 25 Subgroup Analysis of Duration of Response Based on BICR Assessment (RECIST v1.1) - Subjects with a Confirmed CR or PR in the Full Analysis Set (IA1)

Subgroup	Avelumab + Axitinib (N=227)			Sunitinib (N=114)		
	n (%) [1]	# Events (%) [2]	Median DR (95% CI) (Months) [3]	n (%) [1]	# Events (%) [2]	Median DR (95% CI) (Months) [3]
ECOG Performance Status (Randomization Stratification Factor):						
ECOG PS = 0 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region (Randomization Stratification Factor):						
United States (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada/Western Europe (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age:						
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender:						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race:						
Caucasian / White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Geographic Region:						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MSKCC prognostic criteria at baseline:						
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:						
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status:						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] The denominator to calculate percentages is N, the number of patients with confirmed complete response or partial response in the full analysis set in each treatment group.
[2] The denominator to calculate percentages is the number of patients with confirmed complete response or partial response in the full analysis set in each treatment group and subgroup.
[3] Based on the Brookmeyer and Crowley Method.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Table 26 Subgroup Analysis of Duration of Response Based on BICR Assessment (RECIST v1.1) - Subjects with a Confirmed CR or PR in the Full Analysis Set (IA2)

Subgroup	Avelumab + Axitinib (N=227)			Sunitinib (N=114)		
	n (%) [1]	# Events (%) [2]	Median DR (95% CI) (Months) [3]	n (%) [1]	# Events (%) [2]	Median DR (95% CI) (Months) [3]
ECOG Performance Status (Randomization Stratification Factor):						
ECOG PS = 0 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region (Randomization Stratification Factor):						
United States (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada/Western Europe (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rest of the World (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age:						
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender:						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race:						
Caucasian / White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Geographic Region:						
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC prognostic criteria at baseline:						
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:						
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HENG: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status:						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] The denominator to calculate percentages is N, the number of patients with confirmed complete response or partial response in the full analysis set in each treatment group. [2] The denominator to calculate percentages is the number of patients with confirmed complete response or partial response in the full analysis set in each treatment group and subgroup.[3] Based on the Brookmeyer and Crowley Method. Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Table 27 Subgroup Analysis of Overall Survival - Full Analysis Set (IA1)

	Avelumab + Axitinib (N=442)			Sunitinib (N=444)		Avelumab + Axitinib vs Sunitinib		
Subgroup	**n (%) [1]**	**# Events (%) [2]**	**Median OS (95% CI) (Months) [3]**	**n (%) [1]**	**# Events (%) [2]**	**Median OS (95% CI) (Months) [3]**	**HR [4]**	**95% CI [4]**
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada/Western Europe (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age:								
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender:								
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race:								
Caucasian / White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Geographic Region:								
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No																
MSKCC prognostic criteria at baseline:																
MSKCC: Favorable																
MSKCC: Intermediate																
MSKCC: Poor																
Heng prognostic criteria at baseline:																
HENG: Favorable																
HENG: Intermediate																
HENG: Poor																
PD-L1 Status:																
Positive																
Negative																
Unknown																

[1] The denominator to calculate percentages is N, the number of patients in the full analysis set in each treatment group.
[2] The denominator to calculate percentages is the number of patients in the full analysis set in each treatment group and subgroup. [3] Based on the Brookmeyer and Crowley method.
[4] Unstratified Cox proportional hazard model used.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Figure 27 Forest Plot of Overall Survival by Subgroups - Full Analysis Set (IA1)

N is the number of subjects in the full analysis set within each subgroup and treatment group.

[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.

[2] Stratification is by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.

Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Table 28 Subgroup Analysis of Overall Survival - Full Analysis Set (IA2)

	Avelumab + Axitinib (N=442)			Sunitinib (N=444)		Avelumab + Axitinib vs Sunitinib		
Subgroup	**n (%) [1]**	**# Events (%) [2]**	**Median OS (95% CI) (Months) [3]**	**n (%) [1]**	**# Events (%) [2]**	**Median OS (95% CI) (Months) [3]**	**HR [4]**	**95% CI [4]**
ECOG Performance Status (Randomization Stratification Factor):								
ECOG PS = 0 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1 (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region (Randomization Stratification Factor):								
United States (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada/Western Europe (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World (per IRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age:								
< 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender:								
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race:								
Caucasian / White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled Geographic Region:								
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy at baseline:								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC prognostic criteria at baseline:								
MSKCC: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC: Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria at baseline:								
HENG: Favorable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HENG: Intermediate	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
HENG: Poor	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
PD-L1 Status:																
Positive	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Negative	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
Unknown	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	

[1] The denominator to calculate percentages is N, the number of patients in the full analysis set in each treatment group.
[2] The denominator to calculate percentages is the number of patients in the full analysis set in each treatment group and subgroup. [3] Based on the Brookmeyer and Crowley method.
[4] Unstratified Cox proportional hazard model used.
Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

Figure 28 Forest Plot of Overall Survival by Subgroups - Full Analysis Set (IA2)

N is the number of subjects in the full analysis set within each subgroup and treatment group. [1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.[2] Stratification is by ECOG PS (0 vs 1) and Geographical Region (United States vs Canada/Western Europe vs Rest of the World). IRT stratification values used. Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified. Subgroups with < 5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is < 5% of the patient population).

e. Hazard Ratio and 95% CI for PFS2 in Table B5.66 of Appendix L.

Stratified Hazard Ratio (HR) and 95% confidence interval for PFS2 in IA1: HR=0.56 (95% CI: 0.421, 0.735), with Kaplan Meier graph is reported below in

Figure **29***. HR and 95% confidence interval in IA2: [redacted], with Kaplan Meier graph reported in Figure 30.*

Figure 29 Kaplan-Meier analysis of PFS after second-line treatment (PFS2) (IA1)

*PFS2 is defined as the time from the date of randomization to discontinuation of next-line treatment after first objective disease progression by investigator assessment, second objective disease progression by investigator assessment after initiation of next-line treatment, or death from any cause, whichever occurs first.; NE, not estimable

Figure 30 Kaplan-Meier analysis of PFS after second-line treatment (PFS2) (IA2)

A5. Patient reported outcomes (PROs):

a. Please test proportional hazards for time to deterioration in the FKSI-Disease Related Symptoms subscale using a statistical significance test (e.g. by testing Schoenfeld residuals or testing the significance of a time-varying covariate in a Cox proportional hazards model). (Document B Section B.2.6.1.7.3)

The plot of Schoenfeld residuals from the stratified Cox proportional regression model for time to deterioration in the FKSI-Disease Related Symptoms for the full analysis set is reported below in Figure 31. The p-value for Schoenfeld's residual test is: 0.100.

Figure 31 Plot of Schoenfeld Residuals from Stratified Cox Proportional Regression Model for Time to deterioration in the FKSI-Disease Related Symptoms - Full Analysis Set (IA1)

b. Mean change data are reported for patient reported outcomes in the CS graphically (Figure B.2.6, Figure B.2.7 and Figure B.2.8). Please clarify the length of time at which each assessment was made in the 'long term follow-up period' (i.e. for LFUP1, LFUP2, etc).

The schedule of assessments within the latest amendment of the protocol for the JAVELIN Renal 101 study defines the follow-up periods as follows:

"Short- and Long-Term Follow-up: All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of investigational product or until the time of initiation of new anticancer treatment. Beyond the 90 days until the end of the study, all patients will be followed every 3 months (±14 days) for survival, ECOG PS, and new systemic anticancer treatment within the long-term follow-up."

The follow-up time is not based on a common calendar (study) time for all patients and varies by patient depending on their date of last dose

In Figure B.2.6, Figure B.2.7 and Figure B.2.8 of the CS, short-term follow-up assessments are abbreviated with "FU" (FUPD30, FUPD60, FUPD90) and Long-Term Follow-up assessments are abbreviated with "LFUP" (LFUP1, LFUP2, LFUP3, LFUP4, LFUP5, LFUP6). Using the definition above, the following specific definitions apply:

FUPD30	*30 days (±3 days) after the last dose of investigational product*
FUPD60	*60 days (±3 days) after the last dose of investigational product*
FUPD90	*90 days (±3 days) after the last dose of investigational product*
LFUP1	*3 months (±14 days) after FUPD90*
LFUP2	*6 months (±14 days) after FUPD90*
LFUP3	*9 months (±14 days) after FUPD90*
LFUP4	*12 months (±14 days) after FUPD90*
LFUP5	*15 months (±14 days) after FUPD90*
LFUP6	*18 months (±14 days) after FUPD90*

Section B: Clarification on cost-effectiveness data

B1. Priority request: Please provide in a separate document the Kaplan-Meier analyses listed in a) to c) and to the following specifications

- Study data set: JAVELIN Renal 101 trial, January 2019 data cut.
- Format: please present analysis outputs using the format of the sample table provided at the end of section B (to include censoring times).
- Population: include all patients who were lost to follow-up or withdrawn from the trial.
- Stratification: all Kaplan-Meier analyses to be stratified by treatment and by risk group (ITT, favourable and intermediate/poor risk group).

a. Investigator-assessed PFS

b. BIRC-assessed PFS

c. Time to study treatment discontinuation (TTD) for avelumab, axitinib and sunitinib.

This data has been provided in a separate file.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B2. Priority request: Please clarify the current status of any existing or expected commercial access agreements or patient access schemes for avelumab and axitinib. Please provide scenario analyses with all corresponding acquisition costs.

In light of the maturing survival data in JAVELIN Renal 101, the Merck/ Pfizer alliance are proactively seeking funding for avelumab + axitinib through the Cancer Drugs Fund. In accordance to the CDF protocol and following confirmation by the NICE CDF team, Merck submitted a draft commercial access agreement (CAA) on the 15th July (NICE submission deadline) to the CDF team at NHSE (england.cdfteam@nhs.net) copying in Robert Fernley. This confidential arrangement is specific to avelumab + axitinib when given within this combination and does not limit, advantage or affect in any way any existing arrangements for either drug outside of the 1L aRCC setting. A Patient Access Scheme submission is outside the requirements of a CDF drug and therefore was not pursued at this point in time for this indication, where the clinical uncertainty is likely to lead to a CDF recommendation.

The base-case results in the CS are inclusive of the proposed CAA rebate. The draft CAA has been provided for avelumab only (which currently does not have a PAS in place), whilst axitinib currently has an existing PAS. The alliance is engaged in ongoing discussions with NHSE and finalisation of the draft CAA is expected following the first appraisal committee meeting in January 2020.

Section C: Textual clarification and additional points

No additional queries.

References

[1] GetData. Graph Digitizer. 2019. Available at: http://www.getdata-graph-digitizer.com/ [Accessed 8 August 2019].
[2] Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012; 12: 9.
[3] Motzer RJ, 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. J Clin Oncol. 2013;31(30):3791-9
[4] Tomita Y, Naito S, Sassa N, et al. Sunitinib versus sorafenib as first-linetherapy for patients with metastatic renal cell carcinoma with favorable or intermediate MSKCC risk group. Genitourinary Cancers Symposium San Francisco, California. 30 Jan -1 Feb 2014. Poster
[5] 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. Eur J Cancer. 2018; 94:115-25

NICE National Institute for Health and Care Excellence

Patient organisation submission

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma ID1547

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	xxxxxxxxxxxxx

2. Name of organisation	Kidney Cancer Support Network
3. Job title or position	xxxxxxxx
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 Rose Woodward and Julia Black, 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 avelumab 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 communicate on a regular basis, and we receive in the order of 5-600 posts a day on our closed Facebook group.

carers to include in your submission?	
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 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.

	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 most 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 avelumab plus axitinib combination has been proven to be a clinically effective and well-tolerated treatment and was designated a breakthrough therapy and approved by the FDA for the treatment of advanced RCC earlier this year (2019). As a breakthrough therapy, this combination treatment has been fast tracked for approval in a number of countries and is currently under consideration for the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS) in the UK. The avelumab plus axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in metastatic RCC. Patients and carers opinions of the avelumab plus axitinib combination are based on their experience of 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 JAVELIN Renal 101 study in which the combination of avelumab plus axitinib significantly improved median progression-free survival by 6.6 months in PD-L1 positive patients and 3.2 months in the overall population compared to sunitinib in patients with previously untreated advanced RCC. In addition, 51% of patients had an objective response rate with avelumab plus axitinib, compared with 26% of patients on sunitinib. These response rates are twice as good as current standards of care; however, it remains to be seen whether this will translate into improved overall survival, as seen with other immunotherapy combinations. The improvement in progression-free 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 first-line treatments. Patients are optimistic that this synergistic effect will result in improved overall survival.

	In addition, the safety profile of the avelumab plus axitinib combination is no worse than that for the individual drugs alone, and is, therefore, seen as being better tolerated than standard first-line VEGFR inhibitor treatments, such as sunitinib and pazopanib. This results in improved quality of life to enable patients to contribute both socially and economically to society. The following quote is taken from a patient with stage 4 clear cell RCC who was one of the first patients in the JAVELIN Renal 101 trial: *"I have been taking Avelumab and Axitinib as part of the Javelin Renal 100 trial since January 2015. Before I found out I had cancer, I was enjoying early retirement, travelling abroad and in the UK, meeting friends for pub lunches, doing some physical voluntary work, walking long distances and doing DIY jobs. The drug combination … has been good to me and I had clear scans for 2 years. The cancer has returned but even now my condition is stable, and I am still taking the drugs. I believe that the drugs have extended my life expectancy.* *"I have had a wide variety of side effects….. I have very little energy, I sleep most afternoons, I am short of breath and I am no longer able to walk long distances, the most I can manage now is a mile but often I can't even manage that. At times I had sore hands and feet which further reduced my mobility. I also suffered from a very sensitive mouth for periods that meant spicy food had to stop and I had to use children's toothpaste. I have a chronic cough and my voice fades after talking for a while so even socialising is a problem. I also suffer from periods of constipation and diarrhoea.* *"I had already retired so work was not a problem, but I did have to give up my voluntary work. I manage my time well; I plan ahead and try and get as much done as possible in the mornings. I have had had great support and understanding from almost everybody around me, but I am fairly self-sufficient in day to day things. I still do the shopping cooking etc. I just have to plan everything."*

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 access this latest clinically effective drug combination; failure to do so would be seen as failure of professional competence. Avelumab is given intravenously over 60 minutes every 2 weeks until disease progression or drug intolerance. This requires hospital visits every 2 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 avelumab 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,	No

please describe them and explain why.	
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?	Avelumab 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 avelumab 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 avelumab plus axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in advanced RCC, and has been designated a breakthrough therapy by the FDA
- The avelumab plus axitinib combination is well tolerated, as well as proven to be more effective at extending progression-free survival and improving overall response rates compared to standard first-line treatment with sunitinib
- Adding the avelumab plus axitinib combination as a choice in the first-line enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life
- The extended progression-free survival and relative toxicity of the avelumab plus axitinib combination enhances quality of life and enables patients to contribute socially and economically to society
- The avelumab plus axitinib combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

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Patient organisation submission

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma ID1547

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.

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- 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]
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	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.

carers to include in your submission?	
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 said “I feel restricted. I must be careful with my general health. I feel like I am on high vigilance, am I drinking enough water? is my diet ok? am I exercising enough?” Carers of patients with kidney cancer can find the situation very difficult. Their family members can have times of acute illness, daily side effects of treatment or pain and this can cause much disruption in the family. One carer said I still get anxious, depressed, scared and overwhelmed by the "what ifs" Carers can feel overprotective of their relatives and often not know what to say. A Carer said;” I think we all put on a brave face, which to the world (and each other) makes it look like we are coping”
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 patients is unfit for surgery. Many people have a good life expectancy after surgical intervention and are able to continue with their lives, whilst having surveillance. This does not always negate the sense of anxious and anticipation of reoccurrence the patients may live with. Once the kidney cancer has become metastatic, which can be within a variable amount of time (months to

	years) from initial diagnosis depending on the grade of the tumour then other treatment is needed. Sometimes solitary metastases can be surgically removed, or radio ablation or cryotherapy can be used. If the metastatic disease is more widespread systemic treatment is the next step. Although over the last few years the options of treatment for kidney cancer are expanding, the most commonly used 1st line treatments are tyrosine kinase inhibitor (sunitinib, pazopanib, tivozanib or cabozantinib) and more recently has become nivolumab and ipilimumab for the intermediate to poor risk patients. Kidney Cancer UK feel that there are significant improvements that could be made in this area. A wider range of options with improved efficacy and fewer side effects. The most commonly used Tyrosine kinase inhibitors (sunitinib and pazopanib) act to extend life and in some cases, they work very well and extend life for many years, although this is always with numerous side effects. The most common side effects (occurring in over 30% of all patients) are nausea and vomiting, diarrhoea, fatigue, heartburn, hypertension, anaemia, low white blood cell count and skin yellowing. One patient described the restricting side effects of sunitinib stating; my scans look good, but I am unable to get out of bed most days. I don't have a life; I would like to see my granddaughter go to school in a few months, but I am not hopeful. For others, although the extension of life maybe a matter of months these can be invaluable for individuals and their families. The newly licenced treatment of nivolumab and ipilimumab has a high rate of immune side effects, which can be very serious; such as colitis, pneumonitis, encephalitis, hepatitis, nephritis, hormone gland problems, skin problems and infusion reactions. One patient reports the perfuse diarrhoea she experienced due to immune related colitis was one of the worse experiences she had been through. It was subsequently treated and resolved with steroids after several months. Patients in the UK feel very fortunate to be able to be involved in cutting edge clinical trials that are changing the face of how kidney cancer is being treated. A patient said "The options from the NHS are being expanded all the time and the licencing of this new technology will be adding to the options available. This is good as not all treatments suit all patients; a new option could be just right for some people." Generally, patients feel hopeful that they are in this golden era of treatment for kidney cancer and it helps them to feel that whatever treatment they are on it is not the end of the road.

	The combination of immunotherapy and TKI could dramatic change the landscape since it is using two targeted pathways to treat the cancer and the clinical trial has shown a greater overall survival and longer period of progression free survival.
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. The other important aspect to patients is a good quality of life whilst they are on treatment, this may be managed side effects. Another unmet need for this community is psychological and emotional support whilst they are on treatment to deal with side effects and the impact of their cancer on their life.,
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. 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 many who are able use online platforms or attend support groups as available. Patients reported despite mild and manageable side effects, they were able to carry on with daily activities. One patient reports still being able to maintain his job with negotiation of his working schedule to

	have treatment. He felt that for the 3 years he was on treatment his life was able to continue how he wanted to live. The combination of avelumab and axtinib in the clinical study showed an impressive median progression free survival of 13.8 months compared to 7.2 months with sunitinib. This is significantly longer, nearly double and a great advantage of the technology. The overall survival was also advantageous at 11.6 months for avelumab and axitinb compared to 10.6 months for sunitinib.
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 side effects mostly 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. One lady stated although the side effects were difficult once her dose of axitinib was titrated to an acceptable dose she was able to go about her normal life without restrictions. Two of the patients who talked to us suffered from ulcers on their skin which were attributed to the medication. For one whose skin changes ulcer with associated sensitive skins were on their foot, the consequences were reduced mobility and an inability to wear normal shoes or to work as a mechanic. Another states; “The treatment that I am having has changed my life, I have no energy, I am always tired, I get breathless, feel nauseous and I have a constant cough. On the upside I am sure my life has been significantly extended, if it wasn’t for the treatment, I don’t think I would be alive today.” 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 avelumab and axitinib in May 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 avelumab and axtinib in the clinical study showed an impressive median progression free survival of 13.8 months compared to 7.2 months with sunitinib. This is significantly longer, nearly double and a great advantage of the technology.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma ID1547

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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

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

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted], submitting on behalf of:
2. Name of organisation	NCRI-ACP-RCP-RCR

3. Job title or position	[redacted]
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):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
5b. Do you have any direct or indirect links with, or funding	**No**

from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To obtain extended control of metastatic disease and thereby improve length and quality of life
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement of median PFS > 3/12
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With combination ipi+nivo or TKI as per previous NICE STAs. This is the first combination treatment of immunotherapy with a TKI.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes
• What impact would the technology have on the current pathway of care?	None
10. Will the technology be used (or is it already used) in the same way as current care	Yes – will be managed by oncologists with specialist interest.

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	More patients having iv infusions (avelumab is 2/52 infusion schedule).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist cancer centre
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil significant
11. 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	Mature OS data awaited

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No biomarker available
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	Additional iv infusions due to avelumab schedule

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard response assessment using imaging
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes – the QALY calculation is insensitive to many improvements that cancer patients experience from therapy.
16. Do you consider the technology to be innovative in its potential to make a	This is the first immunotherapy/TKI combination

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This is the first immunotherapy/TKI combination
• Does the use of the technology address any particular unmet need of the patient population?	Good prognosis RCC patients currently do not receive immunotherapy as a first line treatment. This would be an improvement.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Standard s/e management
Sources of evidence	
18. Do the clinical trials on the	Yes

technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	RR, PFS as per standard. OS not yet significant although these patients now have multiple lines of treatment and OS maty be confounded by post progression treatment.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic	no

review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	No real worl data for IO-TKI yet
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- First IO-TKI combination
- Shows superiority vs TKI alone
- Good prognosis RCC patients not currently treated with IO first line – this would be an improvement in their standard of care
- May also be a preferred option for patients for whom IO-IO combination may have toxicity concerns
-

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NHS England submission on the NICE appraisal of the combination of avelumab 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 avelumab 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 avelumab 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 as current 1st line therapy options of sunitinib or pazopanib or tivozanib, there is 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 tyrosine kinase inhibitor that can be used in all IMDC prognostic groups.
4. The Javelin 101 RCC avelumab plus axitinib trial did not incorporate a 2 year stopping rule in its design and planned to treat patients until disease progression or unacceptable toxicity or patient decision to discontinue treatment. The Keynote 426 trial with pembrolizumab plus axitinib stopped the pembrolizumab part of the duo after a duration of 35 cycles (in effect after 2 years) but, at subsequent relapse, allowed patients who had completed 35 cycles without progression 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 number of patients completing 2 years of therapy, both the proportion of these that relapse and when and subsequently the response to re-treatment.
5. In the case of avelumab plus axitinib, NHS England notes that the company's 2 year stopping rule would apply to both avelumab and axitinib. Not only will there be no future prospective trial evidence as to the longer term efficacy and consequences of such a stopping rule with this combination but (as far as NHS England is aware), there is no robust evidence of a stopping rule for TKI therapy in RCC (other than some retrospective evidence in patients who attain a complete remission).
6. NHS England also notes that the company wishes the combination of avelumab plus axitinib to go into the CDF. Whist the immaturity of the Javelin trial survival data is

clearly apparent, there is a logical mismatch between waiting for the maturation of data from a clinical trial with an open treatment duration and the CDF collecting data on a capped treatment duration.

7. If NICE recommends avelumab plus axitinib with a treatment duration capped at 2 years on the basis of cost effectiveness, then a capped treatment duration at 2 years is exactly what NHS England will commission. There will be no funding of re-treatment with avelumab plus axitinib and there will be no commissioning of 2nd line therapy with nivolumab in patients previously treated with avelumab plus axitinib.
8. 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. The company's treatment waning effect in this appraisal is so optimistic that its removal does not affect the ICER to a great degree.
9. NHS England notes the rather dramatic effect that removal of the stopping rule has on the ICER in this appraisal.
10. 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 and no re-starts were commissioned, then clinicians would still wish to use the combination of a VEGF inhibitor and a checkpoint inhibitor.
11. If NICE recommends the combination of avelumab plus axitinib in the treatment of all risk categories (favourable, intermediate and poor) of 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 avelumab 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 as such an

appropriate displaced current 1st line option after failure of avelumab plus axitinib as tivozanib's mode of action is 'cleaner'.

12. NHS England notes that with a median duration of follow up of 19 months, there is as yet no statistical difference in overall survival (OS) in the Javelin trial. NHS England is confident that further data maturation will demonstrate such a difference in OS. Although the Keynote 426 trial with pembolizumab plus axitinib has shown an early statistically significant survival difference, NHS England wonders whether this could be due to how the statistical design of the trial was set up as the clinical data for these 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.
13. NHS England is comfortable with the switch from the trial 10mg/kg dosing of avelumab to the fixed 800mg dose administered every 2 weeks. Similar switches have occurred via data from drug modelling analyses for pembrolizumab and nivolumab.
14. NHS England notes that the 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 and thus if avelumab plus axitinib is recommended by NICE, then NHS England would commission its 1st line use in patients with locally advanced or metastatic bpapillary RCC.

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

January 2020

ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 129584

Completed 18 September 2019
Revised 10 October 2019

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

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Date completed: 18 September 2019

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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.

Declared competing interests of the authors: Within the last 3 years, Shien Chow has received reimbursement for attending symposiums organised by EUSA, Ipsen and Novartis ,fees for speaking from Novartis and Pfizer and funds for nursing post from Novartis. Within the last 3 years, Tom Waddell has received consultancy fees for participating on advisory boards for Bristol-Myers Squibb, Ipsen, Novartis, Pfizer and Roche, reimbursement for attending symposiums organised by Bristol-Myers Squibb, EUSA and Ipsen, fees for speaking from Bristol-Myers Squibb, EUSA, Ipsen, Novartis and Pfizer and funds for a member of staff from Novartis. Within the last 3 years, Fiona Thistlethwaite has received consultancy fees from Bristol-Myers Squibb and GlaxoSmithKline, reimbursement from Bristol-Myers Squibb and Ipsen for attending European Society for Medical Oncology symposiums, fees for organising education from Novartis, fees for speaking from Bristol-Myers Squibb, hospitality from Novartis and and funds for research from Novartis.

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Contributions of authors:

Nigel Fleeman	Project lead, critical appraisal of the clinical evidence and supervised the final report
Tosin Lambe	Critical appraisal of the economic evidence
Sarah Nevitt	Critical appraisal of the statistical evidence
James Mahon	Critical appraisal of the economic evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Cross checking of the submission search strategies
Ashley Marsden	Critical appraisal of the company submission
Shien Chow	Clinical advice and critical appraisal of the clinical sections of the company submission
Tom Waddell	Clinical advice and critical appraisal of the clinical sections of the company submission

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LIST OF ABBREVIATIONS

AE	adverse event
AIC	Akaike information criterion
aRCC	advanced renal cell carcinoma
AWMSG	All Wales Medicine Strategy Group
BIC	Bayesian information criterion
BICR	blinded independent central review
BNF	British National Formulary
CAA	commercial access agreement
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CS	company submission
CSR	clinical study report
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-3L	EuroQol 5-Dimension 3-Level
EQ-5D-5L	EuroQol 5-Dimension 5-Level
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	full analysis set
FKSI-19	Functional Assessment of Cancer Therapy-Kidney Symptom Index-19
FKSI-DRS	Functional Assessment of Cancer Therapy-Disease Related Symptoms
HR	hazard ratio
HRQoL	health-related quality of life
IA1	first interim analysis
IA2	second interim analysis
ICER	incremental cost effectiveness ratio
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IPD	individual patient data
IV	intravenous
kg	kilogram
K-M	Kaplan-Meier
mg	milligram
MSKCC	Memorial Sloan Kettering Cancer Center
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme

PD	progressed disease
PD-1	Programmed cell death protein 1
PD-L1	programmed death receptor ligand 1
PF	progression-free
PFS	progression-free survival
PFS2	progression-free survival on next-line therapy
PH	proportional hazards
PR	partial response
PRO	patient-reported outcome
PS	performance status
PSA	probabilistic sensitivity analysis
Q2W	every 2 weeks
QALY	quality adjusted life year
RCC	renal cell carcinoma
RCT	randomised controlled trial
RDI	relative dose intensity
SAE	serious adverse event
SD	standard deviation
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
TA	technology appraisal
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
ToT	time on treatment
TRAE	treatment-related adverse event
TTD	Time to treatment discontinuation
TTR	Time to response
UK	United Kingdom
VEGFR	vascular endothelial growth factor receptor

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Merck KGaA/Pfizer Ltd in support of the use of avelumab (Bavencio) in combination with axitinib (Inlyta) for the treatment of advanced renal cell carcinoma (aRCC). Avelumab+axitinib (as a combination therapy) has not yet received a European marketing authorisation for the treatment of aRCC; axitinib is already authorised for patients with previously treated aRCC. The European Medicines Agency Committee for Human Medicine Products (EMA CHMP) opinion for avelumab+axitinib is expected in [redacted].

1.2 Critique of the decision problem in the company submission

The decision problem addressed by the company largely matched that described in the final scope issued by NICE.[1] The population described in the final scope issued by NICE[1] was for patients with untreated aRCC; however, the JAVELIN Renal 101 trial, the main source of evidence for the effectiveness of treatment with avelumab+axitinib, only included patients with clear cell aRCC patients. The proportion of patients in NHS clinical practice with non-clear cell aRCC may be as high as 25%. The comparators listed in the final scope were sunitinib, pazopanib, tivozanib and, in patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor risk disease, cabozantinib.

1.3 Summary of the clinical evidence submitted by the company

1.3.1 Identified evidence

The company undertook searches to identify relevant evidence for inclusion in a systematic review. Searches of MEDLINE, Embase, the Cochrane Library, Health Technology Assessment and relevant conference websites were searched on 9 May 2018 and updated on 8 March 2019. In addition, bibliographies of systematic literature reviews published between 2015 and 2018 were also searched. The scope of the eligibility criteria was broader than was required for the decision problem as studies of treatments not included as comparators (e.g. sorafenib) were included. The company considered a broader range of treatment options was necessary to conduct network meta-analyses (NMAs).

Evidence of the effectiveness of avelumab+axitinib versus sunitinib was obtained from the ongoing Phase III, randomised, open-label JAVELIN Renal 101 trial of avelumab+axitinib

versus sunitinib in patients with previously untreated, aRCC with a clear-cell component. The company conducted progression-free survival (PFS) and overall survival (OS) NMAs to generate evidence for avelumab+axitinib versus tivozanib and, in patients with IMDC intermediate/poor risk status aRCC, cabozantinib. Although it was possible to generate evidence for PFS and OS for avelumab+axitinib versus pazopanib from the NMAs, the company assumed that the relative treatment effects were the same as the relative treatment effects for avelumab+axitinib versus sunitinib from the JAVELIN Renal 101 trial. The company adopted this approach because, during previous NICE Technology Appraisals (TA512 and TA581), Appraisal Committees concluded that sunitinib and pazopanib were of equal efficacy.

1.3.2 Summary of direct evidence

In the JAVELIN Renal 101 trial, patients were randomised to receive avelumab+axitinib (N=442) or sunitinib (N=444). Avelumab was administered at the dose of 10mg/kg as a 1-hour intravenous infusion once every 2 weeks (Q2W) in a 6-week cycle (Days 1, 15 and 29 of each cycle). Axitinib (5mg twice daily) was administered orally, on a continuous dosing schedule. Sunitinib (50mg once daily) was administered orally in 6-week cycles (four consecutive weeks of treatment followed by a 2-week off-treatment period). Patients in the avelumab+axitinib arm were permitted to stop treatment with one of the agents and continue in the study by receiving treatment with the other agent. Patients received treatment until confirmed disease progression, global deterioration of health status requiring discontinuation, unacceptable toxicity or death. Treatment with single-agent avelumab, single-agent axitinib, avelumab+axitinib or sunitinib could continue beyond confirmed disease progression if the patient was experiencing clinical benefit. Crossover between treatment arms was not permitted.

PFS assessed by blinded independent central review was statistically significantly longer in the avelumab+axitinib arm compared to the sunitinib arm at the time of the first interim analysis (IA1) of 20 June 2018 (median PFS 13.8 months compared to 8.4 months; hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.56 to 0.84; one-sided p-value <0.0001). The company states that results at the time of the second interim analysis (IA2) of 28 January 2019 reinforced these earlier results (median PFS [redacted] months compared to [redacted] months; HR [redacted], 95% CI [redacted]; one-sided p-value [redacted]).

OS was immature at IA1 (25.8% of the 535 deaths required for final OS analysis) and median OS was not reached in either treatment arm. Results showed no statistically significant difference between arms at the pre-specified significance level of 0.025 (HR 0.78, 95% CI 0.55 to 1.08). As with IA1, OS data were immature at the time of IA2 ([redacted] of the 535 deaths

required for final OS analysis). [redacted].

The patient reported outcome (PRO) data do not suggest that health-related quality of life (HRQoL) is improved with avelumab+axitinib versus sunitinib. However, as PRO assessments occurred at the end of the 2-week off-treatment period for sunitinib, the company highlights that PRO analyses may have been biased in favour of sunitinib versus avelumab+axitinib. To support this argument, the company cites a study of sunitinib that found HRQoL reported during the 4 week sunitinib on-treatment period to be statistically significantly worse than HRQoL reported during the 2 week off-treatment period.

Diarrhoea and hypertension were the most common any grade treatment-related adverse events (TRAEs) reported for patients treated with avelumab+axitinib (54.1% and 47.9%, respectively) and also very common for patients treated with sunitinib (44.6% and 32.3%, respectively). The most common Grade ≥3 TRAE in both arms was hypertension (24.4% in the avelumab+axitinib arm, 15.3% in the sunitinib arm). [redacted].

1.3.3 Summary of indirect evidence

Due to uncertainties regarding the validity of the proportional hazards (PH) assumption, the company conducted standard Bayesian NMAs assuming PH (PH NMAs) and also NMAs using parametric survival curves which do not require an assumption of PH (non-PH NMAs).

Results from the company's PFS fixed effects PH NMA show that treatment with avelumab+axitinib leads to a statistically significant reduction in PFS compared to treatment with sunitinib or pazopanib but not tivozanib or, in the IMDC intermediate/poor risk status population, cabozantinib. There were no statistically significant differences for OS between avelumab+axitinib and any of the comparators.

Results from the company's non-PHS NMAs found PFS probabilities in the all risk status population to be generally higher for avelumab+axitinib compared to all of the comparators at 1, 2 and 10 years. Estimated OS probabilities are similar across all treatments at 1 and 2 years, and a slightly higher OS probability is estimated for avelumab+axitinib compared to all of the comparators at 10 years. Estimated PFS and OS probabilities for the IMDC intermediate/poor risk status population are similar for avelumab+axitinib and cabozantinib at 1, 2 and 10 years.

The company presented data for some of the most common adverse events (AEs) identified with other comparators in CS, Appendix D. The AEs for which data are reported are anaemia, decreased appetite, diarrhoea, fatigue, hand-foot syndrome (palmar-plantar erythrodysaesthesia), hypertension, neutropenia, rash, stomatitis/mucositis and thrombocytopenia. Data are also reported for withdrawal of study drug due to AEs and/or withdrawal due to any cause.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

1.4.1 Critique of identified evidence

Clinical advice to the ERG is that, as is common with all clinical trials, patients with some comorbidities who might otherwise be considered for treatment in clinical practice were excluded from the JAVELIN Renal 101 trial (and from all trials included in the NMAs). It is also noted that the JAVELIN Renal 101 trial only included patients with a clear cell component and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1. Of the studies included in the NMAs, there was one randomised sequential trial of sorafenib followed by sunitinib versus sunitinib followed by sorafenib that enrolled a minority of patients with clear cell aRCC (13%). Only one trial included in the NMAs (which compared cabozantinib versus sunitinib in patients with IMDC intermediate/poor risk status aRCC) included >1% of patients with ECOG PS 2 (13%).

The ERG notes that the two randomised sequential trials included in the company's NMAs met the company's exclusion criteria. However, their inclusion was necessary for formation of a connected network to allow an indirect comparison between avelumab+axitinib and tivozanib for patients with all risk status aRCC.

1.4.2 Critique of direct evidence

The ERG considers that the JAVELIN Renal 101 trial is a well-designed and good quality trial with an appropriate and pre-defined statistical approach to the analysis of efficacy outcomes (including PROs) and safety outcomes. The ERG agrees that the data show a PFS benefit for avelumab+axitinib versus sunitinib but that definitive conclusions cannot yet be drawn for OS due to the immaturity of the OS data. Due to PRO assessments occurring at the end of the 2-week off-treatment period for sunitinib, the ERG agrees with the company that the PRO results may be biased in favour of sunitinib. Avelumab+axitinib was generally well tolerated as AEs were typically manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies.

1.4.3 Critique of indirect evidence

The ERG agrees with the company that there are uncertainties around the validity of the PH assumption for PFS and OS across the trials included in the NMAs and considers that the company approach of conducting PH and non-PH NMAs was appropriate.

The ERG considers that, for PFS, from the PH and non-PH NMAs, the magnitude of the observed differences between avelumab+axitinib and the comparator treatments is uncertain. The ERG has concerns regarding the validity of the OS NMAs (PH and non-PH) due to the inclusion of trials of randomised sequential design, trials permitting treatment crossover and differences in subsequent therapies. Therefore, the ERG considers that no reliable conclusions can be drawn from the OS NMAs.

It is not possible to compare avelumab+axitinib versus pazopanib, tivozanib or cabozantinib using PROs. The ERG notes that the safety data presented in CS, Appendix D show differences in the frequencies of the same types of AEs (e.g., large differences in the incidence of neutropenia and thrombocytopenia in the sunitinib arms across trials). As the ERG considers that heterogeneity exists between the trials, it is difficult to draw conclusions about how avelumab+axitinib may compare to pazopanib, tivozanib or cabozantinib in terms of PROs or safety outcomes, either using statistical methods or by simply naively comparing the data.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo economic partitioned survival model in Microsoft Excel to compare the cost effectiveness of avelumab+axitinib versus NHS standard of care for the treatment of untreated aRCC. For the all risk status population, the comparators were sunitinib, pazopanib and tivozanib and for the IMDC intermediate/poor risk status population the comparator was cabozantinib. The model comprised three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. All patients started in the PF health state. The model time horizon was set at 40 years, the cycle length was 1 week and the perspective was that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs) and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE.

For the comparison of avelumab+axitinib versus sunitinib and versus pazopanib, the company used the generalised gamma and log-logistic functions to extrapolate IA1 JAVELIN Renal 101 trial PFS and OS Kaplan-Meier (K-M) data respectively. For the comparisons of avelumab+axitinib versus tivozanib and versus cabozantinib, the company used survival

estimates from the non-PH NMAs to represent the experience of patients receiving avelumab+axitinib.

Survival of patients receiving sunitinib was modelled by extrapolating PFS and OS K-M data from the sunitinib arm of the JAVELIN Renal 101 trial using log-logistic functions. Based on evidence from previous NICE appraisals, the company assumed that treatment with pazopanib delivered the same PFS and OS as treatment with sunitinib. PFS and OS estimates from the company's NMAs were used to model survival for patients treated with tivozanib (generalised gamma) and cabozantinib (PFS=generalised gamma, OS=log-logistic).

Time on treatment (ToT) for patients treated with avelumab+axitinib and those treated with sunitinib was estimated by extrapolating JAVELIN Renal 101 trial time to treatment discontinuation (TTD) K-M data using parametric functions. For patients treated with pazopanib, ToT was assumed to be equal to that for patients treated with sunitinib and ToT for patients treated with tivozanib was assumed to be the same as the non-PH PFS estimate for tivozanib. ToT for patients treated with cabozantinib was estimated based on published CABOSUN trial TTD K-M data.

The dose of avelumab used in the JAVELIN Renal 101 trial was calculated based on patient weight; however, in the company model, a flat dosing schedule of 800mg was used. This latter dose reflects the proposed licensed dose and is similar to the mean JAVELIN Renal 101 trial dose. For axitinib and comparators, wastage was calculated for each cycle, using drug regimen, ToT and percentage relative dose intensity (RDI). The RDI values for avelumab, axitinib and sunitinib were obtained from the JAVELIN Renal 101 trial and RDI values for the other treatments were obtained from their respective trials.

The treatment stopping rule applied by the company meant that treatment with avelumab and axitinib was stopped at 2 years. The company assumed that this would result in a loss of treatment effectiveness for 33% of patients (estimated, by clinicians, to be between 20% and 50%). This effect (a treatment waning effect) was modelled so that progression and mortality hazards of one third of patients who had ever been treated with avelumab+axitinib would gradually merge (over the subsequent 2 years) with the progression and mortality hazards of patients receiving the comparator treatment. The remaining two-thirds of patients were assumed to accrue a lifetime treatment benefit from treatment with avelumab+axitinib.

HRQoL data were collected during the JAVELIN Renal 101 trial and used to represent the quality of life of patients in the PF and PD health states. Resource use and costs were estimated based on information from the JAVELIN Renal 101 trial and published sources.

The company used a combination of confidential discounts (for avelumab and axitinib), non-confidential discounts (for sunitinib and pazopanib) and list prices (for all other drugs) to estimate drug costs.

The company's deterministic base case cost effectiveness results showed that, for the all risk status population, the pairwise incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of avelumab+axitinib versus sunitinib, versus pazopanib and versus tivozanib were £26,242, £29,542 and £9,220 respectively. For the IMDC intermediate/poor risk status population, avelumab+axitinib dominated cabozantinib [redacted].

The results from the company's probabilistic sensitivity analysis are consistent with the company's base case (deterministic) analysis. The company carried out a range of deterministic sensitivity analyses. The most influential parameters were the RDIs of avelumab+axitinib and its comparators.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the most important issue is the immaturity of the IA1 JAVELIN Renal 101 trial OS results. For the IMDC intermediate/poor risk status population, the data are so uncertain that the company considers that definitive conclusions about relative effectiveness (OS) cannot be drawn for this population (CS, Appendix E, p1). The ERG considers that incorporating uncertain clinical effectiveness evidence into the economic model means that it is difficult to have confidence in any of the cost effectiveness results generated by the company or the ERG.

There is no trial evidence to support the company's assumption that treatment with avelumab and axitinib will be stopped at 2 years. Neither is there any trial evidence to support the company's assumption that once treatment with avelumab or axitinib is discontinued, the benefits from these treatments (in terms of improved PFS and OS) will, for a third of patients, wane. The ERG considers that, due to an absence of evidence, these assumptions should not be implemented in the company base case, rather, their effect on cost effectiveness estimates should only be explored in scenario analyses. Furthermore, the ERG considers that, if a treatment waning effect does occur, there is no rationale for restricting the effect to one third of patients.

When modelling survival for the all risk status population, the company representations of OS and PFS for avelumab+axitinib differ depending on the comparator: estimates were obtained

from either the extrapolation of the JAVELIN Renal 101 trial (versus sunitinib and versus pazopanib) or the company's non-PH NMAs (versus tivozanib). The ERG considers that OS and PFS for avelumab+axitinib for a specified population should be the same, irrespective of comparator.

The OS results, for the all risk status population, from the JAVELIN Renal 101 trial, for patients treated with avelumab+axitinib and for those treated with sunitinib were not statistically significantly different. The ERG considers that the available trial evidence does not support the company's approach to modelling OS representations using two different distributions.

The company used results from their non-PH NMA to model OS for patients treated with tivozanib. The ERG considers that these results are not robust and should not be used to generate cost effectiveness estimates.

1.7 Summary of company's case for NICE End of Life criteria being met

The company has not presented evidence to support treatment with avelumab+axitinib being considered as a NICE 'End of Life' treatment.

1.8 ERG commentary on NICE End of Life criteria

The ERG does not consider that treatment with avelumab+axitinib meets the NICE End of Life criterion that the treatment should be indicated for patients with a short life expectancy, normally less than 12 months. The ERG highlights that results from the company base case show that, for patients receiving current NHS standard of care, mean OS is at least 5 years and median OS is at least 3 years, even for the IMDC intermediate/poor risk status population.

1.8.1 Strengths

Clinical evidence

- The company provided a detailed submission that met the requirements of NICE's scope for the clinical effectiveness analysis. The ERG's requests for additional information were addressed to a good standard.

- The ERG considers that the JAVELIN Renal 101 trial was generally well-designed and well conducted. Direct evidence demonstrates avelumab+axitinib to have superior PFS versus sunitinib.

- Direct evidence has been presented for avelumab+axitinib versus a relevant comparator (sunitinib) in the JAVELIN Renal 101 trial. The patient population in the JAVELIN Renal 101 trial appears to be broadly similar to the patient population that

would be treated in NHS clinical practice (with the possible exception of excluding patients with some comorbidities, patients with ECOG PS ≥2 and non-clear cell aRCC).

- Despite some differences in patient characteristics across the trials included in the NMAs, all patient populations appear to be broadly similar to the patient population that would be treated in NHS clinical practice (with the possible exception of excluding few patients with some comorbidities, ECOG PS ≥2 and non-clear cell aRCC).

Cost effectiveness evidence

- The company model was easy to navigate.
- Company model parameter values matched those documented in the CS.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- The JAVELIN Renal 101 trial evidence is presented for a dosing regimen of avelumab at a dose of 10mg/kg of body weight as a 1-hour intravenous infusion Q2W. However, the expected licensed dose for avelumab will be a flat dosing schedule of 800mg Q2W. Although the company states pharmacology data support this flat dosing schedule, there is no relative clinical effectiveness evidence provided using this dosing regimen.
- Clinical advice to the ERG is that clinicians would hope to be able to consider avelumab+axitinib as a treatment option for patients with non-clear cell aRCC as well as for some patients with ECOG PS 2. However, evidence is only presented in the CS for patients with clear cell aRCC treated with avelumab+axitinib and ECOG PS 0-1 treated with avelumab+axitinib.
- It is known that there are potential cardiovascular events associated with vascular endothelial growth factor receptor-tyrosine kinase inhibitor agents such as axitinib, sunitinib, tivozanib and cabozantinib. Clinical advice to the ERG is that immune-related reactions may therefore be the AEs to be most concerned about with regard to treatment with avelumab+axitinib, particularly since immune-related reactions can be irreversible, severe and life-threatening. In the avelumab+axitinib arm of the JAVELIN Renal 101 trial, the proportion of patients with severe (Grade ≥3) immune-related reactions was 9.0% and the proportion of patients with fatal immune-related reactions was [redacted]. However, it is not reported if any immune-related reactions were reversible or irreversible.

- The ERG considers that for PFS from the PH and non-PH NMAs, the magnitude of the any observed differences between avelumab+axitinib and the comparator treatments is uncertain.

- The ERG has concerns regarding the validity of the OS NMAs (PH and non-PH) due to the inclusion of trials of randomised sequential design, trials permitting treatment crossover and differences in subsequent therapies. Therefore, the ERG considers that no reliable conclusions can be drawn from the NMAs of OS.

Cost effectiveness evidence

- The immaturity of the OS data from the JAVELIN Renal 101 trial means that all cost effectiveness results (company and ERG) generated by the model using these data (either directly or indirectly via an NMA) are highly uncertain.

- The company has assumed, for patients treated with avelumab+axitinib, that treatment will be stopped at 2 years. There is no trial evidence to support this assumption.

- The company has assumed that, at 2 years, for patients treated with avelumab+axitinib, the benefits of treatment, for one third of patients who had ever received treatment will wane and progression and survival hazards will gradually, over the subsequent 2 years, become equal to those of comparator treatments. There is no trial evidence to support this assumption.

- For the all risk status population, the company has modelled PFS and OS for patients treated with avelumab+axitinib in ways that differ depending on the comparator. The ERG considers that such an approach is inappropriate.

- For the comparison of treatment with avelumab+axitinib versus sunitinib, OS results from the JAVELIN Renal 101 trial are not statistically significantly different. The ERG, therefore, considers that different approaches to extrapolating these two sets of trial data should not have been taken.

- Concerns relating to the company's non-PH OS NMAs mean that the reliability of data used by the company to model survival for the comparisons of cost effectiveness of treatment with avelumab+axitinib versus tivozanib and versus cabozantinib is highly uncertain.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has implemented the following revisions to the company base case:

- Removed the avelumab+axitinib treatment stopping rule and retained the company's treatment waning effect (R1)
- Removed the company's treatment waning effect and retained the company's treatment stopping rule (R2)
- Set the treatment waning effect to apply to all patients who had been treated with avelumab+axitinib and who were are alive at 2 years and retained the company's treatment stopping rule (R3)
- Used the company's exponential function to extrapolate OS K-M data from the avelumab+axitinib arm and the sunitinib arm of the JAVELIN Renal 101 trial (most optimistic extrapolation for the company excluding log-logistic and log-normal distributions) (R4)
- For the comparison with tivozanib, PFS and OS estimates for avelumab+axitinib were set to be the same as the PFS and OS estimates used for avelumab+axitinib in the comparison with sunitinib and pazopanib (modelled on data from the JAVELIN Renal 101 trial) (R5)
- Set OS estimates for sunitinib, pazopanib and tivozanib to be the same as the OS estimates for avelumab+axitinib (modelled on data from the JAVELIN Renal 101 trial) (R6)

Once the stopping rule and associated waning are disabled, the lowest revised base case ICER is for the comparison of avelumab+axitinib versus tivozanib (£73,554 per QALY gained).

For the all risk status population, for the comparison of treatment with avelumab+axitinib versus any comparator, if all of the ERG's revisions are implemented, the ICERs are in excess of £1,000,000 per QALY gained.

For the IMDC intermediate/poor risk status population, for the comparison of treatment with avelumab+axitinib versus cabozantinib, if all of the ERG's revisions are implemented, the ICERs range from £172,657 to £795,993 per QALY gained.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem (renal cell carcinoma [RCC]) is presented in Section A1 and Section B1.3 of the company submission (CS). The Evidence Review Group (ERG) considers that the company's description presents an accurate summary of the underlying health problem. Key points made by the company and considered by the ERG to be most relevant to the current appraisal are presented in Box 1.

Box 1 Key points from the company's description of underlying health problem

Description of disease

- Renal cell carcinoma (RCC), where cancerous cells develop within the epithelia of the renal tubules, is the most common form of kidney cancer, accounting for 85% to 90% of cases.[2-4]
- There are five major histological subtypes of RCC; of which clear cell RCC is the most common (approximately 75% of cases). Other subtypes include papillary (10%), chromophobe (5%), cystic-solid (1–4%), collecting duct (1%) and non-classified RCC (4–6%).[5]
- Kidney cancers often remain asymptomatic until the advanced stage.[6]
- Mortality is strongly associated with stage at diagnosis, with 1-year and 5-year survival rates for those diagnosed at Stage I-II being 93.4% and 76.7%, respectively, compared with 37.2% and 10.7% for those diagnosed at Stage III and IV (advanced RCC [aRCC]), respectively.[7]

Epidemiology

- In 2017 there were 9298 cases of RCC (17.1 per 100,000 person-years) in England, of which 37% were diagnosed at the advanced stage (1560 at Stage III and 1834 at Stage IV).

Burden of disease

- As well as high levels of mortality, aRCC is associated with a significant humanistic burden on patients and carers.
- Due to the poor prognosis and symptom burden associated with aRCC, there is a considerable negative impact on health-related quality of life (HRQoL), with baseline utility scores for newly diagnosed aRCC of 0.69 to 0.76[8-11] compared with 0.86 for the general population.[12]
- HRQoL continues to deteriorate as the disease progresses.[13]
- The majority of costs associated with RCC are related to hospital care, accounting for approximately 70% to 80% of total costs.[14]
- RCC is also associated with indirect costs, in part due to the time spent supporting patients by informal carers, which represents time not spent pursuing usual activities, including work.

Source: CS, Section A1 (epidemiology data) and Section B.1.3

The ERG notes that within the CS, the terms advanced RCC (aRCC) and metastatic RCC are used interchangeably; metastatic RCC can be considered a more advanced type of aRCC. Patients with metastatic RCC have Stage IV disease, whereas patients with aRCC may also have Stage III (locally advanced) disease (Table 1).

Note: throughout this ERG report, locally advanced or metastatic RCC is referred to as aRCC.

Table 1 Staging of advanced renal cell carcinoma

Stage	Description
Stage III	The tumour extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia (T3, N0, M0), and/or has metastasised to a single regional lymph node (T1–3, N1, N0)
Stage IV	The tumour extends beyond Gerota's fascia (T4, Any N, M0), or has metastasised to distant site(s) (Any T, Any N, M1)

M=presence or absence of distant metastases; N= lymph node involvement; T=local tumour growth
Source: CS, Section B.1.3.1.1, p17

As summarised in Box 1 of this ERG report, the company states that in 2017 there were 9298 cases of RCC of which 37% were diagnosed with aRCC (Section A1). The ERG notes that this figure is a proportion of all new cases, including those whose disease stage was unknown to Public Health England's National Cancer Registration and Analysis Service (NCRAS). If these cases are excluded, the proportion of patients with aRCC in England in 2017 was 42% (19% Stage III and 23% Stage IV).

2.2 Company's overview of current service provision

The company's overview of current service provision is presented in the CS, Section A2 and Section B1.3. The ERG considers that the company's overview presents an accurate summary of current service provision and highlights the key points made by the company in Box 2. The ERG notes that treatment aims and options remain the same for patients with Stage III and Stage IV RCC.

Box 2 Key points from the company's overview of current service provision

Treatment aims

- As health-related quality of life continues to deteriorate as the disease progresses,[13] largely driven by the worsening of symptoms, treatments that delay progression could help to delay deterioration in HRQoL.[15]

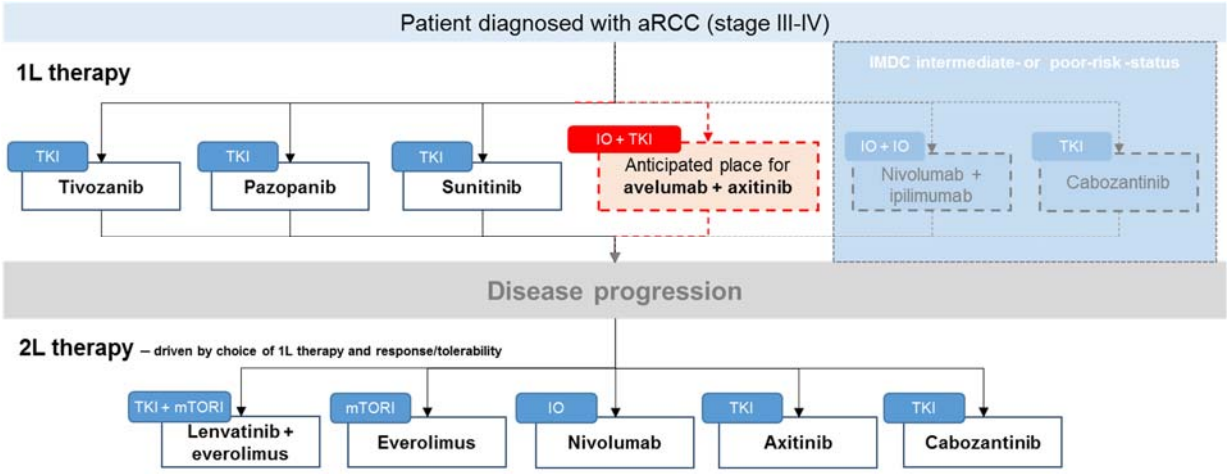
Treatment options

- NICE currently recommends monotherapy with the vascular endothelial growth factor receptor tyrosine kinase inhibitors sunitinib, pazopanib, tivozanib, and cabozantinib as options for the first-line treatment of aRCC[16-19] [cabozantinib is only a first-line treatment option for patients defined as being at International Metastatic Renal Cell Carcinoma Database Consortium intermediate/poor risk status].
- Despite improvements in outcomes following the development of targeted therapies for advanced RCC, patients treated with current first-line monotherapies often fail to achieve progression-free survival of longer than 1 year and survival outcomes remain poor.[20-23]
- Given that only 50% of patients treated in the first-line setting go on to receive second-line therapies (typically due to a lack of fitness for treatment),[24,25] it is important to ensure that patients are treated with the most effective treatments at first-line.

Source: CS, extracted from Section B1.3.5

In addition to the treatment options listed in Box 2, the company highlights that a combination treatment of two immune-oncology (IO) agents (i.e., nivolumab+ipilimumab) has been recommended by NICE (TA581)[26] for use within the Cancer Drugs Fund (CDF) for patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

intermediate/poor risk status (CS, Section B.1.3.5). The ERG has reproduced the company's depiction of the current treatment pathway in Figure 1 of this ERG report. This includes the anticipated positioning of the use of avelumab+axitinib (the combination of an IO and vascular endothelial growth factor receptor [VEGFR]-targeted tyrosine-kinase inhibitor [TKI] agent which is the focus of the current appraisal) in the treatment pathway. Further discussion of the treatment options available is presented in Sections 2.2.1 to 2.2.3 of this ERG report and further information about avelumab+axitinib is presented in Section 3.2 of this ERG report.



1L=first-line; 2L=second-line; aRCC=advanced renal cell carcinoma; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IO=immuno-oncology; mTORI=mammalian target of rapamycin inhibitor; TKI= tyrosine kinase inhibitor

Figure 1 Clinical pathway of care and anticipated place of avelumab+axitinib in the treatment pathway

Source: CS, Figure B.1.3

2.2.1 First-line treatment options

As is evident from Figure 1, the choice of first-line treatment can depend on a patient's risk status. Risk status can be determined by the IMDC or Memorial Sloan Kettering Cancer Center (MKSCC) classification systems. Data from studies cited by the company and ERG in a recent NICE appraisal,[26] including randomised controlled trials (RCTs)[27,28] and observational studies,[29-31] suggest that the majority of patients have aRCC of intermediate risk status with estimates varying from 52%[30] to 62%,[31] depending on the classification system of risk status used. Estimates of proportions of patients with favourable risk status were between 12%[31] to 28%[27] and estimates of poor risk status were between11%[27] to 30%.[30] The study by Kubackova et al 2015[31] was the only study that used both the IMDC and MKSCC risk status classification systems. The authors found that the proportions of intermediate risk status patients were similar across both systems (61% and 62%) but that the proportions of favourable risk status patients ranged from 12% (MKSCC) to 22% (IMDC) and the proportions of poor risk status patients varied from 16% (IMDC) to 27% (MKSCC), depending on which classification system of risk status was used.

Clinical advice to the ERG is that the group of patients who are classified as having aRCC of intermediate risk status are a heterogeneous group, representing a spectrum of patients whose prognosis, at one extreme, is similar to patients with aRCC of favourable risk status and at the other extreme, patients whose prognosis is similar to patients with aRCC of poor risk status.

The ERG notes that treatment with nivolumab+ipilimumab is only indicated for patients with previously untreated aRCC of IMDC intermediate/poor risk status.[32] Similarly, it is only recommended by NICE for use within the CDF for this same group of patients (TA581).[26] Since the VEGFR-targeted TKI agent cabozantinib can be used in the first-line or second-line setting,[16,33,34] clinical advice to the ERG is that currently, nivolumab+ipilimumab tends to be the preferred first-line treatment for patients with aRCC of IMDC intermediate/poor risk status.

Clinical advice to the ERG is that prior to treatments with (i) cabozantinib or (ii) nivolumab+ipilimumab being available, all patients tended to be treated with the VEGFR-targeted TKI agents, sunitinib or pazopanib, regardless of risk status. Sunitinib and pazopanib are now generally used to treat patients with aRCC of favourable risk status (and those considered to be at lower risk in the IMDC intermediate risk status population).

In general, pazopanib is considered to be better tolerated than sunitinib and has also been found to be preferred to sunitinib by most patients who have experience of both treatments.[35] However, liver dysfunction is a recognised adverse event (AE) associated with pazopanib[36] and initially requires stringent requirement around the conduct of regular liver function tests.

Tivozanib, another VEGFR-targeted TKI agent, is the most recent first-line treatment to be recommended by NICE.[19] Clinical advice to the ERG is that it is considered less toxic than all other currently available first-line treatment options. Therefore, tivozanib is increasingly preferred as a first-line treatment option for patients with favourable risk status (and those considered to be at lower risk in the IMDC intermediate risk status population).

The ERG notes that observations regarding first-line treatments made in this section are general and that, in clinical practice, the treatment pathway will differ depending on individual preferences and clinical need. For example, there is a 2-week break in treatment with sunitinib (after 4 weeks on treatment) and, for this reason, clinical advice to the ERG is that some patients may prefer sunitinib to pazopanib. As another example, cabozantinib may be preferred for patients if a fast response to treatment for bone metastases is required.

If recommended by NICE, avelumab+axitinib would likely be a treatment option for patients with aRCC of any IMDC risk status.

2.2.2 Second-line and third-line treatment options

As shown in Figure 1, current second-line treatment options recommended by NICE include everolimus (a mammalian target of rapamycin inhibitor), either alone[37] or in combination with lenvatinib[38] (a VEGFR-targeted TKI agent), axitinib monotherapy or nivolumab monotherapy.[39] The ERG notes that the company considers that: "If the combination [of avelumab+axitinib] is recommended by NICE for first-line treatment, it is anticipated that patients are likely to receive cabozantinib, lenvatinib plus everolimus or everolimus as subsequent therapy" (CS, Section B.1.3.7). However, the ERG has received clinical advice that if avelumab+axitinib were to be recommended, then current first-line VEGFR-targeted TKI agents (sunitinib, pazopanib and tivozanib) would likely to become second-line options alongside existing the second-line treatment options, with the exception of nivolumab monotherapy and axitinib monotherapy. Given the lack of evidence for the use of one IO agent after another, clinical advice to the ERG is that it is unlikely that nivolumab monotherapy would be considered a treatment option following treatment with avelumab+axitinib. However, it is noted that the IO agents (nivolumab, ipilimumab and avelumab) have different mechanisms of action; avelumab is directed against the immune checkpoint protein programmed death receptor ligand 1 (PD-L1)[40] whereas nivolumab and ipilimumab are checkpoint inhibitors of the programmed cell death protein 1 (PD-1)[32] and cytotoxic T-lymphocyte-associated protein 4,[41] respectively. Thus, clinical advice to the ERG is that, in the future, nivolumab could be used following treatment with avelumab+axitinib (assuming robust real-world evidence of safety and effectiveness emerges).

As noted in Box 2 of this ERG report, the company estimates that approximately 50% of patients treated in the first-line setting will receive second-line treatment. Evidence for this estimate is from two sources: a conference presentation from Fife et al 2018[25] who analysed 257 UK patients with aRCC treated with first-line therapy from 2012 to 2016 and found 48% received second-line treatment; a paper by Eggers et al 2017,[24] who analysed 161 German patients with aRCC who had been treated in the first-line setting with TKI agents from 2005 to 2012 and found 65% received second-line treatment. Clinical advice to the ERG is that, historically, the proportion of patients who received second-line treatment in UK clinical practice has been 50% or lower; however as more effective first-line treatment options become available, the proportion of patients who receive second-line treatment is increasing.

2.2.3 Clear-cell and non-clear cell renal cell carcinoma

As noted by the company (Section B.1.3.1, p17), approximately 75% of all aRCC is clear cell aRCC,[42] although it has been reported to be higher (90% to 95%).[32] Clinical advice to the ERG is that as non-clear cell aRCC is rarer than clear cell aRCC and consists of heterogeneous

histologies with worse prognoses than clear cell aRCC (non-clear cell aRCC is a more aggressive form of the disease[43]), the unmet need is much higher for this group of patients. However, in general, the clinical community would like to be able to have the same treatment options available for patients with clear cell and non-clear cell aRCC.

The ERG notes that most trials of aRCC have only included patients with a clear cell histology, including all of the pivotal trials[20-23,44-48] for the treatments recommended by NICE[16-19,34,37-39,49] referred to in Sections 2.2.1 and 2.2.2 of this ERG report. However, when assessing nivolumab+ipilimumab, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) did not restrict the use of nivolumab+ipilimumab to clear cell aRCC even though the pivotal CheckMate 214 trial[28] only included patients with clear cell aRCC. This is because, based on the mechanism of action of nivolumab+ipilimumab, it was not expected that efficacy would be restricted to the clear cell histological subtype.[32] The EMA CHMP noted that data (from a retrospective study) confirmed the efficacy of nivolumab in non-clear cell RCC.[50] Furthermore, the EMA CHMP noted that not limiting nivolumab+ipilimumab to non-clear cell RCC had a regulatory precedent (nivolumab in the second line treatment of RCC).[32]

In the NICE appraisal of nivolumab+ipilimumab,[26] the ERG observed[51] that sunitinib is commonly used as a first-line treatment for patients with non-clear-cell RCC as clinical efficacy has been demonstrated using data from a large post-marketing prospective single arm study.[29] Anecdotal evidence and evidence from small retrospective studies including pazopanib in the first-line setting[52-55] and the nivolumab monotherapy study for treatment of refractory patients with RCC[50] referred to by the EMA CHMP[32] suggest that these agents may also be suitable for patients with non-clear cell RCC.

2.3 Number of patients potentially eligible for first-line treatment

In the CS (Table B.1.3), the company estimates the number of patients with aRCC to be [redacted]. The ERG considers that the company's own method for estimating the number of patients with aRCC leads to an underestimate. This is because as Nabi et al 2018[2] have stated, RCC accounts for 85% of all kidney cancer cases and thus the company adjusted the data. However, unlike kidney cancer data reported by Cancer research UK,[56] which is collected from data coded as kidney cancer using World Health Organization International Classification of Diseases (ICD) codes C64, C65, C66 and C68, NCRAS data used by the company is only data coded as ICD C64.[7,57] The ICD website states: "The ICD code C64 is used to code Renal cell carcinoma"[58] and therefore the 85% adjustment is unnecessary and the correct estimate is [redacted] (CS, Table B.1.3).

In the company's budget impact analysis submission, the company assumes all patients with aRCC are potentially eligible for treatment with avelumab+axitinib in current practice. However, the company also states that avelumab+axitinib is "an additional first-line treatment option" (CS, Section B.1.3.7) rather than the only first-line treatment option. Hence it is likely that only a proportion of patients will receive avelumab+axitinib. The ERG notes that the company has made no adjustment for patients with non-clear cell aRCC and assumes that the company considers that all patients with aRCC will be potentially eligible for treatment with avelumab+axitinib.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[1] and that addressed within the CS is presented in Table 2. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.5).

Table 2 Comparison between NICE scope and company's decision problem

Parameter	Specification in the final scope issued by NICE	ERG comment regarding company's decision problem
Population	Adults with untreated advanced or metastatic renal cell carcinoma (aRCC)	As per scope (however the JAVELIN Renal 101 trial population is limited to those with clear cell aRCC
Intervention	Avelumab with axitinib	As per scope
Comparator (s)	▪ Pazopanib ▪ Sunitinib ▪ Tivozanib ▪ Cabozantinib (only for intermediate/poor risk status disease as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria)	Data for the comparison of avelumab+axitinib versus sunitinib are derived from the JAVELIN Renal 101 trial Data for the comparisons of avelumab+axitinib versus tivozanib and avelumab+axitinib versus cabozantinib are derived from network meta-analyses The company has assumed that the effectiveness of pazopanib is equivalent to that of sunitinib; nonetheless, pazopanib is included distinctly from sunitinib in the company network meta-analyses
Outcomes	The outcome measures to be considered include: ▪ overall survival ▪ progression-free survival ▪ response rates ▪ adverse effects of treatment ▪ health-related quality of life	All outcome measures are considered for the comparison of avelumab+axitinib versus sunitinib in the main body of the CS. While data for all outcomes other than health-related quality of life have been presented for all comparators in CS, Appendix D, only overall survival and progression-free survival have been included in the company's network meta-analyses
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	As per scope
Subgroups	None specified	The comparison of avelumab+axitinib versus cabozantinib is restricted to a subgroup of patients with advanced renal cell carcinoma of intermediate/poor risk status (as per the cabozantinib licence)

Source: extracted from final scope issued by NICE[1] and CS, Table B.1.1

3.1 Population

The population addressed by the company's decision problem is identical to that specified in the final scope issued by NICE,[1] i.e., adults with untreated advanced renal cell carcinoma. This is in line with the wording of the anticipated licence for avelumab+axitinib. Data for the intervention of interest (avelumab+axitinib) are derived from the JAVELIN Renal 101 trial. As highlighted in of this ERG report, patients in this trial only had aRCC with a clear cell component. Similar to patients seen in clinical practice, approximately 60% of patients had aRCC of IMDC intermediate risk status.

3.2 Intervention

The intervention addressed by the company's decision problem is identical to that specified in the final scope issued by NICE,[1] i.e., avelumab+axitinib. Avelumab+axitinib (as a combination therapy) has not yet received a marketing authorisation for the treatment of aRCC. The EMA CHMP opinion is expected in [redacted] (CS, Section B.1.2). Although avelumab+axitinib does not yet have a positive opinion from the EMA, the company highlights that avelumab+axitinib was designated Promising Innovative Medicine status in January 2019 and received an Early Access to Medicine Positive Scientific Opinion from the Medicines and Healthcare products Regulatory Agency on 15 July 2019 (CS, Section B.2.12).

In the pivotal JAVELIN Renal 101 trial, avelumab and axitinib were given in combination: avelumab at a dose of 10mg/kg of body weight as a 1-hour intravenous infusion every 2 weeks (Q2W) and axitinib orally at a starting dose of 5mg twice daily on a continuous dosing schedule. Dose escalations and reductions of axitinib were permitted in the JAVELIN Renal 101 trial but dose reductions of avelumab were not. However, subsequent avelumab infusions could be omitted in response to persisting toxic effects. While the avelumab and axitinib doses administered in the JAVELIN Renal 101 trial were in line with the marketing authorisations for these two agents as monotherapies,[40,59] it is stated in the CS (p15) that the expected indication for avelumab will be a flat dosing schedule of 800mg Q2W. The ERG notes that in the cost effectiveness evidence presented by the company, avelumab+axitinib is costed using this expected indication, not the schedule used in the JAVELIN Renal 101 trial. Although the company states pharmacology data support this flat dosing schedule, there is no relative clinical effectiveness evidence provided in the CS using this dosing regimen

The company presented cost effectiveness evidence assuming a stopping rule applies to avelumab+axitinib after 2 years. However, in the JAVELIN Renal 101 trial, patients received treatment until confirmed disease progression, global deterioration of health status requiring discontinuation, unacceptable toxicity or death. Patients in the avelumab+axitinib arm were permitted to stop treatment with only one of the agents and continue in the study by receiving

treatment with the other agent. Patients were also permitted to continue treatment beyond confirmed disease progression, with one or both agents, if experiencing clinical benefit.

In order to mitigate infusion-related reactions, patients in the avelumab+axitinib arm were given an antihistamine and paracetamol prior to each dose of avelumab. Some concomitant medications such as those intended solely for supportive care were permitted in either arm of the trial; other concomitant medications such as anti-cancer therapies (other than the study drugs to which the patients were assigned) or the use of strong cytochrome P450 enzyme-3A4/5 inhibitors/inducers were not permitted. See CS, Section B.2.3.3.4 for further information about the types of concomitant medications which patients could and could not take.

3.3 Comparators

The comparators addressed by the company's decision problem are identical to those specified in the final scope issued by NICE.[1] However, direct evidence is only available from the JAVELIN Renal 101 trial for comparison of treatment with avelumab+axitinib versus sunitinib. Effectiveness estimates to allow comparisons of the effectiveness of treatment with avelumab+axitinib versus pazopanib, tivozanib and cabozantinib have been generated by the company's network meta-analyses (NMAs); however, the company cost effectiveness results have been generated based on the assumption that sunitinib and pazopanib have equal efficacy. This assumption is supported by conclusions reached by NICE ACs in previous appraisals.[19,26] Cabozantinib is only recommended by NICE for treating patients with aRCC of IMDC intermediate/poor risk status.[16] The company's NMAs and cost effectiveness analyses for the comparison of avelumab+axitinib versus cabozantinib are appropriately confined to this risk status population.

As highlighted in Section 2.2.1 of this ERG report, nivolumab+ipilimumab is currently a treatment option available to NHS patients with IMDC intermediate/poor risk status via the CDF. Since it is only available via the CDF, it is not considered to be an appropriate comparator by NICE.

3.4 Outcomes

Clinical evidence is reported in the CS for avelumab+axitinib versus sunitinib from the JAVELIN Renal 101 trial for all five outcomes specified in the final scope issued by NICE: overall survival (OS), progression-free survival (PFS), response rates, AEs of treatment and health-related quality of life (HRQoL). However, it should be noted that OS data from the JAVELIN Renal 101 trial are immature. Response rates are reported as objective response rate (ORR) including complete response (CR) and partial response (PR) along with the supporting outcomes of time to response (TTR) and duration of response (DoR). Only OS and

PFS data have been included in the company's NMAs. However, data have been presented from individual trials for OS, PFS, ORR and selected AEs for all comparators in the CS, Appendix D (Tables B.5.9 to Table B.5.12). No HRQoL data have been presented for pazopanib, tivozanib or cabozantinib.

3.5 Economic analysis

As specified in the final scope issued by NICE,[1] cost effectiveness of treatments was expressed in terms of incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 40-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

No subgroups were specified in the final scope issued by NICE.[1] However, the comparison of avelumab+axitinib versus cabozantinib is only presented for patients with aRCC of IMDC intermediate/poor risk status since cabozantinib is only licensed and recommended by NICE for these patients. The company also states that other pre-specified subgroup analyses (including by IMDC risk status) were performed for PFS, ORR and DoR in the JAVELIN Renal 101 trial (CS, Section B.2.7.1). The subgroup results for OS, PFS and ORR were requested by the ERG, and provided by the company, during the clarification process (clarification letter, question A4d).

3.7 Other considerations

Axitinib is currently available to NHS patients as a second-line or later treatment option for aRCC if it is made available in accordance with the agreed terms of a Patient Access Scheme (PAS).[49] Avelumab is available to NHS patients via a CDF managed access scheme for first-line treatment of metastatic Merkel cell carcinoma.[60] Avelumab is also available to NHS patients through baseline commissioning for second-line treatment of metastatic Merkel cell carcinoma.[60] It is stated in the CS that, if made available to NHS patients, both agents would be provided at discounted prices (CS, Table B.1.2).

Sunitinib, pazopanib, tivozanib and cabozantinib are available to NHS patients only if the treatments are made available in accordance with the agreed arrangements of respective PASs.[16-19] For sunitinib this means offering the first cycle of treatment for free and for pazopanib this means offering the drug at a 12.5% discount off the list price. The PAS arrangements for tivozanib and cabozantinib are confidential.

Second-line treatment options included in the company's model (everolimus, lenvatinib+everolimus, nivolumab and cabozantinib for previously treated patients[34,37-39]) are

also only available via confidential PAS agreements. However, as the discounts are confidential and not known to the company, the discounts are not applied as part of the company base case analysis.

As stated in the CS (Section B.1.4), there are no known equality issues relating to the use of avelumab+axitinib to treat patients with aRCC.

Avelumab+axitinib is described by the company as an innovative and novel treatment approach in aRCC (CS, Section B.1.3.6, p24, Section B.2.12, p99, Section B.3.11.6, p172). Clinical advice to the ERG is that it could be considered to be a novel treatment as it is the first combination of immunotherapy with a VEGFR-targeted TKI agent.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to the technology being appraised are presented in CS, Appendix D. The ERG assessed whether the review was conducted in accordance with important aspects of review methods; key conclusions are summarised in Table 3. Overall, the ERG considers the methods used by the company were appropriate. Results from the ERG's own searches confirm that no relevant publications have been missed.

Table 3 ERG appraisal of systematic review methods

Review process	Response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.2, Table B.5.3
Were appropriate sources searched?	Yes	The following electronic databases were searched: MEDLINE, Embase, the Cochrane Library, Health Technology Assessment websites and relevant conference websites were searched In addition, bibliographies of systematic literature reviews published between 2015 and 2018 were also searched
Was the timespan of the searches appropriate?	Yes	The searches were originally run on 9 May 2018 and were updated on 8 March 2019
Were appropriate search terms used?	Yes	Search terms for MEDLINE, Embase and the Cochrane Library are presented in the CS, Appendix D.1.2, Table B.5.1
Were the eligibility criteria appropriate to the decision problem?	Yes	The scope of the eligibility criteria (CS, Appendix D.1.2, Table B.5.3) was actually broader than the decision problem as studies of other treatment options (e.g., sorafenib) were included; including a broader range of treatment options was necessary to conduct NMAs The ERG notes that according to the eligibility criteria, studies of sequential therapies were to be excluded; however, the company did include two randomised sequential trials[61,62] (in both trials, patients were randomised to receive sunitinib followed by sorafenib, or sorafenib followed by sunitinib)
Was study selection applied by two or more reviewers independently?	Yes	In CS, Appendix D.1.2 it is stated that study screening of titles and abstracts and study selection based on full text articles were conducted by two independent reviewers. Uncertainty at both stages was resolved by a third reviewer
Was data extracted by two or more reviewers independently?	Partially	In the CS, Appendix D.1.4 it is stated that extracted data were verified by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	For ERG comment, see Sections 4.4 and 4.7.2 of this ERG report
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Responsibility for quality assessment is not reported
Were attempts to synthesise evidence appropriate?	Yes	For full details of the NMAs, see Section 4.7 of this ERG report

NMA=network meta-analyses; RCT=randomised controlled trial
Source: CS, extracted from Appendix D and ERG comment

4.2 Identified trials

4.2.1 Studies of avelumab+axitinib

The ongoing phase III JAVELIN Renal 101 trial was the only trial that compared avelumab+axitinib with sunitinib. No trial was identified that compared avelumab+axitinib with pazopanib, tivozanib or cabozantinib.

Supportive evidence for avelumab+axitinib is provided in the CS from the single-arm phase Ib JAVELIN Renal 100 study;[63-66] as this study was not an RCT, it was not identified by the company's literature search. Given the lack of a comparator arm in the JAVELIN Renal 100 trial,[65] this ERG report focuses on evidence from the JAVELIN Renal 101 trial.

4.2.2 Studies of comparator treatments

Aside from the JAVELIN Renal 101 trial, the company's systematic review included 58 other unique trials that assessed a range of interventions for aRCC (CS, Appendix D, Section D.12, Figure B.5.1). A total of seven trials were included in the NMAs, which were undertaken for the following populations, defined by risk status:

- All risk status population: JAVELIN Renal 101 trial (avelumab+axitinib versus sunitinib), COMPARZ trial[27] (pazopanib versus sunitinib), TIVO-1 trial[22] (tivozanib versus sorafenib) plus two additional randomised sequential trials,[61,62] both of which compared one sequential regimen (sunitinib-sorafenib) with another sequential regimen (sorafenib-sunitinib).

- IMDC intermediate/poor risk status population: JAVELIN Renal 101 trial (subgroup analysis of avelumab+axitinib versus sunitinib) and CABOSUN trial[67] (cabozantinib versus sunitinib - all patients in this trial had IMDC intermediate/poor risk status aRCC).

As noted by the ERG in Table 3 of this ERG report, the two randomised sequential trials met the company's exclusion criteria. However, their inclusion was necessary in order to be able to create a link in the network between sunitinib and sorafenib for patients in the aRCC all risk status population. Trials of sorafenib were also necessary to be included in order to create a link in the network to enable a comparison with tivozanib. Further information about the NMAs conducted by the company and the trials included in the NMAs is provided in Section 4.7 of this ERG report.

4.3 Characteristics of the JAVELIN Renal 101 trial

4.3.1 Trial characteristics

The JAVELIN Renal 101 trial is an ongoing Phase III, randomised, open-label study of avelumab+axitinib versus sunitinib in patients with previously untreated, aRCC with a clear cell component. Randomisation was stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or 1) and region (United States, Canada/Western Europe, or rest of the world).

Key eligibility criteria are summarised in Table 4. Clinical advice to the ERG is that, as is common with all clinical trials, patients with some comorbidities who might otherwise be considered for treatment in clinical practice were excluded. It is also noted that the trial only included patients with a clear cell component. As previously noted in this ERG report (Section 2.2.3), sunitinib is often used to treat patients with non-clear cell aRCC, which is a more aggressive form of the disease.[43]

Table 4 Key JAVELIN Renal 101 trial eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years (≥20 years in Japan) • Histologically or cytologically confirmed aRCC* with a clear cell component • At least one measureable lesion (as defined by RECIST version 1.1) that had not been previously irradiated • Estimated life expectancy of ≥3 months • ECOG PS 0 or 1 • No evidence of uncontrolled hypertension • Adequate bone marrow, renal and liver functions • Serum pregnancy test negative at screening (for females of childbearing potential) and the use of two highly effective methods of contraception throughout the study and for at least 90 days after the last dose (for male patients able to father children and female patients of childbearing potential)	• Prior systemic therapy for advanced or metastatic RCC • Prior adjuvant or neoadjuvant therapy for RCC if disease progression or relapse has occurred during or within 12 months after the last dose of treatment • Prior immunotherapy with any antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways • Prior therapy with any VEGF pathway inhibitors • Newly diagnosed brain metastases or known symptomatic brain metastases requiring steroids (patients with previously diagnosed brain metastases who had completed their treatment and recovered from the acute effects of radiation therapy or surgery prior to randomisation, had discontinued corticosteroid treatment for these metastases for at least 4 weeks and were neurologically stable, were eligible) • Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomisation (prior palliative radiotherapy to metastatic lesion(s) was permitted, if completed ≥48 hours prior to randomisation)

aRCC=advanced renal cell carcinoma; ECOG=Eastern Cooperative Oncology Group; PS=performance status; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; VEGF=vascular endothelial growth factor
* aRCC included unresectable locally advanced and metastatic disease
Source: CS, Table B.2.3

Between 29 March 2016 and 19 December 2017, at total of 886 patients were randomly assigned to treatment at 144 sites in 21 countries; 442 patients were assigned to treatment with avelumab+axitinib and 444 were assigned treatment with sunitinib. A total of 32 (3.6%)

patients were included in the trial from 6 sites in the UK (CS, Section B.2.3.1, Table B.2.2 and CS, Section B.2.13.2, p102).

Study treatment in the JAVELIN Renal 101 trial was administered on an outpatient basis: avelumab 10mg/kg as a 1-hour intravenous infusion Q2W in a 6-week cycle (Days 1, 15 and 29 of each cycle), axitinib 5mg twice daily, administered orally on a continuous dosing schedule and sunitinib 50mg once daily, administered orally in 6-week cycles (4 consecutive weeks of treatment followed by a 2-week off-treatment period). Patients received treatment until confirmed disease progression, global deterioration of health status requiring discontinuation, unacceptable toxicity or death. Patients in the avelumab+axitinib arm were permitted to stop treatment with one of the agents and continue in the study by receiving treatment with the other agent. Treatment with single-agent avelumab, single-agent axitinib, avelumab+axitinib or sunitinib could continue beyond confirmed disease progression if the patient was experiencing clinical benefit. Crossover between treatment arms was not permitted.

The first interim analysis (IA1) occurred on 20 June 2018 at which point approximately half of patients were still on treatment in the avelumab+axitinib arm (52.0% avelumab and 55.7% axitinib) and 37.6% were still on treatment in the sunitinib arm. Outcome data presented in the CS are primarily from IA1, however, some results are now available from a second interim analysis (IA2) (28 January 2019) and have been presented in the CS. The median length of follow-up at these data-cuts differed by the outcome measured at both IA1 and IA2 (see Sections 4.6.1 (Table 7) and Section 4.6.2 (Table 8) of this ERG report for more information.

4.3.2 Baseline characteristics of patients enrolled in the JAVELIN Renal 101 trial

The company has summarised the baseline characteristics of patients in the JAVELIN Renal 101 trial in the CS (Table B.2.8). As highlighted by the company, baseline characteristics were well balanced between treatment arms. In summary, the majority of patients were [redacted], males (74.5%), [redacted], with a mean [standard deviation (SD)] age of [redacted] years. The majority of patients had aRCC of IMDC intermediate risk status (61.7%), with 21.4% categorised as having IMDC favourable risk status and 16.1% categorised as having poor risk status. Nearly all randomised patients had had a prior nephrectomy (79.8%). The mean (SD) time from diagnosis was [redacted] months. Clinical advice to the ERG is that the patient population is generalisable to clinical practice in England, with the common caveat associated with clinical trials that the patients are generally younger and fitter than those seen in NHS clinical practice. It was also noted that the proportion of patients who had a prior

nephrectomy may also be higher than in clinical practice in England, but this was not considered to be important in terms of having any impact on the results from the trial.

4.4 Quality assessment for the JAVELIN Renal 101 trial

The company conducted a quality assessment of the JAVELIN Renal 101 trial using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[68] The company's assessments and ERG comments are presented in Table 5.

Overall, the ERG agrees with the company's assessments and considers that the JAVELIN Renal 101 trial was generally well designed and well conducted. The ERG highlights that for the PFS and ORR outcomes, the use of blinded independent central review (BICR) minimises bias associated with the open-label design.

Table 5 Quality assessment for the JAVELIN Renal 101 trial

Quality assessment item	Company assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Agree
Was the concealment of treatment allocation adequate?	No (due to the unblinded nature of the trial)	Disagree. The ERG notes that concealment of treatment allocation relates to whether treatment allocation could have been known prior to randomisation while the open-label design of the trial relates to knowledge of treatment allocation after randomisation Randomisation was conducted via an interactive response technology system, therefore treatment allocation could not have been predicted prior to randomisation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Agree. The JAVELIN Renal 101 trial was an open-label trial which provides an opportunity for differential use of second-line therapies and for subjective results and investigator-assessed outcomes to be biased. However, for PFS and ORR outcomes, BICR was used to minimise bias
Were there any unexpected imbalances in drop-outs between groups?	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	Agree
Were appropriate methods used to account for missing data?	Yes	Agree

BICR=blinded independent central review; ERG=Evidence Review Group; PFS=progression-free survival; ORR=objective response rate.
Source: CS, extracted from Section B.2.5 (Table B.2.9) and ERG comment

4.5 Statistical approach adopted for the JAVELIN Renal 101 trial

Information relevant to the statistical approach taken by the company has been taken from the clinical study report (CSR) of IA1,[69] the trial statistical analysis plan (TSAP, version 5.0, dated 16 July 2018),[70] the trial protocol (Final Amendment 7, dated 5 September 2018)[71] and from the CS. A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Table 6.

Table 6 ERG assessment of statistical approach used to analyse data from the JAVELIN Renal 101 trial

Item	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	The analysis populations are reported in the CS (Table B.2.7, p36). The ERG is satisfied that these analysis populations (FAS, SAS and PP) are clearly defined and pre-defined in the JAVELIN Renal 101 TSAP v5.0 (Section 4, pp22-23).
Was an appropriate sample size calculation pre-specified?	The sample size calculation of the JAVELIN Renal 101 trial is reported in the CS, Section B.2.4.2 (p39). Four statistical hypotheses were tested in the JAVELIN Renal 101 trial to address the two primary objectives (PFS and OS in patients with PD-L1 positive tumours), followed by two of the secondary objectives (PFS and OS in patients unselected for PD-L1 expression, i.e. FAS population). A gatekeeping procedure was employed for statistical testing as outlined in the CS (Figure B.2.1, p38) and the statistical significance levels for each of the four tests took into account the sequential testing nature of the design as described in the CS (Section B.2.4.1, p38). The ERG is satisfied that this sample size calculation and approach to statistical testing is appropriate and pre-specified in the JAVELIN Renal 101 TSAP v5.0 (Section 5.1, pp24-30).
Were all protocol amendments carried out prior to analysis?	The final protocol amendment 7 of the JAVELIN Renal 101 trial, a list of all amendments made from the original trial protocol and the rationale for these amendments were included as references to the CS. Most amendments were administrative or related minor language changes (for example to clarify inclusion and exclusion criteria) and the first five amendments were made before the data-cut off dates for interim analyses (IA1: 20 June 2018; IA2: 28 January 2018) and therefore not driven by any results of the interim analyses. The largest amendments were amendments 5 and 6: • Within amendment 5, the primary objective of the JAVELIN Renal 101 trial was changed to demonstrate superiority of avelumab in combination with axitinib compared to sunitinib alone based on PFS by BICR and OS in patients with PD-L1 positive tumours based on the results of the JAVELIN Renal 100 study[65] and two trials of immune checkpoint inhibitors[28,46] that showed an overall survival benefit among patients with PD-L1 positive renal-cell carcinoma. Version 3.0 of the JAVELIN Renal 101 TSAP was also updated in line with the protocol amendment 5. • Within amendment 6, a third interim analysis for OS was added to occur 15 months after IA2 for OS as the observed number of deaths in the trial at the date of the amendment (27 June 2018) was substantially lower than expected per protocol, leading to a substantially longer duration between the originally expected time of IA2 for OS and the final analysis for OS. The ERG acknowledges that amendment 6 of the protocol was related to results of the IA1 for OS, but the ERG understands the rationale for this protocol amendment and notes that the definitions and statistical analysis approach for OS in the third interim analysis have remained the same in protocol amendment 6.

Item	Statistical approach with ERG comments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	The co-primary efficacy outcomes (PFS and OS in patients with PD-L1 positive tumours) and secondary efficacy outcomes (PFS and OS in patients unselected for PD-L1 expression, OR, DC, TTR, DoR and PFS on next-line therapy) are defined in the CS (Section B.2.3.4.3, p34). The statistical analysis approach for the co-primary and secondary efficacy outcomes is reported in the CS (Section B.2.4.3, pp39-40). The ERG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-defined in the JAVELIN Renal 101 TSAP v5.0 (definitions: Section 3.1-3.2, pp15-16 and analysis approaches: Section 6.1-6.2, pp39-55) and that the definitions and analysis approaches are appropriate. Results of primary and secondary efficacy outcomes are further discussed in Section 4.6 of this ERG report.
Was the analysis approach for PROs appropriate and pre-specified?	PROs were FKSI-19 and EQ-5D-5L, measured in the FAS. The primary PRO endpoint was the time to deterioration in the FKSI-DRS subscale, defined as the time from date of randomisation to the first ≥3-point decrease from baseline. These outcomes are described in the CS (Section B.2.3.4.5, p35). The ERG is satisfied that the safety outcome definitions and analysis approaches were pre-defined in the JAVELIN Renal 101 TSAP v5.0 (Section 6.3.2, pp64-66) and that the definitions and analysis approaches are appropriate. Results of PROs are further discussed in Section 4.8 of this ERG report.
Was the analysis approach for AEs appropriate and pre-specified?	AEs were assessed using the MedDRA classification system with severity graded according to the National Cancer Institute CTCAE version 4.03. Other safety outcomes are described in the CS (Table B.2.2). The ERG is satisfied that the safety outcome definitions and analysis approaches were pre-defined in the JAVELIN Renal 101 TSAP v5.0 (definitions: Section 6.6, pp79-94) and that the definitions and analysis approaches are appropriate. The ERG is also satisfied that all summary tables of AEs are provided in the JAVELIN Renal 101 CSR of IA1 (p182 to p210); all AEs, AEs of special interest, AEs leading to permanent or temporary treatment discontinuation, SAEs and deaths are presented and summarised by grade and by treatment arm.Treatment-related and treatment-emergent AEs are further discussed in Section 4.9 of this ERG report.
Were modelling assumptions (e.g. proportional hazards) assessed?	It was pre-specified in the JAVELIN Renal 101 TSAP v5.0 (Section 6.1, pp39-43) that PFS and OS would be analysed using a Cox PH model. As part of the clarification process, the company tested the PH assumption using Schoenfeld's residual test and by plotting log (-log(PFS or OS)) versus log(time) within each randomisation stratum. Based on these investigations, there was no evidence that the PH assumption was violated for either PFS (JAVELIN Renal 101 CSR of IA1, p116) or OS (JAVELIN Renal 101 CSR of IA1, p121). The ERG is satisfied that it is appropriate for the Cox PH model to be used and for HRs to be presented for PFS and OS.
Was a suitable approach employed for handling missing data?	The approach to managing missing data is described in Section 5.3 (pp33-39) of the JAVELIN Renal 101 TSAP v5.0. The ERG is satisfied that the approach is suitable.
Were all subgroup and sensitivity analyses pre-specified?	The ERG is satisfied that all of the subgroup analyses defined in the CS (Section B.2.7, p61) and presented in the CS, Appendix E and in response to clarification question A4d (Table 21 to Table 28 and Figure 23 to 28) were pre-specified in the JAVELIN Renal 101 TSAP v5.0 (Section 6.4, pp65-67). Sensitivity analyses of PFS and OS are referred to in the CS, Appendix L and numerical results were provided in response to clarification question A4b for PFS (Table 7 to Table 16) and clarification question A4c for OS (Table 17 to Table 20). The ERG is satisfied that these sensitivity analyses were pre-specified in the JAVELIN Renal 101 TSAP v5.0 (Section 6.2.2.3–6.2.2.4, pp 44-48).

AE=adverse event; CS=company submission; CSR=clinical study report; DC=disease control; CTCAE=common terminology criteria for adverse events; DoR=duration of response; EQ-5D-5L=EuroQoL five dimensions score; ERG=Evidence Review Group; FAS=full analysis set; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index-19; FKSI-DRS=FKSI-Disease Related Symptoms; HR=hazard ratio; IA=interim analysis; MedDRA=medical dictionary for regulatory activities; PD-L1=programmed death receptor ligand 1 PFS=progression-free survival; OR=objective response; OS=overall survival; PH=proportional hazards; PP=per protocol; PRO=patient reported outcome; SAS=safety analysis set; TSAP=trial statistical analysis plan; TTR=time to response

Source: extracted from the CS, JAVELIN Renal 101 CSR of IA1;[69] JAVELIN Renal 101 trial protocol (final protocol amendment 7), [71] TSAP (version 5.0),[70] the company's response to the clarification letter, and ERG comment

The ERG considers that the pre-planned statistical approach employed by the company is adequate and appropriate. The ERG notes that the sixth amendment to the JAVELIN Renal 101 protocol was data driven, related to the IA1 results for OS. However, the ERG acknowledges the rationale for this protocol amendment was due to a substantially lower number of deaths than expected per protocol in the JAVELIN Renal 101 trial at the time of IA1.

4.6 Efficacy results from the JAVELIN Renal 101 trial

The co-primary efficacy outcomes of the JAVELIN Renal 101 trial were PFS and OS in patients with PD-L1 positive tumours. However, in the CS, efficacy data were presented for the full analysis set (FAS) population, i.e. all patients unselected for PD-L1 expression, representing the proposed licensed indication. Efficacy results for patients with PD-L1 positive tumours are presented in CS, Appendix L and within the 2019 publication of the JAVELIN Renal 101 trial.[72] According to the pre-specified gatekeeping strategy for statistical testing (see Table 6 of this ERG report and CS, Section B.2.4.1 for further details), PFS and OS in the FAS could be analysed and statistically tested due to the statistically significant difference in PFS for avelumab+axitinib versus sunitinib in patients with PD-L1 positive tumours.[72]

Clinical advice to the ERG is that it is reasonable to consider all patients unselected for PD-L1 expression and the ERG notes that efficacy results for patients with PD-L1 positive tumours were very similar to the efficacy results for all patients in the FAS.

Efficacy results presented in this section are based on IA1 (data cut-off date 20 June 2018) and IA2 (data cut-off date 28 January 2019), where available, at the time of submission.

4.6.1 Progression-free survival (PFS)

A summary of PFS results by BICR assessment in the FAS at the time of IA1 and IA2 is provided in Table 7. The company also provided Kaplan-Meier (K-M) plots of PFS by BICR assessment at the time of IA1 and IA2 in the CS (Figure B.2.2 and Figure B.2.3 respectively).

Table 7 Summary of JAVELIN Renal 101 trial PFS results by BICR assessment (FAS; IA1 and IA2)

	IA1 (data cut-off 20 June 2018)		IA2 (data cut-off 28 Jan 2019)	
	Avelumab+ axitinib (N=442)	**Sunitinib (N=444)**	**Avelumab+ axitinib (N=442)**	**Sunitinib (N=444)**
Median follow-up time (95% CI), months	10.8 [redacted]	8.6 [redacted]	[redacted]	[redacted]
Events, n (%)	180 (40.7)	216 (48.6)	229 (51.8)	258 (58.1)
PD	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	262 (59.3)	228 (51.4)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (95% CI), months	13.8 (11.1 to NE)	8.4 (6.9 to 11.1)	13.3 (11.1 to 15.3)	8.0 (6.7 to 9.8)
HR (95% CI)	0.69 (0.56 to 0.84)		0.69 (0.57 to 0.83)	
One-sided p-value	0.0001		<0.0001	
Two-sided p-value	[redacted]		[redacted]	
Probability (95% CI) of being event-free at:				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

BICR=blinded independent central review; CI=confidence interval; FAS=full analysis set; HR=hazard ratio; IA1=first interim analysis; IA2=second interim analysis; NE=not estimable; PD=progressive disease; PFS=progression-free survival
Source: CS, extracted from Table B.2.11 and Table B.2.12 and Table 6 of the company response to the clarification letter

PFS was statistically significantly longer in the avelumab+axitinib arm compared to the sunitinib arm at the time of IA1 (median PFS 13.8 months compared to 8.4 months; hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.56 to 0.84; one-sided p-value 0.0001). The company states that results at the time of the second interim analysis (IA2) reinforced these earlier results (median PFS 13.3 months compared to 8.0 months; HR 0.69, 95% CI 0.57 to 0.83; one-sided p-value <0.0001). Clinical advice to the ERG is that the PFS gain observed for avelumab+axitinib versus sunitinib is clinically meaningful.

The ERG notes that results for PFS assessed by investigator assessment (CSR of IA1, Section 11.4.1.3.1.3, p116) are consistent with the BICR assessment. A range of sensitivity analyses of PFS by BICR were performed and the ERG is satisfied that results of these sensitivity analysis are numerically similar to the results of the analysis of PFS by BICR in the FAS (Table 7) and that conclusions are unchanged; see CS, Appendix L.1.1 for details of sensitivity analyses and the company response to question A4b of the clarification letter for results of the sensitivity analyses.

Results of pre-specified subgroup analyses of PFS at the time of IA1 and IA2 are provided in Figure 23 and Figure 24 respectively of the company response to question A4d of the clarification letter. The ERG considers that PFS results for all pre-specified subgroups are

generally consistent with the PFS results presented in Table 7 of this ERG report but notes that the imprecision of these results should be considered when drawing conclusions due to small sample sizes and imbalanced group sizes of some of the subgroups.

4.6.2 Overall survival (OS)

A summary of OS results in the FAS at the time of IA1 and IA2 is provided in Table 8.

Table 8 Summary of JAVELIN Renal 101 trial OS results (FAS; IA1 and IA2)

	IA1 (data cut-off 20 June 2018)		IA2 (data cut-off 28 Jan 2019)	
	Avelumab+ axitinib (N=442)	**Sunitinib (N=444)**	**Avelumab+ axitinib (N=442)**	**Sunitinib (N=444)**
Median follow-up time (95% CI), months	12.0 [redacted]	11.5 [redacted]	[redacted]	[redacted]
Events, n (%)	63 (14.3)	75 (16.9)	109 (24.7)	129 (29.1)
Censored, n (%)	379 (85.7)	369 (83.1)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (95% CI), months	NE [redacted]	NE [redacted]	NE (30.0 to NE)	NE (27.4 to NE)
HR (95% CI)	0.78 (0.55 to 1.08)		0.80 (0.62 to 1.03)	
One-sided p-value	0.0679		0.0392	
Two-sided p-value	[redacted]		[redacted]	
Probability (95% CI) of being event-free at:				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; FAS=full analysis set; HR=hazard ratio; IA1=first interim analysis; IA2=second interim analysis; NE=not estimable; OS=overall survival
Source: CS, extracted from Table B.2.16 and Table B.2.17

It should be noted that, at both the time of IA1 and of IA2, OS data were immature with 25.8% and [redacted] of the 535 deaths required for final OS analysis at the time of IA1 and IA2 respectively. Median OS was not reached in either treatment arm at the time of IA1. There was no statistically significant in OS between avelumab+axitinib and sunitinib at the pre-specified significance level of 0.025 Median OS was not reached in either treatment arm at the time of IA2. Results again showed no statistically significant difference between arms at the pre-specified significance level of 0.025 (HR 0.80, 95% CI 0.62 to 1.03).

Two sensitivity analyses of OS were performed at the time of IA1 and IA2 and the ERG is satisfied that results of these sensitivity analysis are numerically similar to the results of the FAS analysis of OS and that conclusions are unchanged; see CS, Appendix L.1.2 for details of sensitivity analyses and the company response to question A4c of the clarification letter for results of the sensitivity analyses.

Results of pre-specified subgroup analyses of OS at the time of IA1 and IA2 are provided in Table 27 and Table 28 respectively of the company response to question A4d of the clarification letter. The ERG considers that OS results for most of the pre-specified subgroups are generally consistent with the results of the FAS analysis of OS but notes that the imprecision of these results should be considered when drawing conclusions due to small sample sizes and imbalanced group sizes of some of the subgroups.

The ERG agrees with the company assessment that, at the time of IA1, definitive conclusions cannot yet be drawn based on the results of these analyses due to the immaturity of the OS data. [redacted]

Progression-free survival on next-line therapy (PFS2)

As a supportive analysis of the immature OS data, the company presents PFS on next-line therapy (PFS2); the company states PFS2 data may provide an indication of long-term survival improvements.[73] A summary of PFS2 by investigator assessment in all patients in the FAS at the time of IA1 and IA2 is provided in Table 9. Formal statistical testing of PFS2 was not planned within the JAVELIN Renal 101 TSAP.[70]

Table 9 Summary of JAVELIN Renal 101 trial PFS2 results by investigator assessment (FAS; IA1 and IA2)

	IA1 (data cut-off 20 June 2018)		IA2 (data cut-off 28 Jan 2019)	
	Avelumab+axitinib (N=442)	Sunitinib (N=444)	Avelumab+axitinib (N=442)	Sunitinib (N=444)
Events, n (%)	[redacted]	[redacted]	133 (30.1)	192 (43.2)
Discontinuation of next-line treatment after first PD	[redacted]	[redacted]	[redacted]	[redacted]
Second PD after next-line treatment	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS2 (95% CI), months	NE (19.9 to NE)	18.4 (15.7 to 23.6)	NE (26.3 to NE)	19.4 (16.9 to 23.8)
HR (95% CI)	0.56 (0.42 to 0.74)		0.55 (0.44 to 0.69)	
Probability (95% CI) of being event-free at:				
12 months	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; FAS=full analysis set; HR=hazard ratio; IA1=first interim analysis; IA2=second interim analysis; NE=not estimable; PD=progressive disease; PFS2=progression-free survival on next-line therapy
Source: CS, extracted from Table B.2.18 and Table B.2.19

Median PFS2 was not reached in the avelumab+axitinib arm at the time of IA1 or IA2. Results of the two interim analyses suggest that PFS2 may be longer in the avelumab+axitinib arm

compared to the sunitinib arm. The ERG agrees with the company that there is no clear evidence of any negative impact of first-line treatment with avelumab+axitinib on any subsequent benefit gained from second-line treatment.

4.6.3 Objective response

A summary of objective response results by BICR assessment in all patients in the FAS at the time of IA1 and IA2 is provided in Table 10.

Table 10 Summary of JAVELIN Renal 101 trial objective response results by BICR assessment (FAS; IA1 and IA2)

	IA1 (data cut-off 20 June 2018)		IA2 (data cut-off 28 Jan 2019)	
	Avelumab+axitinib (N=442)	**Sunitinib (N=444)**	**Avelumab+axitinib (N=442)**	**Sunitinib (N=444)**
Objective response, n (%)	227 (51.4)	114 (25.7)	232 (52,5)	121 (27.3)
CR, n (%)	15 (3.4)	8 (1.8)	[redacted]	[redacted]
PR, n (%)	212 (48.0)	106 (23.9)	[redacted]	[redacted]
ORR (%) (95% CI)	51.4 (46.6 to 56.1)	25.7 (21.7 to 30.0)	52.5 (47.7 to 57.2)	27.3 (23.2 to 31.6)
OR (95% CI)	3.10 (2.30 to 4.15)		3.00 (2.23 to 4.00)	

BICR=blinded independent central review; CI=confidence interval; CR=complete response; FAS=full analysis set; IA1=first interim analysis; IA2=second interim analysis; PR=partial response; OR=odds ratio; ORR=objective response rate;
Source: CS, extracted from Table B.2.13 and Table B.2.14

The company highlights in the CS (Section B.1.3.6, p23) that current NICE recommended first-line treatments have demonstrated ORRs of ≤33%.[22,23,27,67] The ORR in the avelumab+axitinib arm was around double that of the sunitinib arm at the time of IA1 (51.4% compared to 25.7%) and at the time of IA2 (52.5% compared to 27.3%). The proportions of patients with CR and PR were higher in the avelumab+axitinib arm than the sunitinib arm at the time of IA1 and IA2.

For patients with a CR or PR, TTR and DoR was summarised in the CS (Table B.2.15 and Figure B.2.5). At the time of IA1, median response time occurred earlier on avelumab+axitinib compared to sunitinib (2.6 months compared to 3.2 months) and an ad-hoc analysis of DoR favoured avelumab+axitinib over sunitinib.

The ERG notes that ORR results assessed by investigator assessment (CSR of IA1, Section 11.4.1.3.3.3.2, p129) are consistent with the BICR assessment.

Results of pre-specified subgroup analyses of ORR at the time of IA1 and IA2 are provided in Table 23 and Table 24 respectively and of DoR at the time of IA1 and IA2 are provided in Table 25 and Table 26 respectively of the company response to question A4d of the clarification letter. The ERG considers that ORR and DoR results for all of the pre-specified subgroups are generally consistent with the ORR and DoR results presented in Table 10 of

this ERG report but notes that the imprecision of these results should be considered when drawing conclusions due to small sample sizes and imbalanced group sizes of some of the subgroups.

4.7 ERG critique of the indirect evidence

4.7.1 Trials identified and included in the NMAs

In addition to the JAVELIN Renal 101 trial,[72] the company identified five RCTs[10,22,27,61,62] for inclusion in the NMAs for the all risk status population and one additional RCT[67] for inclusion in the NMAs for the IMDC intermediate/poor risk status population. The company included RCTs with published PFS or OS HRs and/or K-M plots. For all of the included trials, except for the JAVELIN Renal 101 trial (which had co-primary efficacy outcomes of PFS and OS in patients with PD-L1 positive tumours), the primary outcome was PFS.

Network diagrams for the all risk status and IMDC intermediate/poor risk status populations are shown in Figure 2 and Figure 3 respectively.

The company assessed feasibility and heterogeneity by examining:

- Differences in trial design, patient populations and characteristics (CS, Section B.2.9.2**,** Table B.2.20 and Section B.2.9.3.2, Table B.2.22; CS, Appendix D, Table B.5.6 and Table B.5.8).

- Outcomes and relative treatment effects (CS, Section B.2.9.3.1, Table B.2.21 [PFS and OS]; CS, Appendix D, Table B.5.9 [ORR], Table B.5.10 [PFS and OS], Table B.5.11 [types of AEs] and Table 5.1.2 [withdrawals due to AEs]).

Table 11 of this ERG report includes a summary of the key design features and patient characteristics of the trials included in the company's PFS and OS NMAs. A summary of the PFS and OS data included in the company's proportional hazards (PH) and non-PH NMAs is presented in Table 12.

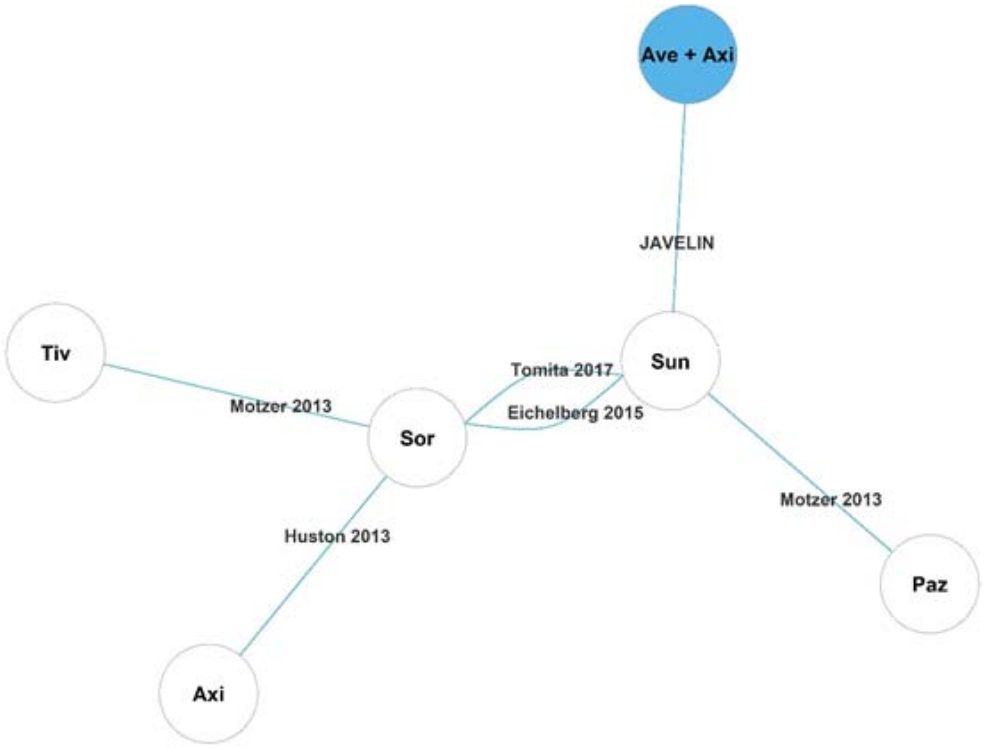


Figure 2 Network diagram for PFS and OS in the all risk status population

Ave=avelumab; Axi=axitinib; Paz=pazopanib; OS=overall survival; PFS=progression-free survival; Sor=sorafenib; Sun=sunitinib; Tiv=tivozanib
Source: CS, Figure B.2.13

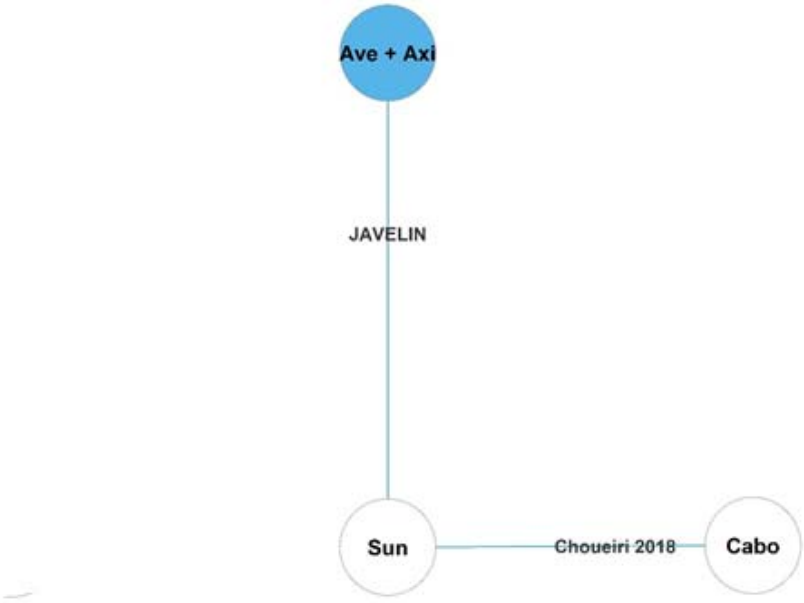


Figure 3 Network diagram for PFS and OS in the IMDC intermediate/poor risk status population

Ave=avelumab; Axi=axitinib; Cabo=cabozantinib; IMDC=International Metastatic RCC Database Consortium; OS=overall survival; PFS=progression-free survival; RCC=renal cell carcinoma; Sun=sunitinib
Source: CS, Figure B.2.14

Table 11 Summary of key design and patient characteristics in the trials included in the NMAs

Trial	Design	Population	Clear cell	Treatment arms	ECOG PS[a]	MSKCC risk score[a]	IMDC risk score[a]
All risk status population							
Motzer 2019[72] (JAVELIN Renal 101)	Phase III, open-label, multicentre, global, parallel arms	Previously untreated aRCC	100%	AVE+AXI (n=442) SUN (n=444)	0-1: 99.8% 2: 0.1%	Favourable: 22.1% Intermediate: 65.0% Poor: 10.8%	Favourable: 21.4% Intermediate: 61.7% Poor:16.1%
Motzer 2013[27] (COMPARZ)	Phase III, open-label, multicentre, global, parallel arms	Previously untreated aRCC	100%	PAZ (n=557) SUN (n=553)	NR	Favourable: 27.3% Intermediate: 58.6% Poor: 10.7%	Favourable: NR Intermediate: NR Poor: NR
Motzer 2013[22] (TIVO-1)	Phase III, open-label, multicentre, European, parallel arms	Previously untreated aRCC or one prior therapy for aRCC	100%	TIV (n=260; n=181 previously untreated) SOR (n=257; n=181 previously untreated)	0-1: 100% 2: 0%	Favourable: 30.4%[b] Intermediate: 64.4%[b] Poor: 5.2%[b]	Favourable: NR Intermediate: NR Poor: NR
Hutson 2013[10] (A4061032)	Phase III, open-label, multicentre, global, parallel arms	Previously untreated aRCC	100%	AXI (n=192) SOR (n=96)	0-1: 100% 2: 0%	Favourable: 51.0% Intermediate: 43.1% Poor: 3.1%	Favourable: NR Intermediate: NR Poor: NR
Eichelberg 2015[61] (SWITCH)	Phase III, open-label, multicentre, European, crossover arms	Previously untreated aRCC	87%	SOR → SUN (n=182) SUN → SOR (n=183)	0-1: 97.0% 2: 0.3%	Favourable: 45.0% Intermediate: 55.0% Poor: 0.5%	Favourable: NR Intermediate: NR Poor: NR
Tomita 2014[62] (CROSS-J-RCC)	Phase III, open-label, multicentre, Japan, crossover arms	Previously untreated aRCC,	100%	SOR → SUN (n=63) SUN → SOR (n=57)	NR	Favourable: 21.7% Intermediate: 88.3% Poor: 0%	Favourable: NR Intermediate: NR Poor: NR
IMDC intermediate/poor risk status population							
Motzer 2019[72] (JAVELIN Renal 101, subgroups)	Phase III, open-label, multicentre, global, parallel arms	Previously untreated aRCC, intermediate or poor IMDC risk	100%	AVE+AXI (n=343) SUN (n=347)	0-1: 99.8%[b] 2: 0.1%[b]	Intermediate: 85.7%[c] Poor: 14.3%[c]	Intermediate: 79.3%[c] Poor:20.3%[c]
Choueiri 2018[67] (CABOSUN)	Phase II, open-label, multicentre, US, parallel arms	Previously untreated aRCC, intermediate or poor IMDC risk	100%	CAB (n=79) SUN (n=78)	0-1: 87% 2: 13%	Intermediate: NR Poor: NR	Intermediate: 80.9% Poor: 19.1%

a. Percentage of total patients randomised. Where percentages do not sum to 100%, the characteristic was not reported for the remaining percentage
b. Based on all randomised patients, not reported for subgroup of previously untreated aRCC patients
c. Proportion of patients with known intermediate/poor risk status in subgroups based on IMDC risk status

aRCC=advanced renal cell carcinoma; AVE=avelumab; AXI=axitinib; CABO=cabozantinib; CS=company submission; ECOG=Eastern Cooperative Oncology Group; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan Kettering Cancer Centre; NR=not reported; NMA=network meta-analysis; PAZ=pazopanib; PS=performance status; SOR=sorafenib; SUN=sunitinib; TIVO=tivozanib

Source: CS, extracted from CS, Appendix D, Table B.5.6 and Table B.5.8; additional data extracted from journal publications[10,22,27,61,62,67,72] of trials included in the NMAs

Table 12 Summary of PFS and OS outcomes in the trials included in the company NMAs

Trial	Treatment arms	PFS			OS	
		Assessment method	Median (95% CI), months	HR (95% CI)	Median (95% CI), months	HR (95% CI)
All risk status population						
Motzer 2019[72] (JAVELIN Renal 101)	AVE+AXI (n=442)	BICR	13.8 (11.1 to NE)	0.69 (0.56 to 0.84)	NE [redacted]	0.78 (0.55 to 1.08)
	SUN (n=444)	BICR	8.4 (6.9 to 11.1)		NE [redacted]	
Motzer 2013[27] (COMPARZ)	PAZ (n=557)	BICR	8.4 (8.3 to 10.9)	1.05 (0.90 to 1.22)	28.3 (26 to 35.5)[a]	0.92 (0.79 to 1.06)[a]
	SUN (n=553)	BICR	9.5 (8.3 to 11.1)		29.1 (25.4 to 33.1)[a]	
Motzer 2013[22] (TIVO-1)	TIV (n=181 previously untreated)	BICR	12.7 (NR to NR)	0.76 (0.58 to 0.99)	NR	1.23 (0.90 to 1.67)
	SOR (n=181 previously untreated)	BICR	9.1 (NR to NR)		NR	
Hutson 2013[10] (A4061032)	AXI (n=192)	BICR	10.1 (7.2 to 12.1)[c]	0.77 (0.56 to 1.05)[c]	21.7 (18.0 to 31.7)	0.99 (0.73 to 1.36)
	SOR (n=96)	BICR	6.5 (4.7 to 8.3)[c]		23.3 (18.1 to 33.2)	
Eichelberg 2015[61] (SWITCH)	SOR → SUN (n=182)	Investigator	5.9 (5.5 to 7.9)[d]	1.19 (0.97 to 1.47)[d]	30.0 (23.3 to 34.7)[d]	0.99 (0.70 to 1.27)[d]
	SUN → SOR (n=183)	Investigator	8.5 (7.1 to 11.2)[d]		27.4 (22.3 to 35.9)[d]	
Tomita 2014[62] (CROSS-J-RCC)	SOR → SUN (n=63)	Unclear	8.7 (NR to NR)	0.67 (0.42 to 1.08)	38.4 (NR to NR)	0.93 (0.59 to 1.49)
	SUN → SOR (n=57)	Unclear	7.0 (NR to NR)		30.9 (NR to NR)	
IMDC intermediate/poor risk status						
Motzer 2019[72] (JAVELIN Renal 101, subgroup)[e]	AVE+AXI (n=271, intermediate)	BICR	13.8 (9.7 to NE)	0.74 (0.57 to 0.95)	[redacted]	[redacted]
	SUN (n=276, intermediate)	BICR	8.4 (7 to 11.2)		[redacted]	
	AVE+AXI (n=72, poor)	BICR	6.0 (3.6 to 8.7)	0.57 (0.38 to 0.88)	[redacted]	[redacted]
	SUN (n=71, poor)	BICR	2.9 (2.7 to 5.5)		[redacted]	
Choueiri 2018[67] (CABOSUN)	CAB (n=79)	Investigator	8.6 (6.8 to 14)	0.48 (0.31 to 0.74)	26.6 (14.6 to NE)	0.80 (0.53 to 1.21)
	SUN (n=78)	Investigator	5.3 (3.0 to 8.2)		21.2 (16.3 to 27.4)	

a. OS data (digitised from the corresponding K-M curve) included in the non-PH parametric NMAs. The company included different data within the PH NMA provided in response to question A1 of the clarification letter (median OS PAZ=28.4 [95% CI 26.2 to 35.6]; SUN=29.3 [95% CI 25.3 to 32.5]; HR=0.91 [95% CI 0.76 to 1.08]). The company clarified during the factual accuracy check that the PFS data reflects independent review PFS while PFS data reported in papers published earlier (2013)[10] and later (2017)[76] reflects investigator assessed PFS (median PFS axitinib=10.1 months; sorafenib=6.5 months; HR=0.77 [95% CI 0.56 to 1.05])[10,76]

b. The company states in response to question A1 of the clarification letter and clarified within the factual accuracy check that OS data for the previously untreated subgroup, unadjusted for treatment cross-over from NICE TA512[19] was incorporated into its NMAs. However, the ERG is unsure whether OS data for the previously untreated population or for the whole population has been included in the NMAs (and whether the OS data adjusted for treatment crossover or unadjusted OS data were used)

c. PFS data (digitised from the corresponding K-M curve) included in the non-PH parametric NMAs. The company included different data within the updated PH NMA provided in response to question A1 of the clarification letter (median PFS AXI=11.1; SOR=7.4; HR=0.77 [95% CI 0.57 to 1.04])[74]

d. 90% confidence intervals reported in the Eichelberg 2015 publication.[61]

e. In the CS (Appendix E, p1), the company states that the subgroup data from the JAVELIN Renal 101 trial are immature and definitive conclusions cannot yet be drawn

aRCC=advanced renal cell carcinoma; AVE=avelumab; AXI=axitinib; ; BICR=blinded independent central review; CI=confidence interval IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=Not estimable; NR=not reported; OS=overall survival; PAZ=pazopanib; PFS=progression-free survival; SOR=sorafenib; SUN=sunitinib; TIV=tivozanib

Source: CS, extracted from Table B.2.16 and clarification letter, Table 1 and Table 27

ERG critique of trial design and patient population

The ERG notes that all of the RCTs in the network for the all risk status population were generally of a similar design i.e., they were open-label, phase III studies. The ERG also highlights that the CABOSUN trial,[67] one of the studies used in the IMDC intermediate/poor risk status network, was a phase II study which only recruited 157 patients; the only other trial in this network was the JAVELIN Renal 101 trial which included 690 patients with IMDC intermediate/poor risk status. These differences may lead to statistical heterogeneity and therefore uncertainty in the NMAs of the IMDC intermediate/poor risk status population.

The ERG agrees with the company's assessment that the age, sex, metastatic sites, ECOG PS and prior therapies of patients at baseline were broadly similar across all trials included in the company's NMAs (CS, Appendix D, Table B.5.8). Within all of the trials contributing to the all risk status population NMAs, >99% of patients were functioning at a high level (ECOG PS 0-1). Within the CABOSUN trial,[67] which contributed to the IMDC intermediate/poor risk status population NMAs, the PS of 87% of patients was defined as ECOG PS 0-1, and the PS of the remaining 13% was defined as ECOG PS 2. Clinical advice to the ERG is that within clinical practice, some patients defined at ECOG PS 2 and would still be eligible for treatment with avelumab+axitinib or VEGFR-targeted TKI agents such as sunitinib, pazopanib and tivozanib.

All of the patients recruited to six of the trials included in the company's NMAs had clear cell aRCC, whilst in the remaining trial,[61] 13% of recruited patients had tumours of a non-clear cell histology.[61] While it is considered that tumours of a clear cell histology respond differently to treatment compared to tumours of a non-clear cell histology (see Section 2.2.3), the ERG does not consider that including results from this small proportion of patients in the NMAs is likely to have a major effect on NMA results.

In the all risk status NMAs, in which all of the trials reported risk status using the MKSCC classification system, the proportions of patients defined as having a favourable risk status varied from around 22% to 51%, the variation in terms of intermediate risk status was from approximately 43% to 88%, and that for poor risk status was from approximately 0% to 11%. One trial recruited only patients of favourable or intermediate risk status[62] and one trial recruited <1% of patients with poor risk status.[61] The IMDC risk status of patients was only reported in the two trials in the IMDC intermediate/poor risk status population NMAs, i.e. the JAVELIN Renal 101 trial and in the CABOSUN trial.[67] The proportions of patients with intermediate and poor risk status aRCC within the intermediate/poor risk status populations of the two trials were similar. The ERG notes that MSKCC and IMDC risk status scores are considered to be important prognostic criteria,[30,75] and the variation between trials in terms of

the proportions of patients in each risk status category may have an impact on the results, particularly on the precision of the results, from the NMAs for the all risk status population.

The ERG notes that two of the trials (Eichelberg et al 2015[61] and Tomita et al 2017[62]) were of a randomised sequential design (patients were randomised to receive sunitinib followed by sorafenib, or sorafenib followed by sunitinib). Both of the randomised sequential trials measured first-line PFS (i.e. PFS on the first randomised treatment, sorafenib or sunitinib) and therefore PFS could be included within the NMAs for both of these trials. However, OS data were not available from the two trials for the first randomised treatment only; OS data were only available at the end of the treatment sequence (i.e. sorafenib followed by sunitinib or sunitinib followed by sorafenib). Therefore the ERG considers that the link between the nodes of sunitinib and sorafenib that is assumed by the design of the OS network for the all risk status population (Figure 2) is not a valid link to make as there is no actual comparison of OS resulting from treatment with sorafenib versus treatment with sunitinib in either of the trials. Therefore, the ERG considers that the entire network for OS in the all risk status population is invalidated.

Furthermore, the TIVO-1 trial[22] permitted crossover from the sorafenib arm to the tivozanib arm (61% patients who progressed on sorafenib crossed over to tivozanib). While the design of the remaining trials[10,22,27,67,72] did not permit treatment crossover,[10,22,27,67,72] between 18%[10] and 65%[67] of patients received at least one subsequent systemic or anti-cancer therapy. Furthermore, in the JAVELIN Renal 101 trial, subsequent therapy included immunotherapy (the PD-1 checkpoint inhibitor, nivolumab): 24% of patients the sunitinib arm and 3% of patients in the avelumab+axitinib arm (or 65% and15% those who received any subsequent therapy in these respective arms). Immunotherapy was not widely available to patients at the time the other trials were conducted (although it is reported that 18% of all patients in the CABOSUN trial[67] received a PD-1 checkpoint inhibitor as subsequent therapy, 29% of all those who received any subsequent therapy in this trial). The ERG considers that the subsequent therapies that participants went to receive after disease progression within these trials raises concerns about the validity the network structures for OS in the all risk status population and in the IMDC intermediate/poor risk status population. Thus, it could be argued that the treatment nodes within the network do not represent the effect of the treatment alone.

ERG critique of PFS and OS outcomes reported in the trials included in the NMAs

The company reports the statistical approaches used to analyse the PFS and OS outcomes from the trials included in the NMAs in the CS (Appendix D, Table B.5.7). The ERG considers that, for all trials, the statistical approaches used were appropriate but notes that one trial

which was reported as an abstract only, limited information was available regarding the statistical approach.[62]

The ERG notes that PFS by BICR is included in the NMA for four of the trials,[10,22,27,72] PFS by investigator assessment is included in the NMA for two trials[61,67] and for one trial,[62] the assessment method of PFS was unclear.

It should be noted that all of the trials included in the company's NMAs recruited previously untreated patients, except for the TIVO-1 trial,[22] for which 30% of recruited patients had received one previous therapy. However subgroup data were available from this trial for patients who were previously untreated for metastatic disease. It is these subgroup data which are used in the NMAs for PFS but as highlighted above, the ERG is unsure whether OS data for the previously untreated population or for the whole population have been included in the NMAs (Table 12).

Sunitinib was included as a treatment arm in five of the seven trials.[27,61,62,67,72] Median PFS and OS estimates were broadly consistent across the sunitinib arms of the five trials[27,61,62,67,72] for the all risk status population (median PFS was approximately 8 to 9 months and median OS was approximately 27 to 38 months). In the CABOSUN trial,[67] median PFS and OS were lower in the sunitinib arm compared to the sunitinib arms of the JAVELIN Renal 101 trial (median PFS 5.3 months and median OS 21.2 months); the ERG considers that this may reflect survival expectations for the recruited population (IMDC intermediate/poor risk status and the only trial which recruited >1% of participants with ECOG PS 2 [13%]).

4.7.2 Assessment of risk of bias of the trials included in the NMAs

The company performed a quality assessment of the trials included in the NMAs for the two populations using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[68] The company's quality assessment is presented in the CS (Appendix D, Table B.5.13). The ERG disagrees with some of the company's conclusions (see Table 13).

Due to a lack of detail it is not clear whether the randomisation and allocation concealment processes used in two trials[22,62] were acceptable. A method of central and/or web based randomisation was used in all five of the other trials used in the company's NMAs; the ERG considers that this method of randomisation is adequate.

All of the trials included in the company NMAs were of an open-label design. The bias associated with the magnitude of PFS and ORR outcomes from trials of this design was minimised in four of the trials[10,22,27,72] as these outcomes were assessed by BICR. PFS and

ORR were assessed by investigators in two trials [61,67] and the method of assessment was unclear in the remaining trial.[62]

Three of the trials[61,67,72] reported adequate methods to account for missing data, while the other four trials[10,22,27,62] did not report any methods used to account for missing data.

The ERG considers that for six out of the seven trials used in the company's NMAs, treatment arms were similar at baseline in terms of prognostic factors, there were no unexpected imbalances between treatment groups, an intention-to-treat approach was used and there was no evidence to suggest authors measured more outcomes than they reported. For the remaining trial,[62] which was reported as an abstract only, limited information on trial design made it impossible to assess quality with any certainty.[62]

Table 13 ERG quality assessment for the trials included in the NMAs

Quality assessment item	Motzer 2019[72] JAVELIN Renal 101	Eichelberg 2015[61] (SWITCH)	Hutson 2013[10] (A4061032)	Motzer 2013[27] (COMPARZ)	Motzer 2013[22] (TIVO-1)	Tomita 2014[62] (CROSS-J-RCC)[a]	Choueiri 2018[67] (CABOSUN)
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No (BICR used)	No (Investigator review used)	No (BICR used)	No (BICR used)	No (BICR used)	Not clear	No (Investigator review used)
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	No	Not clear	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	Not clear	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	Yes	Yes	Yes	Yes	Not clear	Yes
Were appropriate methods used to account for missing data?	Yes	Yes	Not clear	Not clear	Not clear	Not clear	Yes

a. Abstract only available

BICR=blinded independent central review; CS=company submission; ERG=evidence review group; NMA=network meta-analysis

Source: ERG quality assessment

4.7.3 NMA methods

Proportional hazards assumption

In the CS, the company stated that they assessed the validity of the PH assumption for PFS and OS in all of the trials included in the NMAs by visually inspecting log-cumulative hazard plots. These log-cumulative hazard plots were not provided in the CS but were provided in response to question A2a of the clarification letter.

The ERG considers that visual inspection of log-cumulative hazard plots is subjective and, therefore, may not always be an adequate method of judging the validity of the PH assumption. Therefore, during the clarification process, the ERG asked the company to also perform a statistical test which would corroborate or contradict results obtained by visual assessment (clarification letter, question A2b). The company's response to the clarification letter included Schoenfeld residual plots and tests for PFS data from six of the trials[10,22,27,61,62,67] and for OS data from five of the trials.[10,22,27,61,67] The company judged that for two of the trials,[22,62] the Schoenfeld residual plots and tests suggested violation of the PH assumption for PFS and for OS, but, for all of the other trials, the Schoenfeld residuals plots and tests did not suggest the PH assumption for PFS and OS had been violated (despite many of the log-cumulative hazard plots showing crossing of curves). The ERG generally agrees with the company assessments of the log-cumulative hazard plots and the Schoenfeld residual plots and tests and agrees that there are uncertainties around the validity of the PH assumption for PFS and OS across the trials included in the NMAs.

Due to uncertainties regarding the validity of the PH assumption, the company conducted both a standard Bayesian NMA assuming PH (PH NMAs) and also NMAs using methods which do not require an assumption of PH (non-PH NMAs). The ERG agrees that this approach was appropriate.

PH NMA methods

The PH NMAs were conducted according to the methods described in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2 to 4[77-79] and implemented using the R statistical software 'gemtc' package.[80] Both fixed effects and random effects models were fitted. NMA results are presented as HRs and 95% Credible Intervals (CrIs) for avelumab+axitinib versus each of the comparators listed in the final scope issued by NICE.[1]

Non-PH NMA methods

The non-PH NMAs were conducted based on the methods described by Ouwens et al 2010.[81] This approach involves fitting parametric curves to data from each treatment arm of each trial in the network and estimating time-varying treatment effects. The company fitted the following

parametric distributions: Weibull, Gompertz, Log-logistic, Log-normal, Generalised Gamma and Generalised F. The company selected the 'best fitting' parametric curve for the comparison of avelumab+axitinib versus tivozanib or of avelumab+axitinib versus cabozantinib based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual assessment of the extent to which curves fitted published K-M data, and expert assessment of the clinical plausibility of survival outcomes predicted by each curve for PFS and OS (CS, Appendix D.3.1).

The parametric NMA models were fitted with fixed effects using the 'flexsurv' package of R[82] and in response to question A3c of the clarification letter, the company provided example code for fitting these models. The company used individual participant data (IPD) from the JAVELIN Renal 101 trial and re-created pseudo IPD by digitising published K-M data and applying the censoring algorithm of Guyot et al 2012[83] for the other six trials. The company presented NMA PFS and OS results as curves, and as survival probabilities (with accompanying 95% CIs) at 1 year, 2 years and 10 years, for each treatment within the network for PFS and for OS in CS, Appendix D, Section D.4.

Further details of the company's PH and non-PH NMAs methods can be found in CS, Appendix D, Section D.3.

ERG critique of the company's NMA methods

The ERG considers that the NMA methods used by the company were reasonable, given the uncertainties regarding the PH assumption for PFS and OS within many of the trials included in the NMAs. The ERG considers that the company has applied the methods as described in the NICE DSU TSDs 2 to 4[77-79] (PH-NMAs) and in the methods of Ouwens et al 2010[81] (non-PH NMAs) appropriately. The ERG considers the company's approach to selecting the 'best fitting' model for the non-PH NMAs based on model fit statistics, visual assessment, and clinical plausibility is generally appropriate. However, the ERG notes that results from the extrapolations beyond the time-frame of the available trial data are very uncertain.

The ERG also notes that due to the lack of a closed loop within either of the networks (as evident from Figure 2 and Figure 3 of this ERG report), results generated by the company's NMAs are based on indirect evidence and, therefore, the fundamental assumption of consistency between the direct and indirect evidence used to inform an NMA cannot be investigated statistically. The unknown validity of the consistency assumption should be taken into account when interpreting numerical results from the indirect comparisons of avelumab+axitinib versus pazopanib, tivozanib and cabozantinib.

However, as discussed in Section 4.7.1, due to the inclusion of two trials of a randomised sequential design[61,62] and the diverse subsequent therapies received in all of the studies included within the NMAs, the ERG is concerned about the structure of the OS network in the all risk status and the IMDC intermediate/poor risk status population and considers that no conclusions can be reliably drawn from the NMAs of OS.

4.7.4 Results from the NMAs

In response to question A1a of the clarification letter, the company highlighted three minor corrections to the extracted data included within the NMAs and therefore provide updated results for the PH NMAs (company response to question A1 of the clarification letter, Table 2, Table 3 and Table 4) but did not carry out any updates relevant to the non-PH NMAs. The updated PH NMA results are very similar to the original results provided within the CS (numerical results are the same to 1 or 2 decimal places). In this ERG report, the ERG has therefore, presented the original results provided in the CS from both the PH and non-PH NMAs for consistency.

PH NMA: all risk status population and IMDC intermediate/poor risk status population

Results from the PFS and OS PH NMAs for the all risk status and IMDC intermediate/poor risk status populations are presented in Table 14.

Table 14 PFS and OS results of PH NMAs: all risk status population and IMDC intermediate/poor risk status aRCC population

Treatment	PFS: HR (95% CrI)		OS: HR (95% CrI)	
	Fixed-effects	Random-effects	Fixed-effects	Random-effects
all risk status population: avelumab+axitinib versus treatment				
Sunitinib	***0.69 (0.56 to 0.84)***[a]	0.69 (0.01 to 44.25)	0.78 (0.56 to 1.09)	0.78 (0.01 to 45.30)
Pazopanib	***0.66 (0.51 to 0.85)***[a]	0.66 (0.00 to 245.36)	0.86 (0.59 to 1.25)	0.85 (0.00 to 272.88)
Tivozanib	0.73 (0.49 to 1.09)	0.71 (0.00 to 504.80)	0.62 (0.37 to 1.05)	0.62 (0.00 to 387.38)
all risk status population: treatment versus sunitinib				
Pazopanib	1.05 (0.90 to 1.22)	1.05 (0.02 to 66.73)	0.91 (0.76 to 1.08)	0.91 (0.02 to 50.45)
Tivozanib	0.95 (0.67 to 1.33)	0.98 (0.01 to 175.32)	1.26 (0.84 to 1.88)	1.26 (0.01 to 177.25)
IMDC intermediate/poor risk status aRCC population: avelumab+axitinib versus treatment				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]

a. Results in italics are statistically significant

aRCC=advanced renal cell carcinoma; CrI=credible interval; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazards

Source: CS, Appendix D, extracted from Table B.5.19, Table B.5.20, Table B.5.21 and Table B.5.22

Results from the company's PFS fixed effects PH NMA show that treatment with avelumab+axitinib leads to a statistically significant reduction in PFS compared to treatment with sunitinib or pazopanib. HRs from all other PFS comparisons and all OS comparisons are not statistically significant in the fixed effects PH NMA (Table 14).

Results from the company's fixed-effects PH NMAs also show that the effects of treatment with sunitinib and pazopanib on PFS or OS are not statistically significantly different (company response to question A1 of the clarification letter). This finding is in line with data presented in NICE TA512[19] and NICE TA581[26] which showed that these two treatments were clinically similar. The ERG is uncertain regarding the rationale of the company for not using the indirect estimates for the comparison of avelumab+axitinib versus pazopanib from the either the PH NMAs or non-PH NMAs in the economic model (CS, Section B.3.3 and ERG report Section 5.2.5).

The ERG highlights that when the company PFS and OS PH NMAs are conducted with random effects, no results are statistically significant and the CrIs around all of the HRs are very wide, indicating that the magnitude of the effect of treatment with avelumab+axitinib compared to all of the comparator treatments is very uncertain.

However, the ERG recognises that conducting random effects NMAs in small networks, i.e., with small numbers of trials informing each treatment comparison, leads to wide CrIs. However, the ERG suggests that the wide CrIs, rather than being solely due to uncertainty originating from the small network, may reflect some of the between trial heterogeneity.

The ERG emphasises the uncertainties regarding the validity of the PH assumption for the NMAs of PFS and OS (see Section 4.7.1) and, therefore, considers that it is unclear whether the HR results generated by the PH NMAs are meaningful.

Non-PH NMA: all risk status population and IMDC intermediate/poor risk status population

Generalised gamma curves were used as the basis for estimating relative OS and PFS for the all risk status population. The company judged this distribution to be the 'best fitting' for the comparison of avelumab+axitinib versus tivozanib based on AIC and BIC values (CS, Table B.2.23), visual fit to the avelumab+axitinib arm of the JAVELIN Renal 101 trial (PFS: CS, Figure B.2.15, OS: CS, Figure B.2.16) and clinical plausibility.

For the IMDC intermediate/poor risk status population, generalised gamma curves were used as the basis for estimating relative PFS, and log-logistic curves were used as the basis for estimating relative OS. The company selected these distributions based on which distribution was 'best fitting' for the comparison of avelumab+axitinib versus cabozantinib based on AIC and BIC values (CS, Table B.2.24), visual fit to the avelumab+axitinib arm of the JAVELIN Renal 101 trial (PFS: CS, Figure B.2.19, OS: CS, Figure B.2.20) and clinical plausibility.

Estimated survival probabilities at 1, 2 and 10 years are provided in Table 15 of this ERG report for the all risk status population and in Table 16 of this ERG report for the IMDC intermediate/poor risk status population. Estimated survival curves based on the best fitting distribution to avelumab+axitinib data from the JAVELIN Renal 101 trial are provided in the CS (Section B.2.9.5.1.1, Figure B.2.17 [all risk status population] and Section B.2.9.5.1.2, Figure B.2.21 [IMDC intermediate/poor risk status population]) as are OS curves (Section B.2.9.5.1.1, Figure 2.18 [all risk status population] and Section B.2.9.5.1.2, Figure B.2.21 [IMDC intermediate/poor risk status population]).

Table 15 Estimated survival probabilities, generated by the company's non-PH NMA (fixed effects): all risk status population

Time[a]	Treatment[b]	PFS (95% CI)	OS (95% CI)
		Generalised Gamma	Generalised Gamma
1 year	Avelumab+axitinib	0.53 (0.48 to 0.58)	0.86 (0.82 to 0.89)
	Sunitinib	0.38 (0.33 to 0.43)	0.83 (0.78 to 0.86)
	Pazopanib	0.35 (0.26 to 0.43)	0.84 (0.79 to 0.89)
	Tivozanib	0.41 (0.29 to 0.51)	0.82 (0.70 to 0.90)
2 years	Avelumab+axitinib	0.36 (0.31 to 0.42)	0.74 (0.66 to 0.80)
	Sunitinib	0.21 (0.17 to 0.26)	0.67 (0.59 to 0.72)
	Pazopanib	0.17 (0.11 to 0.24)	0.69 (0.60 to 0.76)
	Tivozanib	0.24 (0.13 to 0.35)	0.64 (0.46 to 0.76)
10 years	Avelumab+axitinib	0.10 (0.06 to 0.15)	0.34 (0.16 to 0.47)
	Sunitinib	0.03 (0.02 to 0.05)	0.20 (0.09 to 0.33)
	Pazopanib	0.02 (0.01 to 0.04)	0.21 (0.08 to 0.35)
	Tivozanib	0.04 (0.01 to 0.12)	0.14 (0.01 to 0.32)

a. 1, 2- and 10-year survival estimated as 364, 728 and 3640 days respectively
b. Results presented for avelumab+axitinib and comparators as listed in the final scope issued by NICE.[1] Results for other treatments included within the NMAs but not within the NICE scope (sorafenib and axitinib) can be found in CS, Appendix D, Table B.5.15 and Table B.5.16

CI=confidence interval; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazards
Source: CS, Appendix D, extracted from Table B.5.15 and Table B.5.16

Table 16 Estimated survival probabilities generated by the company's non-PH NMA (fixed effects): IMDC intermediate/poor risk status population

Treatment[a]	Time[b]	PFS (95% CI)	OS (95% CI)
		Generalised Gamma	Log logistic
1 year	Avelumab+axitinib	[redacted]	[redacted]
	Cabozantinib	[redacted]	[redacted]
2 years	Avelumab+axitinib	[redacted]	[redacted]
	Cabozantinib	[redacted]	[redacted]
10 years	Avelumab+axitinib	[redacted]	[redacted]
	Cabozantinib	[redacted]	[redacted]

a. Results presented for avelumab+axitinib and comparators as listed in the NICE scope. Results for other treatments included within the NMAs but not within the NICE scope (sunitinib) can be found in the CS, Appendix D, Table B.5.17 and Table B.5.18
b. 1, 2- and 10-year survival estimated as 364, 728 and 3640 days respectively

aRCC=advanced renal cell carcinoma; CI=confidence interval; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazards
Source: CS, Appendix D, extracted from Table B.5.17 and Table B.5.18

In summary:

- Estimated PFS probabilities in the all risk status population are generally higher for avelumab+axitinib compared to all of the comparators at 1, 2 and 10 years.
- Whereas estimated OS probabilities are similar across all of the treatments at 1 year and 2 years, a slightly higher OS probability is estimated for avelumab+axitinib compared to all of the comparators at 10 years; at 10 years, the estimated OS probability is 34% for avelumab+axitinib compared to ≤20% for the comparator treatments (Table 15).
- Estimated PFS and OS probabilities for the IMDC intermediate/poor risk status population are similar for avelumab+axitinib and cabozantinib at 1, 2 and 10 years (Table 16).

The company notes, and the ERG agrees, that for both PFS and OS, for the all risk status population and the IMDC intermediate/poor risk status population, there is a broad similarity in terms of the statistical fit, visual inspection of estimated survival curves and estimated survival probabilities across several of the parametric distributions applied in the non-PH NMAs. Additional plots of estimated survival curves are presented in CS, Appendix D, Figure B.5.10 to Figure B.5.17 and additional estimated survival probabilities for other good fitting parametric distributions are provided in CS, Appendix D, Table B.5.15 to Table B.5.18.

The ERG notes that the estimated survival probabilities from the non-PH NMAs at 1 and 2 years are fairly close to the observed survival probabilities reported within the published trials.[10,22,27,61,62,67,72] The ERG considers that caution should be taken when using results estimated at 10 years as these results are based on an extrapolation rather than based on trial data. However, the ERG also notes that non-PH NMAs have been conducted with fixed effects, an approach which does not take account of, or adjust for, any potential heterogeneity between trials. As discussed earlier within this section, the ERG considers that the wide CrIs that are evident when random-effects PH NMAs are carried out may reflect heterogeneity between the trials included in the NMAs.

4.7.5 ERG conclusions of PH and non-PH NMAs for PFS and OS

The ERG acknowledges uncertainties around the validity of the PH assumption for PFS and OS across the trials included in the NMAs and considers that the company approach of conducting PH and non-PH NMAs for completeness was appropriate. The ERG considers that given the violation of the PH assumption in at least one trial in NMAs for PFS and OS for the all risk status population, the approach of the non-PH NMAs could be considered to be more

reliable than the PH NMAs. For the IMDC intermediate/poor risk status population NMAs, as there is no clear evidence of PH violation, either the PH NMA or non-PH NMA approach could be used.

The ERG considers that for PFS, generally similar conclusions can be drawn from the results from the PH and non-PH NMAs (i.e. that treatment with avelumab+axitinib may improve PFS compared to sunitinib or pazopanib and that there is no clear evidence of any PFS difference between avelumab+axitinib compared to tivozanib or cabozantinib). However, the magnitude of these differences is uncertain.

The ERG further emphasises concerns with the validity of the OS NMAs (PH and non-PH) due to the inclusion of trials of randomised sequential design, trials permitting treatment crossover and differences in subsequent therapies (see Section 4.7.1 of this ERG report). Therefore the ERG considers that no conclusions can be reliably drawn from the NMAs of OS.

4.8 Patient reported outcomes of health-related quality of life

4.8.1 Patient reported outcomes for avelumab+axitinib versus sunitinib

Patient-reported outcomes (PROs) in the JAVELIN Renal 101 trial were assessed using the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire and the Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index-19 (FKSI-19) (CS, p35). Questionnaires were administered at the time of tumour assessments, i.e., every 6 weeks from randomisation until end of treatment (EOT) for the first 18 months, and every 12 weeks until EOT after 18 months from randomisation (CS, Section B.2.6.1.7.3, p56).

PRO assessments occurred at the end of the 2-week off-treatment period for sunitinib. Results from a previous study[84] (cited by the company) showed that patient quality of life was statistically significantly worse during the 2 week off-treatment period, compared with during the 4 week sunitinib on-treatment period. Therefore, the company highlighted that PRO results from the JAVELIN Renal 101 trial may be biased in favour of sunitinib (CS, B.2.6.1.7.3, p56). The ERG notes that, common to most trials of oncology treatments, as only patients still on treatment completed HRQoL assessments, while rates of questionnaire completions were high (generally ≥90%) at each assessment, the numbers of patients steadily decreased, resulting in small samples of patients completing the questionnaires at later assessments. For example, fewer than half of all patients were 'at risk', i.e., still on treatment and, therefore, eligible to complete the questionnaires, by [redacted] in the avelumab+axitinib arm and by [redacted] in the sunitinib arm.

The primary PRO outcome was time to deterioration in the 9-item FKSI-19 Disease Related Symptoms (FKSI-DRS) subscale, defined as the time from date of randomisation to the first ≥3 point decrease. A change of ≥3 points has been established as a clinically important difference.[85,86] Secondary PRO outcomes were mean changes in EQ-5D-5L, FKSI-19 and FKSI-DRS scores from baseline over time. PRO results are presented in the CS from IA1 only.

Primary PRO outcome

The HR [redacted] for the primary outcome, time to deterioration measured using FKSI-DRS questionnaire, favoured the sunitinib arm. Data presented in the CS (Figure B.2.9) shows that time to deterioration was [redacted] in the sunitinib arm than in the avelumab+axitinib arm, [redacted]. It is reported in the CSR of IA1 (Table 30) that a p-value [redacted] from a pre-specified two-sided Cox-proportional hazards test [redacted].

Secondary PRO outcomes

Results for mean changes in EQ-5D-5L, FKSI-19 and FKSI-DRS scores from baseline over time were reported by the company to be similar between arms (CS, Section B.2.6.1.7, pp53-57); however, no formal statistical tests were planned or conducted by the company. The ERG observes (CS, Figures B.2.6 to B.2.6.8) [redacted].

4.8.2 Patient reported outcomes for avelumab+axitinib versus other relevant comparators (pazopanib, tivozanib, cabozantinib)

The company did not present any PRO outcomes for the comparison of avelumab+axitinib versus pazopanib, tivozanib or cabozantinib. However, the ERG notes that, as highlighted in Section 2.2.1, pazopanib is likely to be preferred to sunitinib by most patients who have experience of both treatments.[35] As also highlighted in Section 2.2.1, clinical advice to the ERG is that tivozanib is considered less toxic than all of the other currently available first-line treatment options. Clinical advice to the ERG is that cabozantinib is considered to be less tolerable than sunitinib.

4.9 Safety data

The majority of the safety data presented in the CS are from the JAVELIN Renal 101 trial. Additional safety data are available from the single-arm JAVELIN Renal 100 study. Given the small size of the JAVELIN Renal 100 study (N=55) and the lack of a comparator arm in this

study, the ERG has focussed on safety data from the JAVELIN Renal 101 trial data in this ERG report.

4.9.1 Extent of exposure in the JAVELIN Renal 101 trial

The extent of exposure is summarised the CS (Section B.2.10.2, p84). Reflecting the improved PFS with avelumab+axitinib versus sunitinib (Section 4.6.1 of this ERG report), the extent of exposure to avelumab and axitinib was marginally longer than the extent of exposure with sunitinib ([redacted] weeks, [redacted] weeks and [redacted] weeks, respectively). The median dose intensities were 91.5% for avelumab, 89.4% for axitinib and 83.9% for sunitinib.

4.9.2 Adverse events in the JAVELIN Renal 101 trial

A summary of the key AEs is provided in Table 17. More detail is provided in Appendix 1 Section 8.1of this ERG report.

Table 17 Summary of adverse events in the JAVELIN Renal 101 trial

Adverse event	Avelumab+axitinib (N=434)	Sunitinib (N=439)
Treatment emergent, n (%)		
- Any grade	432 (99.5)	436 (99.3)
- Grade ≥3	309 (71.2)	314 (71.5)
- SAEs	[redacted]	[redacted]
- AEs leading to death	[redacted]	[redacted]
Treatment-related, n (%)		
- Any grade	414 (95.4)	423 (96.4)
- Grade ≥3	246 (56.7)	243 (55.4)
- SAEs	74 (17.1)	57 (13.0)
- AEs leading to death	5 (1.2)	1 (0.2)
Immune-related reaction		
- Any grade	166 (38.2)	[redacted]
- Grade ≥3	38 (9.0)	[redacted]
Infusion-related reaction		
- Any grade	121 (27.9)	n/a
- Grade ≥3	7 (1.6)	n/a

AE=adverse event; SAE=serious adverse event
Source: CS, extracted from Section B.2.10.3, Table B.2.27 and CS, Section B.2.10.3.1, p86

In summary, in relation to the types of AEs, the ERG notes:

- Diarrhoea and hypertension were the most common any grade treatment-related AEs (TRAEs) reported for patients treated with avelumab+axitinib (54.1% and 47.9%, respectively) and also very common for patients treated with sunitinib (44.6% and 32.3%, respectively).

- The most common Grade ≥3 TRAE in both arms was hypertension (24.4% in the avelumab+axitinib arm, 15.3% in the sunitinib arm).

- Cardiac AEs were reported for [redacted] of patients in the avelumab+axitinib arm and [redacted] of patients in the sunitinib arm. Grade ≥3 cardiac AEs were [redacted] and [redacted] respectively (CSR of IA1, Section 12.2.2.4.3, p198).

- Approximately a quarter (27.9%) of patients treated with avelumab+axitinib reported infusion-related reactions; 1.6% of patients treated with avelumab+axitinib reported Grade ≥3 infusion-related reactions (Section B.2.10.3, p86).

- It is reported on the CSR of IA1 (Section 12.2.2.4.1, pp190-191) that [redacted] of patients treated with avelumab+axitinib had serious immune-related reactions and that [redacted] of patients treated with avelumab+axitinib had fatal immune-related reactions [redacted].

- No treatment-related serious adverse events occurred in ≥2% of patients in either treatment arm (Section B.2.10.3.2, p92).

- Proportionately [redacted] patients treated with axitinib had dose reductions but proportionately [redacted] had dose interruptions in comparison to patients treated with sunitinib ([redacted] versus [redacted] and [redacted] versus [redacted], respectively) (CS, Table B.2.33). Common reasons for dose reduction or dose interruptions in both arms included [redacted] (CS, Section B.2.10.3.5, p95).

- [redacted] (CS, Section B.2.10.3.4, Table B.2.32) The most common reasons given for discontinuing treatment in the avelumab+axitinib am were [redacted] (CSR of IA1, Section 12.2.2.4.1, p191).

The company concludes (CS, Section B.2.10.4, p99) that in the JAVELIN Renal 101 trial, avelumab+axitinib was generally well tolerated as AEs were typically manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies. However, the company highlights that the frequency of Grade ≥3 AEs was higher for the avelumab+axitinib compared to the frequency previously reported for these agents used as monotherapies.

Given the known potential cardiovascular events associated with VEGFR-targeted TKI agents such as axitinib and sunitinib, clinical advice to the ERG is that immune-related reactions are perhaps AEs to be most concerned about with regard to treatment with avelumab+axitinib since immune-related reactions can be irreversible, severe and life-threatening. In the avelumab+axitinib arm of the JAVELIN Renal 101 trial, it is not reported if any immune-related reactions were reversible or irreversible. However, the proportion of patients with severe (Grade ≥3) immune-related reactions was 9.0% and the proportion of patients with fatal immune-related reactions was [redacted]. The most common type of any grade immune-related reactions was [redacted] ([redacted] of all patients in the avelumab+axitinib arm) (CSR of IA1, Section 12.2.2.4.1, p190). Immune-related reactions categorised as [redacted] were the most common Grade ≥3 immune-related reactions [redacted] (CS, Table B.2.34, p97).

4.9.3 Safety in relation to other comparators

No safety data versus the comparators other than sunitinib are presented in the main CS document (Document B). However, there are data for some AEs for other comparators in Appendix D.2.5.6, Tables B.5.11 and B.5.12. The AEs for which data are reported are anaemia, decreased appetite, diarrhoea, fatigue, hand-foot syndrome (palmar-plantar erythrodysaesthesia), hypertension, neutropenia, rash, stomatitis/mucositis, thrombocytopenia. Data are also reported for withdrawal of study drug due to AEs and/or withdrawal due to any cause.

The ERG notes the data presented show differences in the frequencies of the same types of AEs (e.g., large differences in the incidence of neutropenia and thrombocytopenia in the sunitinib arms across trials). This, as the ERG considers that heterogeneity exists between the trials, it is difficult to draw conclusions about how avelumab+axitinib may compare to pazopanib, tivozanib or cabozantinib in terms of safety outcomes, either using statistical methods or by simply naively comparing the data.

4.10 Conclusions of the clinical effectiveness section

Direct evidence for relative effectiveness of avelumab+ axitinib versus a comparator of interest (sunitinib) is derived from the JAVELIN Renal 101 trial. This is a well-designed and good quality trial with an appropriate and pre-defined statistical approach to the analysis of efficacy outcomes (including PROs) and safety outcomes. The patient population is reflective of that specified in the final scope, including patients of all risk status (i.e. IMDC favourable risk status and intermediate/poor risk status). However, patients with clear cell aRCC and patients with ECOG PS ≥2 were excluded from the trial. The proportion of patients in NHS clinical practice with non-clear cell aRCC may be as high as 25%.[5]

For the all risk status population, evidence from the JAVELIN Renal 101 trial shows that avelumab+axitinib improves PFS and ORR versus sunitinib. However, the OS data are currently immature. This means that firm conclusions cannot be drawn regarding the relative effect of treatment with avelumab+axitinib versus sunitinib for OS.

Indirect evidence from NMAs is required to compare avelumab+axitinib with the other comparators of interest (pazopanib, tivozanib and in the intermediate/poor risk status population, cabozantinib). Evidence from the PH and non-PH NMAs suggests that avelumab+axitinib improves PFS versus pazopanib (all risk status population) but not versus tivozanib (all risk status population) or cabozantinib (intermediate/poor risk status population). The ERG has concerns regarding the validity of the OS NMA results (PH and non-PH) due to the inclusion of trials of randomised sequential design, trials permitting treatment crossover and differences in subsequent therapies. The PH OS NMA in the all risk status population is further limited by the violation of the PH assumption in at least one trial in the OS NMA. Therefore, the ERG considers that no firm conclusions can be drawn from any of the OS NMAs.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of avelumab+axitinib versus sunitinib, pazopanib, tivozanib and cabozantinib (IMDC intermediate/poor risk status only) for treating people with previously untreated aRCC. The two key components of the economic evidence presented in the CS are (i) a systematic review of relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Systematic review of cost effectiveness evidence

5.1.1 Objective of the company's systematic review

The company performed a systematic search of the literature to identify published studies to support the development of their cost effectiveness model. The search was carried out to identify cost effectiveness, cost and resource use, and utility studies.

5.1.2 Company searches

The company searched for articles that had been published since 2007. The databases listed in Table 18 were initially searched on 20 September 2017 and updated searches were carried out on 8 March 2019 (see CS, Appendix G). The company states in the CS that a systematic literature review was also conducted on 4 June 2019 (CS, Section B.3.1). However, details of this latest search are not available in the CS, Appendix G.

Table 18 Databases searched for economic evidence

Database	Interface
Medical Literature Analysis and Retrieval System Online (MEDLINE) in process	PubMed
Excerpta Medical Database (Embase)	Embase
EconLit	Ebsco
Health Technology Assessment database (HTAD)	Centre for Reviews and Dissemination York
National Health Service Economic Evaluation Database (NHSEED)	Centre for Reviews and Dissemination York

Source: CS, extracted from Appendix G.1.2

The company also carried out searches to identify relevant proceedings from the following conferences held between 2016 and 2019: American Society of Clinical Oncology (ASCO), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and International Congress and European Society for Medical Oncology (ESMO).

Additionally, the websites of NICE, Scottish Medicine Consortium (SMC), All Wales Medicine Strategy Group (AWMSG) and Canadian Agency for Drugs and Technologies in

Health/Common Drug Review were searched for potentially relevant technology appraisals. Details of the search strategies used by the company are provided in the CS, Appendix G.

5.1.3 Eligibility criteria used in study selection

The main inclusion criteria used by the company to select studies are shown in Table 19. Only relevant studies published in English were included in the review.

Table 19 Key criteria for identification of economic evaluations

Characteristic	Inclusion criteria
Population	• Adult patients with mRCC, and treatment-naïve (previously untreated) mRCC patients
Interventions	• Atezolizumab • Avelumab • Axitinib • Bevacizumab • Cabozantinib • Cediranib • Interferon-α • Interleukin-2 • Ipilimumab plus nivolumab • Lenvatinib • Pazopanib • Pembrolizumab • Sorafenib • Sunitinib • Temsirolimus • Tivozanib • Trebananib
Comparators	• Placebo • Best supportive care • Any other active pharmacological intervention
Outcomes	• Incremental costs, LYs gained and QALYs, and any other measure of effectiveness reported together with costs • Sensitivity analysis
Study design	• Economic evaluations (including cost effectiveness, cost utility, cost benefit, cost minimisation and cost consequence models) • Budget impact studies
Country	• US, Canada, Australia and other EU countries

α=alpha; EU=European Union; LY=life years; mRCC=metastatic renal cell carcinoma; QALY=quality adjusted life year
Source: CS, Appendix G, Table B.5.42

5.1.4 Included and excluded studies

The company did not identify any studies of avelumab+axitinib in its systematic review. Nonetheless, 9 studies of the included studies are from UK Health Technology Assessment websites (NICE=5; SMC=3; AWMSG=1) that were considered to be relevant to the decision problem (Table 20). The company stated that the previous technology appraisals of nivolumab+ipilimumab (TA581),[26] sunitinib (TA169),[18] pazopanib (TA215),[17] tivozanib (TA512)[19] and cabozantinib (TA542)[16] informed the development of the economic model in this appraisal (Section B.3.1 and CS, Appendix G). Full details of the included studies are provided in CS, Appendix G, Table B.5.43.

Table 20 Cost effectiveness studies identified in the company search

Study identifier Line of therapy	Intervention/ comparator (s)	Key model drivers	Reported in Appendix G
NICE [TA169][18] 2009 First-line	• Sunitinib • Pazopanib	• Not reported	No
NICE [TA178][87] 2009 First-line	• Bevacizumab+interferon-alpha • Sunitinib • Temsirolimus • interferon-alpha • Best supportive care	• Cost of sunitinib, bevacizumab, interferon, temsirolimus and best supportive care • Health states utility values assigned to PFS and PD states • Shapes of OS and PFS curves	Yes
NICE [TA215][17] 2010 First-line	• Pazopanib • Sunitinib • Interferon-alpha • Best supportive care	• Drug costs of pazopanib, sunitinib, interferon-alpha and best supportive care • Hazard ratios of OS and PFS	Yes
NICE [TA512][19] 2017 First-line*¤	• Tivozanib • Gefitinib • Erlotinib	• NHS and PSS • 2011 • UK pounds (£)	No
NICE [TA542] [16] 2018 First-line	• Cabozantinib • Sunitinib • Pazopanib	• Cost of cabozantinib and the effect of discounting on cost and outcomes	Yes
NICE [TA581][26] 2018 First-line	• Nivolumab plus ipilimumab • Sunitinib • Pazopanib	• Uncertainties around assumptions associated with long-term survival benefits and stopping rule	Yes
SMC [384/07][88] 2007 First-line	• Sunitinib • Interferon-alpha	• Not reported	Yes
SMC [676/11][89] 2011	• Pazopanib • Sunitinib • Interferon-alpha • Best supportive care	• PFS and OS curves	Yes
SMC [2136][90] 2019 First-line	• Cabozantinib • Sunitinib • Pazopanib	• Cost of cabozantinib	Yes
AWMSG [Ref:294][91] 2007 First-line	• Sunitinib • Interferon-alpha	• Not reported	Yes

*=permits previous treatment with interferon-alpha or interleukins; AWMSG=All Wales Medicine Strategy Group; NICE=National Institute for Health and Care Excellence; OS=overall survival; PD=progressed disease; PFS=progression-free survival; PSS=personal social service; Ref=reference number; SMC=Scottish Medicine Consortium; TA=technology appraisal
Source: CS, Appendix G, Table B.3.1 and Table B.5.43

5.1.5 Findings from cost effectiveness review

The company did not report any findings from the cost effectiveness review.

5.1.6 ERG critique of the company's review of cost effectiveness evidence

The company reports the full details of the searches used to identify the cost effectiveness evidence in the CS, Section 3.1 and Appendix G. These searches included a cost effectiveness filter. The company used population terms and indication terms that the ERG considers to be sufficiently broad and appropriate. However, the ERG notes that the company could have been clearer on the time when the search was last updated. In the CS, Appendix G, it is stated that the latest update was on 8 March 2019 whilst 4 June 2019 was reported in the CS, Section B.3.1. The discrepancy between the information in the CS, Section B.3.1 and the CS, Appendix G extends to the number of studies included in the review. Two previous technology appraisals stated to have been found in the CS (TA169[17] and TA512[19]) were not reported in CS, Appendix G even though those appraisals were published (in 2009 and 2017 respectively) before March 2019. Overall, when the information reported in CS, Section B.3.1 and the CS, Appendix G are jointly considered, the ERG is satisfied that no study of avelumab+axitinib was identified for inclusion in the review (Table 21).

The company also searched for HRQoL data, and cost/resource use data. Full details of the strategy for the two searches are reported in the CS, Appendix G whilst the search results are reported individually in Appendix H and Appendix I of the CS respectively. The searches included appropriated HRQoL and resource use filter, broad population search terms and covered the same time period (conducted on 20 September 2017 and updated on 8 March 2019) as the cost effectiveness searches.

Table 21 ERG appraisal of systematic review methods (cost effectiveness)

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied, independently, by two or more reviewers?	Yes
Were data extracted, independently, by two or more reviewers?	Yes
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted, independently, by two or more reviewers?	Yes
Were any relevant studies identified?	No

Source: CS, extracted from Appendix G and ERG comment

5.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of avelumab+axitinib for the treatment of untreated aRCC. For all risk status populations the comparators were sunitinib, pazopanib and tivozanib and for the IMDC intermediate/poor risk status population the comparator was cabozantinib.

5.2.1 Model structure

The company model structure (a partitioned survival model) is shown in Figure 4. It comprises three mutually exclusive health states that are designed to reflect the natural course of the disease. The patients enter the model in the progression-free (PF) health state. At the end of each weekly cycle patients in the PF health states can remain in that health states or experience disease progression and enter the progressed disease (PD) health state. At the end of each cycle patients in the PD health states can remain in that health states but they cannot return to the PF health state. Transitions to the death health states can occur from either the PF health states or the PD health state. Death is an absorbing health states from which transitions to other health states are not permitted. The company model structure is consistent with that used in previous technology appraisals of aRCC (TA581,[26] TA542,[16] TA215[17] and TA512[19]).

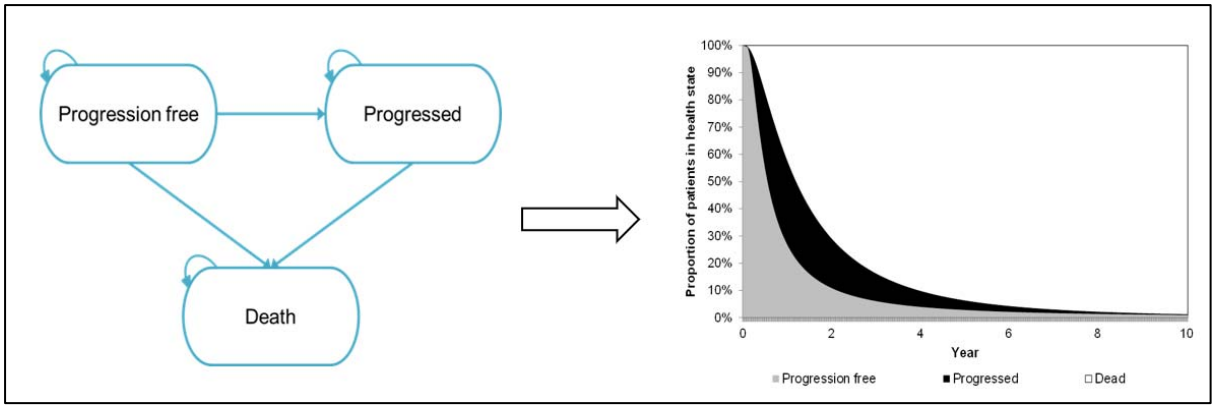


Figure 4 Structure of the company model

Source: CS, Section B.3.2.2 Figure B.3.1

5.2.2 Population

Two populations are considered: the all risk status population when the comparator is sunitinib, pazopanib and tivozanib, and the IMDC intermediate/poor risk status population when the comparator is cabozantinib. These populations are consistent with the populations specified in the final scope issued by NICE.[1]

5.2.3 Interventions and comparators

Intervention

Treatment with avelumab+axitinib is implemented in the model in line with the expected licensed dosing regimen, namely,[1] a flat IV dose of 800mg avelumab Q2W and 5mg axitinib BD. This is similar to the mean weight-based dose observed in the JAVELIN Renal 101 trial (CS, Section B.3.5.1.1, p145). Although use of avelumab+axitinib was not restricted by time in the JAVELIN Renal 101 trial, in the base case a 2-year stopping rule was applied for both avelumab and axitinib.

Comparators

All four comparators (sunitinib, pazopanib, tivozanib and cabozantinib) are administered orally. Sunitib is administered in line with the dosing regimen used in the JAVELIN Renal 101 trial, whilst the doses of the other comparators are those specified in the relevant summary of product characteristics (SmPCs).[33,36,92,93] Dosing regimens for the comparator drugs are provided in Table 22.

Table 22 Comparator treatments and dosing regimens

Comparator	Dosing
Sunitinib	50mg orally OD for 4 consecutive weeks followed by a 2-week off-treatment period (Schedule 4/2).
Tivozanib	1.34mg OD for 21 days followed by a 7-day rest period
Pazopanib	800mg daily
Cabozantinib	60mg OD

mg=milligram; OD=once daily
Source: CS, Table B.3.3

5.2.4 Perspective, time horizon and discounting

The company states that, in line with NICE's Guide to the Methods of Technology Appraisal,[68] the economic evaluation is undertaken from the perspective of the NHS and personal social services. The cycle length is 1 week (a period that is too short to necessitate use of a half-cycle correction), and the time horizon is set at 40 years. Both costs and outcomes are discounted at 3.5% per annum.

5.2.5 Treatment effectiveness and extrapolation in the base case

For the comparison of avelumab+axitinib versus sunitinib, the company utilised patient-level data from the IA1 JAVELIN Renal 101 trial as the basis for representing patient experience.

Data from the IA1 JAVELIN Renal 101 trial were only available for a period of 24 months. The company, therefore, used parametric distributions that reflected the available data to model the experience of patients receiving avelumab+axitinib and sunitinib.

Methods used by the company to determine the best approach to modelling survival

In the company model patient OS, PFS and time on treatment (ToT) experience were represented using parametric distributions.

Patient level data, on which to base OS, PFS (BICR) and ToT model estimates for patients treated with the intervention (avelumab+axitinib) and for those treated with sunitinib were available from the JAVELIN Renal 101 trial. In addition, the company assumed that survival and ToT estimates associated with treatment with sunitinib could be used to represent the experience of patients treated with pazopanib. This assumption was based on previous NICE AC conclusions[26] and clinical feedback to the company which indicated that these treatments have the same effectiveness in a real-world setting. However, for the comparisons of treatment with avelumab+axitinib versus tivozanib and versus cabozantinib the company used data from their NMAs as the basis for estimating the life time experience of patients receiving all three treatments. This means that the model representation of OS, PFS and ToT experience of patients receiving avelumab+axitinib differs depending on the comparator.

Company selection of parametric distributions was determined using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, visual inspection to assess how closely the chosen parametric curves fitted the JAVELIN Renal 101 trial data and expert clinical opinion on expected outcomes based on their experience. This approach is in line with NICE Decision Support Unit guidelines (Technical Document 14).[94]

The approaches used in the company model to represent OS, PFS (based on BICR) and ToT are presented in Table 23, Table 24 and Table 25.

Table 23 Approaches used by the company to model overall survival

Treatment	Company approach to modelling overall survival
Comparison of avelumab+axitinib versus sunitinib and pazopanib (all risk status population)	
Avelumab+axitinib	Log-logistic function fitted to the JAVELIN Renal 101 trial avelumab+axitinib OS data
Sunitinib	Log-logistic function fitted to the JAVELIN Renal 101 trial sunitinib OS data
Pazopanib	Equivalent to overall survival for sunitinib
Comparison of avelumab+axitinib versus tivozanib (all risk status population)	
Avelumab+axitinib	Generalised gamma function fitted to non-PH NMA OS data
Tivozanib	Generalised gamma function fitted to non-PH NMA OS data
Comparison of avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population)	
Avelumab+axitinib	Log-logistic function fitted to non-PH NMA OS data
Cabozantinib	Log-logistic function fitted to non-PH NMA OS data

IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; OS=overall survival
Source: CS, section B.3.3

Table 24 Approaches used by the company to model progression-free survival

Treatment	Company approach to modelling progression-free survival
Comparison of avelumab+axitinib versus sunitinib and pazopanib (all risk status population)	
Avelumab+axitinib	Generalised gamma function fitted to the JAVELIN Renal 101 trial avelumab+axitinib PFS data
Sunitinib	Log-logistic function fitted to the JAVELIN Renal 101 trial sunitinib PFS data
Pazopanib	Log-logistic function fitted to the JAVELIN Renal 101 trial sunitinib PFS data
Comparison of avelumab+axitinib versus tivozanib (all risk status population)	
Avelumab+axitinib	Generalised gamma function fitted to non-PH NMA PFS data
Tivozanib	Generalised gamma function fitted to non-PH NMA PFS data
Comparison of avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population)	
Avelumab+axitinib	Generalised gamma function fitted to non-PH NMA PFS data
Cabozantinib	Generalised gamma function fitted to non-PH NMA PFS data

IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; PFS=progression-free survival
Source: CS, section B.3.3

Table 25 Approaches used by the company to model time on treatment

Treatment	Company approach to modelling time to treatment discontinuation
Comparison of avelumab+axitinib versus sunitinib and pazopanib (all risk status population)	
Avelumab	Log-normal function fitted to the JAVELIN Renal 101 trial avelumab TTD data
Axitinib	Log-logistic function fitted to the JAVELIN Renal 101 trial axitinib TTD data
Sunitinib	Log-normal function fitted to the JAVELIN Renal 101 trial sunitinib TTD data
Pazopanib	Log-normal function fitted to the JAVELIN Renal 101 trial sunitinib TTD data
Comparison of avelumab+axitinib versus tivozanib (all risk status population)	
Avelumab	Log-normal function fitted to the JAVELIN Renal 101 trial avelumab TTD data
Axitinib	Log-logistic function fitted to the JAVELIN Renal 101 trial axitinib TTD data
Tivozanib	ToT assumed equivalent to progression-free survival, i.e., generalised gamma function fitted to non-PH NMA PFS data
Comparison of avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population)	
Avelumab	Log-normal function fitted to the JAVELIN Renal 101 trial avelumab TTD data
Axitinib	Log-logistic function fitted to the JAVELIN Renal 101 trial axitinib TTD data
Cabozantinib	Log-normal function fitted to digitised cabozantinib ToT data in TA542[16]

IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; TA=technology appraisal; ToT=time on treatment; TTD=time to treatment discontinuation
Source: CS, section B.3.3

Treatment waning

A treatment waning effect was employed in the model to reflect the uncertainty around the extent of disease progression following treatment discontinuation. It is suggested that once treatment with avelumab+axitinib is stopped at 2 years, a proportion of patients (estimated, by clinicians, to be between 20% and 50%) will lose some of the accumulated benefit, gradually adopting the PFS and OS hazards associated with treatment with sunitinib. The company assumed that treatment waning would affect 33% of patients who were still receiving avelumab+axitinib at 2 years and the accumulated benefit would be lost over the subsequent 2-year period.

Adjusting for general population mortality

All parametric models used in the model to represent patient survival were checked to ensure that risk of patient transition to death was never lower than that of the general population. In cases where risk became lower than that of the general population the mortality risk was set equal to that of the general population.

5.2.6 Health related quality of life

Patients in the JAVELIN Renal 101 trial completed the EQ-5D-5L questionnaire on day 1 of every treatment cycle until the end of treatment or withdrawal depending on which occurred first. Patients also completed the questionnaire at 30-days, 60-days and 90-days post-treatment discontinuation and every 3 months thereafter or at tumour assessment.[71] Patient responses to the EQ-5D-5L questionnaire were then were mapped to EQ-5D-3L using the van Hout[95] crosswalk mapping algorithm, and utility values were obtained using the UK general

population tariff. This approach is consistent with the NICE position statement[96] on the use of EQ-5D-5L data within its technology appraisal process.

The utility estimates from a regression model that are used in the company model are presented in Table 26. Age related utility decrements were included in the model.

Table 26 Utility values (prior to age-related adjustments) used in the company model

Health state	Utility value (SE)
Progression-free	0.753 (0.026)
Post-progression	0.683 (0.026)

SE=standard error
Source: CS, Table B.3.43

5.2.7 Adverse events

Grade ≥3 AEs occurring in ≥5% of patients were used to represent the experience of patients in the company model. Rates for those treated with avelumab+axitinib and sunitinib were obtained from the JAVELIN Renal 101 trial. The company obtained AE rates from previous technology appraisals of first-line treatments for aRCC (TA215:[17] pazopanib, TA512:[19] tivozanib, and TA542:[16] cabozantinib). The modelled AE rates and unit costs (calculated using NHS Reference Costs[97] and Unit Costs of Health and Social Care[98]) are presented in Table 27 and further details are provided in the CS (Table B.3.48 and Table B.3.49).

Table 27 Adverse events (Grade ≥3) included in the company model: incidence and unit costs

Adverse event	JAVELIN Renal 101 trial		NICE TA512	NICE TA215	NICE TA542	Unit cost
	Avelumab +axitinib	Sunitinib	Tivozanib	Pazopanib	Cabozantinib	
Diarrhoea	5.07	2.51	2.32	3.79	8.97	£1,248.34
Hypertension	24.42	15.26	26.25	4.14	21.79	£843.60
PPE syndrome	5.76	4.33	1.93	0.00	7.69	£615.76
Thrombocytopenia	0.23	5.47	0.39	0.69	0.00	£357.13
Anaemia	0.23	5.01	0.00	0.00	0.00	£357.13
Platelet count decreased	0.00	5.01	0.00	0.00	1.28	£357.13
Neutropenia	0.23	7.74	1.16	1.38	0.00	£357.13
Neutrophil count decreased	0.00	5.69	0.00	0.00	0.00	£357.13
Fatigue	3.00	3.64	5.41	1.72	5.13	£615.76
Hypophosphatemia	0.00	0.00	4.25	0.00	8.97	£357.13
Lipase increase	0.00	0.00	11.20	0.00	0.00	£357.13
Stomatitis	1.84	0.91	0.39	0.00	5.13	£1,248.34
Decreased appetite	1.61	0.91	0.39	0.00	5.13	£615.76

PPE= Palmar-plantar erythrodysaesthesia
Source: CS, extracted from Table B.3.48 and Table B.3.49

5.2.8 Resources and costs

Drug costs

Confidential Commercial Access Agreement (CAA) discounts are in place for avelumab and axitinib when the drugs are given as a combination (CS, Table B.1.2). Non-confidential Patient Access Scheme (PAS) discounts are available for sunitinib (the NHS incurs no cost for the first course) and pazopanib (12.5%). Confidential PAS discounts are also available for tivozanib and cabozantinib. These discounts are not known to the company. After applying the relevant discounts, the cost of each drug was then multiplied by its corresponding relative dose intensity (RDI) to account for wastage. The unit costs of the intervention and comparator treatments are shown in Table 28 and administration costs are shown in Table 29.

Table 28 Unit cost of the intervention and comparators

Drug	Drug form	Available unit amounts	Units in packet	List price	Relative dose intensity	Discounted price
Avelumab	Vial	200mg	1	£768.00	86.8%	[redacted]
Axitinib	Tablet	1mg	56	£703.40	84.2%	[redacted]
		3mg	56	£2,110.20		[redacted]
		5mg	56	£3,517.00		[redacted]
		7mg	56	£4,923.80		[redacted]
Pazopanib	Tablet	200mg	30	£560.50	81.1%	£490.44
		400mg	30	£1,121.00		£980.88
Sunitinib	Tablet	12.5mg	28	£784.70	81.1%	First 4-week cycle provided free of charge
		25mg	28	£1,569.40		
		50mg	28	£3,138.80		
Tivozanib	Tablet	1.34mg	21	£2,052.00	94.0%	Unknown
Cabozantinib	Tablet	20mg	84	£4,800.00	84.0%	Unknown
		80mg	28	£4,800.00		

mg=milligram
Source: CS, Table B.3.45

Table 29 Drug administration costs

Treatment	Administration cost		Administration type	Source
	First cycle	Subsequent cycles		
Avelumab	£174.00	£174.00	Intravenous (Simple)	NHS reference costs 2017/18 - Deliver Simple Parenteral Chemotherapy at First Attendance. Code SB13Z Outpatient[97]
Axitinib (in combination)	£9.60	£9.60	Oral (combination)	PSSRU 2018. Cost of 12 minutes pharmacist time (hospital-based staff: radiographer band 6)[99]
Sunitinib	£163.00	£9.60	Oral monotherapy	First cycle: NHS reference costs 2017/18 - Deliver exclusively oral chemotherapy. Code SB11Z Day and night[97] Subsequent cycles: PSSRU 2018. Cost of 12 minutes pharmacist time (hospital-based staff: radiographer band 6)[99]
Tivozanib	£163.00	£9.60	Oral monotherapy	
Pazopanib	£163.00	£9.60	Oral monotherapy	
Cabozantinib	£163.00	£9.60	Oral monotherapy	

PSSRU = Personal Social Services Research Unit
Source: CS, Table B.3.46

Subsequent treatment costs

Subsequent therapies received by >10 of people in either treatment arm of the JAVELIN Renal 101 trial were considered for in the economic model. Subsequent therapies received by ≤ 10 people in the JAVELIN Renal 101 trial were proportionally distributed across the included subsequent therapies (i.e. reweighted) as shown in Table 30. Everolimus can be prescribed as monotherapy or in combination with lenvatinib. To estimate the number of subsequent therapies whilst accounting for everolimus as monotherapy or combination therapy, the company assumed that the 405 unique drugs (avelumab+axitinib=134, sunitinib=271) reported in the JAVELIN Renal 101 trial[72] were prescribed as 374 subsequent therapies (avelumab+axitinib=122, sunitinib=252).

Thereafter, the company then explicitly assumed that only people who experienced a PFS event (avelumab+axitinib=180; sunitinib=216) would receive a subsequent therapy. Therefore, the number of subsequent therapies (reweighted) was expressed as a proportion of those who had experienced a PFS event (avelumab+axitinib=67.8% [122/180]; sunitinib=116.4% [252/216]). A noteworthy point is that the actual proportion of people with a PFS event who received at least a subsequent therapy in the JAVELIN Renal 101 trial were 51% (92/180) and 81% (174/216) in the avelumab+axitinib arm and sunitinib arm respectively, but these proportions do not account multiple subsequent therapies. The total cost of each subsequent treatment was obtained by multiplying the proportion of people receiving that treatment (Table 30) by its unit cost and estimated time on treatment. The cost of subsequent therapy was applied as a one-off cost upon progression in the economic model.

Table 30 Distribution of subsequent therapies and associated one-off cost used in the economic model

Subsequent therapy	Number of subsequent therapies received by >10 people		Reweighted number of subsequent therapies		Proportion of patients in the PD health states receiving subsequent therapy		Calculated unit cost
	Avelumab +axitinib	Sunitinib	Avelumab +axitinib	Sunitinib	Avelumab +axitinib	Sunitinib	
Cabozantinib	42	28	45.8	34.2	25.4% (45.8/180)	15.8% (34.2/216)	£39,883
Axitinib	15	17	16.3	20.8	9.1% (16.3/180)	9.6% (20.8/216)	[redacted]
Sunitinib	15	23	16.3	28.1	9.1% (16.3/180)	13.0% (28.1/216)	£13,084
Nivolumab	14	107	15.3	130.6	8.5% (15.3/180)	60.5% (130.6/216)	£63,367
Lenvatinib + everolimus: lenvatinib	11	16	12.0	19.5	6.7% (12.0/180)	9.0% (19.5/216)	£32,168
Lenvatinib + everolimus: everolimus	11	16	12.0	19.5			
Pazopanib	7	12	7.6	14.6	4.2% (7.6/180)	6.8% (14.6/216)	£22,958
Everolimus monotherapy	8	3	8.7	3.7	4.9% (8.7/180)	1.7% (3.7/216)	£15,069
Total number of drugs	**123**	**234**	**134**	**271**	**67.8% (122/180)**	**116.4% (251.5/216)**	
Total number of therapies	**112**	**222**	**122**	**251.5**			

PD=progressed disease
Source: CS, extracted from Table B.3.50 and Table B.3.53

Resource use by health state

In addition to drug costs, patients in the PF and PD health states are modelled to incur costs of £19.31 and £101.14 per week, respectively, for routine care (Table 31). Full details of the health resource use estimates in the economic model are provided in the CS, Section B.3.5.

Table 31 Weekly resource use costs used in the company model

Resource use	Unit cost	HRG code/Source	Usage per week	
			PF health state	PD health state
GP visit	£121.94	PSSRU (2018)	0.25	0.25
CT scan	£81.31	NHS Ref Cost (2017/18): RD27Z	0.08	0.00
Blood test	£110.23	NHS Ref Cost (2017/18): DAPS05	0.25	0.00
Specialist community nurse visit	£104.17	PSSRU (2015)	0.00	0.38
Pain medication	£95.52	BNF price morphine	0.00	0.25
Total cost per week			£19.31	£101.14

BNF=British national formulary; CT=computed tomography; GP=general practitioner; HRG=health care resource group; PD=progressed disease; PF=progression-free; NHS Ref Cost=NHS Reference Cost
Source: CS, Table B.3.47

Other costs

In line with administration details documented in the avelumab SmPC,[100] premedication costs (with an antihistamine [£0.34] and with paracetamol [£0.01]) are applied in the model prior to the first four infusions of avelumab. The company also applied a one-off, end of life/terminal care cost to account for palliative/terminal care costs. This cost (£6,351.36[101]) was applied as patients entered the death health state.

5.2.9 Cost effectiveness results

Base case results

Table 32 and Table 33 show the pairwise base case incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of treatment with avelumab+axitinib versus sunitinib and pazopanib and versus tivozanib for the all risk status population. The cost effectiveness results for the comparison of avelumab+axitinib versus cabozantinib for the IMDC intermediate/poor risk status population are shown in Table 34.

Table 32 Base case pairwise incremental cost effectiveness results (all risk status population)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Cost	LYG	QALYs	
Avelumab+axitinib*	[redacted]	[redacted]	[redacted]				
Sunitinib⌂	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,242
Pazopanib⌂	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,542

CAA=commercial access agreement; ICER=incremental cost effectiveness ratio; LYG=life year gained; PAS=patient access scheme; QALY=quality adjusted life year
* Confidential discounted prices used to estimate the cost of treatment; ⌂=non-confidential discounted prices used to estimate the cost of treatment
Source: CS, Table B.3.57

Table 33 Base case pairwise incremental cost effectiveness results (all risk status population)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Cost	LYG	QALYs	
Avelumab+axitinib*	[redacted]	[redacted]	[redacted]				
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,220

CAA=commercial access agreement; ICER=incremental cost effectiveness ratio; LYG=life year gained; PAS=patient access scheme; QALY=quality adjusted life year
* Confidential discounted prices used to estimate cost of treatment
Source: CS, Table B.3.58

Table 34 Base case pairwise incremental cost effectiveness results (IMDC intermediate/poor risk status population)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained)
				Cost	LYG	QALYs	
Avelumab+axitinib*	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

CAA=commercial access agreement; ICER=incremental cost effectiveness ratio; LYG=life year gained; QALY=quality adjusted life year
* Confidential discounted prices used to estimate cost of treatment
Source: CS, Table B.3.62

5.2.10 Sensitivity analyses

The company presented the sensitivity analyses undertaken for the comparison of treatment with avelumab+axitinib versus sunitinib. Sensitivity analyses for the comparison of treatment with avelumab+axitinib versus pazopanib, tivozanib and cabozantinib were not presented in the CS.

Deterministic sensitivity analyses

For the comparison of treatment with avelumab+axitinib versus sunitinib, results from the company's one-way sensitivity analyses (OWSA) showed that the percentage of RDI applied when calculating the cost of treatment with avelumab, axitinib and the comparators (sunitinib,

pazopanib, tivozanib or cabozantinib) had the greatest impact on the size of the ICER per QALY gained (see Figure 5 to Figure 8).

Figure 5 Tornado diagram showing OWSA results for treatment with avelumab+axitinib versus sunitinib

ICER=incremental cost effectiveness ratio; RDI=relative dose intensity; TA=technology appraisal
Source: CS, Figure B.3.32

Figure 6 Tornado diagram showing OWSA results for treatment with avelumab+axitinib versus pazopanib

ICER=incremental cost effectiveness ratio; RDI=relative dose intensity; TA=technology appraisal
Source: Company model

Figure 7 Tornado diagram showing OWSA results for treatment with avelumab+axitinib versus tivozanib

ICER=incremental cost effectiveness ratio; RDI=relative dose intensity; TA=technology appraisal
Source: Company model

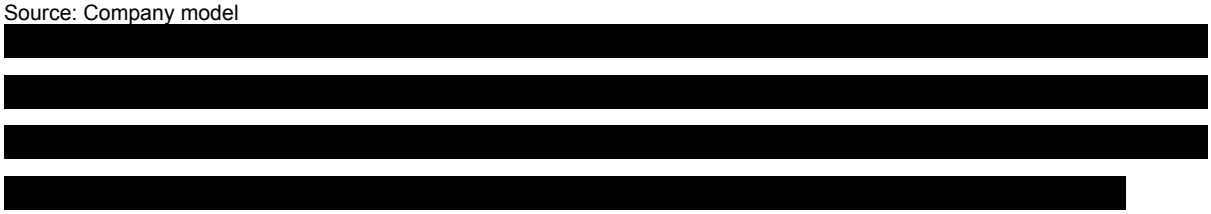


Figure 8 Tornado diagram showing OWSA results for treatment with avelumab+axitinib versus cabozantinib

ICER=incremental cost effectiveness ratio; RDI=relative dose intensity; TA=technology appraisal
Source: Company model

Probabilistic sensitivity analysis

The company varied a large number of input parameters in the probabilistic sensitivity analysis (PSA). The scatter plot (Figure 9) shows the uncertainty around the estimated mean cost per QALY difference for the comparison of treatment with avelumab+axitinib versus sunitinib. The mean probabilistic pairwise ICER of £24,961 per QALY gained for treatment with avelumab+axitinib versus sunitinib was similar to the deterministic pairwise ICER of £26,242

per QALY gained. The cost effectiveness acceptability curve (Figure 10) shows that, at a willingness to pay threshold of £30,000, avelumab+axitinib was cost effective versus sunitinib in 55.5% of PSA iterations (Figure 10).

[redacted]

Figure 9 Scatter plot-cost effectiveness of treatment with avelumab+axitinib versus sunitinib (1,000 iterations)

QALY=quality-adjusted life year; PSA=probabilistic sensitivity analysis
Source: CS, Figure B.3.20

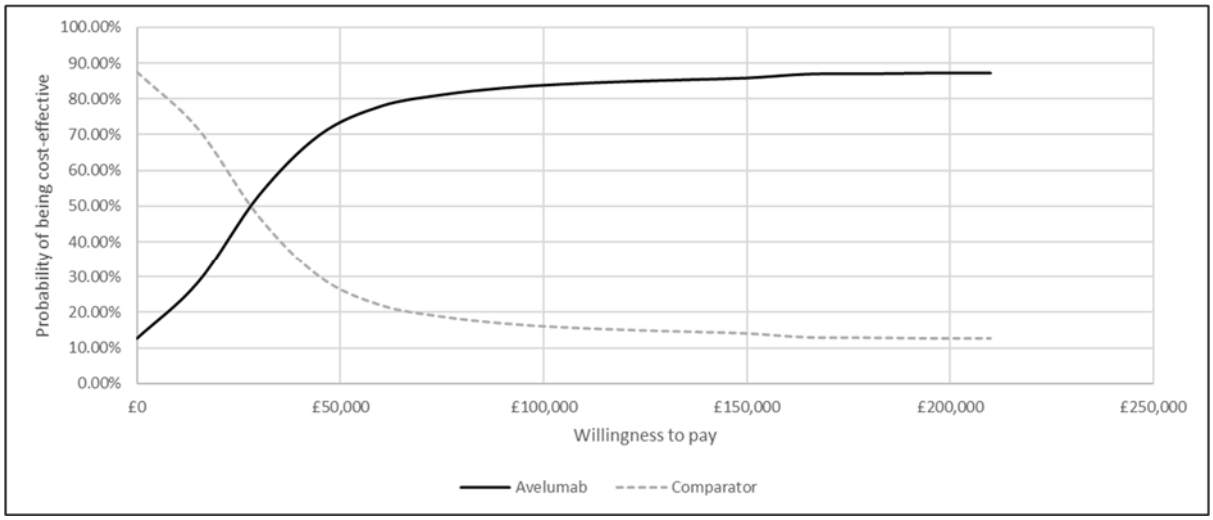


Figure 10 Cost effectiveness acceptability curve of treatment with avelumab+axitinib versus sunitinib

Source: CS, Figure B.3.21

5.2.11 Scenario analyses

Results from all of the company's scenario analyses are provided in the CS (Table B.3.60) and results from the analyses that changed the magnitude of the company's base case ICER per QALY gained by more than £10,000 are shown in Table 35.

Table 35 Scenario analyses: selected results for the comparison of treatment with avelumab+axitinib versus sunitinib

Category	Base case	Scenario description	ICER (£/QALY)
Base case			**£26,242**
	Time horizon 40 years, discounting for costs and QALYs set to 3.5%	Time horizon: 5 years	£101,644
PFS	JAVELIN Renal 101 trial stratified curves used: Gen gamma for avelumab+axitinib; Log-logistic for sunitinib	Avelumab+axitinib: Stratified curves - Weibull (worst survival)	£41,288
		Sunitinib stratified curve as Gen F (best survival), avelumab stratified curve Gen Gamma	£44,369
		Sunitinib stratified curve as Weibull (worst survival), avelumab+axitinib PH NMA, fixed effects	£36,917
OS	JAVELIN Renal 101 trial stratified curves used: Log logistic for avelumab+axitinib and for sunitinib	Avelumab+axitinib: Stratified curves - Exponential (best AIC/BIC)	£41,288
		Sunitinib stratified curve as Gompertz (worst survival), avelumab stratified curve Log-Logistic	£44,369
ToT	JAVELIN Renal 101 trial TTD	Sunitinib - Weibull (highest)	£40,210
Costs	A flat dose of 800mg of avelumab	Weight based dose of avelumab at 10mg/kg	£37,007

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; EoL=end of life; ICER = incremental cost-effectiveness ratio; kg=kilogram; mg=milligram; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazard; QALY=quality-adjusted life year; RDI=relative dose intensity; Tot=time on treatment; TTD=time to treatment discontinuation
Source: CS, extracted from Table B.3.60

5.2.12 Model validation and face validity check

It is stated in the CS that external health economics advisers were consulted on the modelling methodologies that informed this submission and that an independent health economics consultancy reviewed the model for errors, inconsistencies and plausibility of the model inputs. Also, the company highlighted that clinical experts validated the clinical assumptions and provided opinions on the choice of PFS, OS and ToT extrapolation functions.

5.2.13 NICE reference case checklist

Table 36 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE: people with untreated, favourable/intermediate/poor risk status (as per IMDC) aRCC or IMDC intermediate/poor risk status aRCC	Yes
Comparator(s)	As listed in the scope developed by NICE: sunitinib, pazopanib, tivozanib and cabozantinib	Yes
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Data primarily taken from the JAVELIN Renal 101 trial and the NMA conducted by the company	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

aRCC=advanced renal cell carcinoma; EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; IMDC=International Metastatic RCC Database Consortium; NMA=network meta-analysis; PSS=Personal social services; QALY=quality adjusted life year; RCC=renal cell carcinoma
Source: ERG assessment of reference case using NICE checklist

5.3 ERG detailed critique of company economic model

5.3.1 Drummond checklist

Table 37 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Partially	The JAVELIN Renal 101 trial OS data are immature. When the effect of treatment on OS with avelumab+axitinib is compared with sunitinib, results from analysis of the current JAVELIN Renal 101 trial data are not statistically significantly different.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Partially	The company has assumed that treatment with avelumab+axitinib delivers an immunotherapeutic benefit which improves OS. At present, there is no trial evidence to support this assumption. The company has assumed that treatment with avelumab+axitinib will stop at 2 years. There is no evidence base for this assumption as the JAVELIN Renal 101 trial protocol does not include a stopping rule.
Were costs and consequences adjusted for differential timing?	Yes	-
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Partially	The company undertook deterministic, probabilistic and scenario analyses for the comparison of treatment with avelumab+axitinib versus sunitinib, but comparable analyses have not been provided for the comparison of treatment with avelumab+axitinib versus pazopanib, tivozanib or cabozantinib.
Did the presentation and discussion of study results include all issues of concern to users?	Partially	Studies that permitted treatment crossover were included in the NMAs. The impact of treatment crossover should have been discussed in the interpretation of the cost effectiveness results.

NMA=network meta-analysis; OS=overall survival
Source: Drummond and Jefferson (1996)[102] and ERG comment

5.3.2 Overview

The company model is easy to navigate. The ERG is satisfied that accurate algorithms are employed within the model and that parameter values in the model match those described in the CS. The ERG considers that several of the assumptions in the company model relating to the application of a treatment stopping rule, treatment waning effect and modelling OS are not valid. The ERG considers the most important issue is the immaturity of the JAVELIN Renal 101 trial results. The company highlights that the results from this trial are so uncertain for the IMDC intermediate/poor risk status population that definitive conclusions about relative effectiveness (OS) cannot be drawn for this population (CS, Appendix E, p1). The ERG considers that using uncertain clinical effectiveness results as the basis for a cost effectiveness analysis will lead to uncertain cost effectiveness results. The ERG also highlights that approximately 80% of patients recruited to the JAVELIN Renal 101 trial were of IMDC intermediate/poor risk status and, therefore, it is difficult to have confidence in any of the cost effectiveness results generated by the company or the ERG.

5.3.3 ERG revisions to the company base case

Company's treatment stopping rule and waning

In the company model, a treatment stopping rule for avelumab+axitinib has been applied; after 2 years, all patients ceased treatment on avelumab+axitinib even if disease had not progressed. There is no mention of a stopping rule in the protocol for the Early Access to Medicines Scheme for avelumab+axitinib,[103] in the wording of the anticipated EMA licence,[40] or in the JAVELIN Renal 101 trial protocol.[71] The absence of a stopping rule as part of the JAVELIN Renal 101 trial protocol means that evidence to demonstrate the effect of a 2-year stopping rule will not be available from this trial. The ERG, therefore, considers, that the implementation of a stopping rule in the company base case was inappropriate and that the effect should only have been explored in a scenario analysis.

In parallel with applying the stopping rule, the company also modelled a treatment waning effect to account for the impact on PFS and OS of stopping treatment with avelumab+axitinib before progression. Treatment waning was modelled in such a way that mortality and progression hazards of avelumab+axitinib and comparators merged over the period between 2 and 4 years. The company assumed that treatment waning would only affect one third of the patients who started treatment with avelumab+axitinib; the remaining two thirds of patients were assumed to have a lifetime benefit from this treatment. The ERG considers that, in the absence of evidence for a treatment waning effect, modelling such an effect, with or without a stopping rule, as part of the company base case is inappropriate; the effect of treatment waning should only have been explored in a scenario analysis.

For the comparison of treatment with avelumab+axitinib versus sunitinib, removing the stopping rule and associated treatment waning, increases the company base case ICER from £26,242 to £149,872 per QALY gained.

For the comparison of treatment with avelumab+axitinib versus pazopanib, removing the stopping rule and associated treatment waning, increases the company base case ICER from £29,542 to £152,578 per QALY gained.

For the comparison of treatment with avelumab+axitinib versus tivozanib, removing the stopping rule and associated treatment waning, increases the company base case ICER from £9,220 to £73,554 per QALY gained.

For the comparison of treatment with avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population), the consequence of removing the stopping rule and associated treatment waning is that treatment with avelumab+axitinib no longer dominates cabozantinib; the resultant ICER is £172,657 per QALY gained.

ERG approach to modelling survival

Avelumab+axitinib versus sunitinib and versus pazopanib (all risk status population)

The JAVELIN Renal 101 trial was designed to assess the effectiveness of treatment with avelumab+axitinib versus sunitinib. Company model base case results for this comparison show that 93% of the estimated QALY gain arises as a consequence of the modelled OS difference between treatments. However, the OS results from the JAVELIN Renal 101 trial are immature at IA1 (as used in the model) and although the HR result favours treatment with avelumab+axitinib over sunitinib at IA1 (HR=0.78; 95% CI: 0.55 to 1.08), this difference is not statistically significant. Even if IA2 data were used, the data would still be immature (and again, there is no statistically significant difference between arms (IA2: HR=0.80; 95% CI: 0.62 to 1.03).

Until the OS data from the JAVELIN Renal 101 trial are more mature, it will not be possible to determine whether [redacted]. For the purposes of economic modelling, the ERG considers that the correct approach at this stage is to assume equivalent OS. This approach means that model life year and QALY estimates are only dependent on differences between treatments in terms of the effect on PFS. The ERG highlights that IA1 median PFS (by BICR assessment) HR results from the JAVELIN Renal 101 trial show that treatment with avelumab+axitinib is statistically significantly superior to treatment with sunitinib

(HR=0.69; 95% CI: 0.56 to 0.84) as are results at IA2 (HR=0.69; 95% CI: 0.57 to 0.83). The ERG has made no changes to the modelling of PFS in the company model.

The OS K-M data from the two arms of the JAVELIN Renal 101 trial are statistically indistinguishable, so, rather than try to combine the OS K-M data from both arms, the ERG has used the data from the avelumab+axitinib arm to represent the experience of patients receiving avelumab+axitinib and patients receiving sunitinib. As the JAVELIN Renal 101 trial OS data are immature, extrapolation of the OS K-M data beyond the period for which trial data are available is necessary. The ERG highlights that the survival estimates generated using the distributions for OS extrapolation considered by the company vary widely. For example, in the company model, at the 5-year time point, the proportion of patients alive treated with avelumab+axitinib could be [redacted] using a Gompertz function or [redacted] using a log-normal function.

Use of either the log-normal function or the log-logistic function generates clinically implausible OS extrapolations; this is evidenced by the fact that use of these functions within the company model results in the mortality rates for patients treated with avelumab+axitinib falling below those of the general population after 18 years (log-normal) and 20 years (log-logistic) and mortality rates for patients treated with sunitinib falling below those of the general population at 21 years (log-normal and log-logistic). The rates then stay below background mortality for the remainder of the model time horizon. Whilst the company implemented an adjustment to the projections to stop mortality ever falling below that of the general population, the ERG considers that such an approach only masks the fact that the extrapolations are not clinically plausible. Further, the time point at which the projections become implausible cannot be determined; the projections could become implausible at any time point before mortality rates fall below those of the general population.

In view of the immaturity of the JAVELIN Renal 101 trial OS data, there is no way to determine statistically, or clinically, which of the remaining functions considered by the company is the most appropriate. The ERG has used the exponential distribution to extrapolate JAVELIN Renal 101 trial OS K-M data as this function generates the most optimistic cost effectiveness results for the company (after excluding the log-normal and log-logistic functions).

For the comparison of treatment with avelumab+axitinib versus sunitinib, with the OS for sunitinib assumed to be equal to avelumab+axitinib, using the exponential distribution rather than a log-normal distribution, increases the company base case ICER from £26,242 to £158,048 per QALY gained.

The company has assumed that the effectiveness of pazopanib is equivalent to the effectiveness of sunitinib and the ERG considers the company's arguments that support this assumption are reasonable. Previous NICE technology appraisals[19,26] have concluded that sunitinib and pazopanib have equal efficacy. For the comparison of treatment with avelumab+axitinib versus pazopanib, with the OS for pazopanib assumed to be equal to sunitinib and therefore equal to avelumab+axitinib, using an exponential distribution rather than a log-normal distribution increases the base case ICER from £26,242 to £184,021 per QALY gained.

Avelumab+axitinib versus tivozanib (all risk status population)

There is no direct evidence comparing the effectiveness of avelumab+axitinib versus tivozanib. For the comparison of treatment with avelumab+axitinib versus tivozanib, the company has used results from their non-PH NMAs to model the survival of patients treated with avelumab+axitinib, rather than, as used in the comparisons of avelumab+axitinib versus sunitinib and versus pazopanib, data from the JAVELIN Renal 101 trial plus an extrapolation.

This means that the company's modelled representations of OS and PFS for patients treated with avelumab+axitinib differ depending on the comparator. The ERG does not consider this to be an appropriate approach and has, for the comparison of avelumab+axitinib versus tivozanib, used the same representations of OS and PFS for patients receiving avelumab+axitinib as were used when this treatment was compared with sunitinib and pazopanib. The ERG has made no changes to the modelling of PFS in the company model.

The ERG considers that the OS results relating to treatment with tivozanib that are generated by the company's non-PH NMAs are not robust (see Section 4.7) and should not be used to generate cost effectiveness estimates.

In TA512,[19] the Appraisal Committee considered evidence from the TIVO-1 trial[22] which compared the effectiveness of tivozanib versus sorafenib. The Appraisal Committee concluded that the trial evidence showed that, at best, survival between sorafenib and tivozanib was similar. In the NMAs, the two trials that link sorafenib with sunitinib are RCTs[61,62] of a randomised sequential design; this means that these link trials cannot be included in an OS NMA that seeks to compare tivozanib versus sunitinib in the first-line setting only. However, these trials[61,62] show that, in terms of OS, first-line sorafenib followed by second-line sunitinib is not statistically significantly different to first-line sunitinib followed by second-line sorafenib (Eichelberg et al 2015[6] [HR=1.00; CI: 0.77 to 1.30] and Tomita et al 2017[7] [HR=0.93; CI: 0.59 to 1.49]). If the OS HR for tivozanib versus sorafenib is not statistically significant[22] and sorafenib and sunitinib are indistinguishable,[61,62] the ERG considers that the

least biased approach is to assume that the effect of treatment with tivozanib and sunitinib on OS are equivalent.

For the comparison of treatment with avelumab+axitinib versus tivozanib, with the OS for tivozanib assumed to be equal to sunitinib and therefore equivalent to avelumab+axitinib, and the OS and PFS from the JAVELIN Renal 101 trial being used for avelumab+axitinib with OS extrapolated using an exponential distribution, the base case ICER increases from £9,220 to £22,678 per QALY gained.

Avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population)

The company states that the OS data from the JAVELIN Renal 101 trial for this subgroup are immature and definitive conclusions about relative effectiveness cannot be drawn (CS, Appendix E, p1). Nevertheless, the company uses these results in their non-PH NMA for this population. The ERG considers that, if reliable conclusions cannot be drawn from the subgroup OS results, then any cost effectiveness results generated using these data will also be unreliable and should be disregarded. The ERG has, therefore, not presented any revisions that involve amendments to the company's modelled representation of OS.

There is no direct evidence comparing the effectiveness of treatment with avelumab+axitinib versus cabozantinib. Results from the company's non-PH PFS NMA suggest that treatment with cabozantinib leads to better PFS than treatment with avelumab+axitinib. If this result is valid and treatment with avelumab+axitinib is not superior to treatment with cabozantinib in terms of OS, then, as cabozantinib is less costly than avelumab+axitinib, cabozantinib will generate more QALYs at a lower cost and will dominate avelumab+axitinib (for the IMDC intermediate/poor risk status population).

A summary of company's and ERG's approaches to PFS and OS modelling is shown in Table 38 and Table 39.

Table 38 Company and ERG approaches to modelling PFS and OS (avelumab+axitinib)

Intervention	Company approach		ERG approach	
	PFS	OS	PFS	OS
Avelumab+axitinib (versus sunitinib, pazopanib)	*Choice of parametric curve based on assessment of AIC and BIC statistics, visual fit to JAVELIN Renal 101 trial data and clinical advice*		*Data from the JAVELIN Renal 101 trial are immature, AIC and BIC values only show the extent to which distributions reflect trial data, and the immunotherapies are such new drugs that there are no long-term clinical or real world data that can be used to help choose the most appropriate extrapolation. It is difficult to choose between the other distributions*	
				Within the model time horizon, the log-normal and log-logistic distributions generate survival rates that are better than the general population, which is implausible. The ERG has used the exponential distribution to extrapolate JAVELIN Renal 101 trial OS data; this function generates the most optimistic cost effectiveness results for the company
	PFS K-M data/avelumab+axitinib arm of the JAVELIN Renal 101 trial/generalised gamma function	OS K-M data/ avelumab+axitinib arm of the JAVELIN Renal 101 trial/log-logistic function	No change	OS K-M data/ avelumab+axitinib arm of the JAVELIN Renal 101 trial/exponential function
Avelumab+axitinib (versus tivozanib)	*In the absence of direct evidence, the company used NMA results. Uncertainty about the validity of the PH assumption led the company to choose results from the non-PH NMA*		*The effectiveness of the intervention should not be modelled to differ when different comparators are considered. The ERG has, therefore, used single representations of the effect of avelumab+axitinib on PFS and OS*	
	All risk status non-PH NMA (generalised gamma)	All risk status non-PH NMA (generalised gamma)	PFS K-M data/avelumab+axitinib arm of the JAVELIN Renal 101 trial/generalised gamma function	OS K-M data/ avelumab+axitinib arm of the JAVELIN Renal 101 trial/exponential function
Avelumab+axitinib (versus cabozantinib)	*In the absence of direct evidence, the company used NMA results. Uncertainty about the validity of the PH assumption led the company to choose results from the non-PH NMA*		*In the CS (Appendix E, p1) it is stated that, for this population, OS data from the JAVELIN Renal 101 trial are immature and definitive conclusions about relative effectiveness cannot be drawn from these results. The ERG, therefore, considers that these data are too immature for use in any NMA or cost effectiveness analysis and that results from such analyses are unreliable*	
	IMDC intermediate/poor risk status non-PH NMA (generalised gamma)	Intermediate/poor risk status non-PH NMA (log-logistic)	No cost effectiveness results based on remodelling PFS	No cost effectiveness results based on remodelling OS

CS=company submission; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazards

Table 39 Company and ERG approaches to modelling PFS and OS (comparator treatments)

Comparator	Company approach		ERG approach	
	PFS	OS	PFS	OS
Sunitinib	*Choice of parametric curve based on assessment of AIC and BIC statistics, visual fit to JAVELIN Renal 101 trial data and clinical advice*		*Currently available results from the JAVELIN Renal 101 trial show a statistically significant difference in effect on PFS when treatment with avelumab+axitinib is compared with sunitinib*	*Currently available results from the JAVELIN Renal 101 trial show no statistically significant difference in effect on OS when treatment with avelumab+axitinib is compared with sunitinib*
	PFS K-M data/ sunitinib arm of the JAVELIN Renal 101 trial/log-logistic function	OS K-M data/ sunitinib arm of the JAVELIN Renal 101 trial/log-logistic function	No change	OS K-M data/ avelumab+axitinib arm of the JAVELIN Renal 101 trial/exponential function
Pazopanib	*Available evidence suggests that treatment with sunitinib and pazopanib deliver the same survival benefits*			
	Log-logistic function used to extrapolate PFS K-M data from the sunitinib arm of the JAVELIN Renal 101 trial	Log-logistic function used to extrapolate OS K-M data from the sunitinib arm of the JAVELIN Renal 101 trial	No change	OS K-M data/ avelumab+axitinib arm of the JAVELIN Renal 101 trial/exponential function
Tivozanib	*In the absence of direct evidence, the company used NMA results. Uncertainty about the validity of the PH assumption led the company to choose results from the all risk status non-PH NMAs*		*Whilst there is uncertainty around the reliability of the results from the company's all risk status non-PH NMA, this evidence is the best that is available at this time for a comparison of the effectiveness of avelumab+axitinib versus tivozanib*	*There is uncertainty around the reliability of results from the company's all risk status OS non-PH NMA. Based on results from the x trial, the ERG considers that the least biased approach is to assume that treatment with tivozanib and sunitinib deliver the same OS benefit*
	All risk status non-PH NMA (generalised gamma)	All risk status non-PH NMA (generalised gamma)	No change	OS K-M data/ avelumab+axitinib arm of the JAVELIN Renal 101 trial/exponential function
Cabozantinib (IMDC intermediate/poor risk status)	*In the absence of direct evidence, the company used NMA results. Uncertainty about the validity of the PH assumption led the company to choose results from the IMDC intermediate/poor risk status non-PH NMA*		*In the CS (Appendix E, p1) it is stated that, for this population, OS data from the JAVELIN Renal 101 trial are immature and definitive conclusions about relative effectiveness cannot be drawn from these results. The ERG, therefore, considers that these data are too immature for use in any NMA or cost effectiveness analysis and that results from such analyses are unreliable*	
	IMDC intermediate/poor risk status non-PH NMA (generalised gamma)	IMDC intermediate/poor risk status non-PH NMA (log-logistic)	No cost effectiveness results based on remodelling PFS	No cost effectiveness results based on remodelling PFS

CS=company submission; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazards

ERG approach to treatment waning

As stated in Section 5.3.3 the ERG considers that, in the absence of evidence to support a treatment waning effect, the company should only have considered treatment waning in a scenario analysis. Further, the ERG considers that the treatment waning effect should be considered independently of the treatment stopping rule and should apply to all, and not just one third of, patients (as assumed by the company). There is no certainty around whether, or at what point, the mortality and progression hazards of patients treated with avelumab+axitinib and patients treated with the comparators start to converge and equalise. However, results from scenario analyses can indicate the level of impact of treatment waning on relative cost effectiveness.

The ERG disabled the 2-year avelumab+axitinib treatment stopping rule and assumed that **all** patients who had received, or were still receiving, avelumab+axitinib at this time point, would, over the subsequent 2 years, gradually lose their accumulated PFS and OS advantage so that, at 4 years, the PFS and OS hazard rates for patients treated with avelumab+axitinib and those treated with the comparator treatment would converge.

For the comparison of treatment with avelumab+axitinib versus sunitinib, the effect of the ERG's changes was to increase the company base case ICER from £26,242 to £298,409 per QALY gained.

For the comparison of treatment with avelumab+axitinib versus pazopanib, the effect of the ERG's changes was to increase the company base case ICER from £29,542 to £303,784 per QALY gained.

For the comparison of treatment with avelumab+axitinib versus tivozanib, the effect of the ERG's changes was to increase the company base case ICER from £9,220 to £131,167 per QALY gained.

For the comparison of treatment with avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population), the effect of the ERG's changes was to change the company base results which showed avelumab+axitinib being dominant to an ICER of £795,993 per QALY gained.

5.4 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG has implemented the following revisions to the company base case:

- Removed the avelumab+axitinib treatment stopping rule and retained the company's treatment waning effect (R1)
- Removed the company's treatment waning effect and retained the company's treatment stopping rule (R2)
- Set the treatment waning effect to apply to all patients who had been treated with avelumab+axitinib and who were are alive at 2 years and retained the company's treatment stopping rule (R3)
- Used the company's exponential function to extrapolate OS K-M data from the avelumab+axitinib arm and the sunitinib arm of the JAVELIN Renal 101 trial (most optimistic extrapolation for the company excluding log-logistic and log-normal distributions) (R4)
- In the comparison with tivozanib, PFS and OS estimates for avelumab+axitinib were set to be the same as the PFS and OS estimates used for avelumab+axitinib in the comparison with sunitinib and pazopanib (modelled on data from the JAVELIN Renal 101 trial) (R5)
- Set OS estimates for sunitinib, pazopanib and tivozanib to be the same as the OS estimates for avelumab+axitinib (modelled on data from the JAVELIN Renal 101 trial) (R6)

Details of all Microsoft Excel revisions carried out by the ERG to the company's model are presented in Appendix 2 of this ERG report (Section 8.2). A summary of the individual and some combination effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of avelumab+axitinib versus sunitinib, pazopanib, tivozanib and cabozantinib are shown in Table 40, Table 41, Table 42 and Table 43 respectively.

Discounts to the list prices of avelumab, axitinib, sunitinib and pazopanib are known to the company and included in the calculations of the cost effectiveness results presented in this ERG report. Cost effectiveness results calculated using the confidential discounts for tivozanib, cabozantinib and subsequent treatments (nivolumab, lenvatinib and everolimus)

and non-confidential discounts for sunitinib and pazopanib are provided in Confidential Appendix 1.

Table 40 ERG adjustments to company base case: avelumab+axitinib versus sunitinib (all risk status population)

Scenario/ERG amendment	Avelumab+axitinib*			Sunitinib			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£26,242***	
R1. Remove stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,229	+£156,987
R2. Remove treatment waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,000	-£5,242
R3. Apply treatment waning effect to all patients treated with avelumab+axitinib who are alive at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,339	+£17,096
R4. Use exponential function for OS extrapolation of avelumab+axitinib and sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,652	+£7,410
R5. (Tivozanib comparison only) Set avelumab+axitinib PFS and OS to be the same as avelumab+axitinib PFS and OS in the comparison with sunitinib and pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	n/a	n/a
R6. Set OS for sunitinib, pazopanib and tivozanib to be the same as the OS for avelumab+axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£144,040	+£117,798
R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£149,872***	***+£123,630***
R1+R3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£298,409***	***+£272,167***
R1+R2, R4+R6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£1,161,879***	***+£1,135,637***
R1+R3, R4+R6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£1,877,529***	***+£1,851,287***

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year
* Confidential prices applied

Table 41 ERG adjustments to company base case: avelumab+axitinib versus pazopanib (all risk status population)

Scenario/ERG amendment	Avelumab+axitinib*			Pazopanib			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]									***£29,542***	
R1. Remove stopping rule	[redacted]									£186,529	+£156,987
R2. Remove treatment waning effect	[redacted]									£23,706	-£5,836
R3. Apply treatment waning effect to all patients treated with avelumab+axitinib who are alive at 2 years	[redacted]									£48,714	+£19,171
R4. Use exponential function for OS extrapolation of avelumab+axitinib and sunitinib	[redacted]									£38,070	+£8,528
R5. (Tivozanib comparison only) Set avelumab+axitinib PFS and OS to be the same as avelumab+axitinib PFS and OS in the comparison with sunitinib and pazopanib	[redacted]									n/a	n/a
R6. Set OS for sunitinib, pazopanib and tivozanib to be the same as the OS for avelumab+axitinib	[redacted]									£168,525	+£138,983
R1+R2	[redacted]									***£152,578***	***+£123,036***
R1+R3	[redacted]									***£303,784***	***+£274,242***
R1+R2, R4+R6	[redacted]									***£1,184,385***	***+£1,154,843***
R1+R3, R4+R6	[redacted]									***£1,913,048***	***+£1,883,506***

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year
* Confidential prices applied

Table 42 ERG adjustments to company base case: avelumab+axitinib versus tivozanib (all risk status population)

Scenario/ERG amendment	Avelumab+axitinib*			Tivozanib			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]									***£9,220***	
R1. Remove stopping rule	[redacted]									£88,218	+£78,997
R2. Remove treatment waning effect	[redacted]									£8,420	-£800
R3. Apply treatment waning effect to all patients treated with avelumab+axitinib who are alive at 2 years	[redacted]									£11,532	+£2,312
R4. Use exponential function for OS extrapolation of avelumab+axitinib	[redacted]									£10,247	+£1,027
R5. (Tivozanib comparison only) Set avelumab+axitinib PFS and OS to be the same as avelumab+axitinib PFS and OS in the comparison with sunitinib and pazopanib	[redacted]									£8,398	-£822
R6. Set OS for sunitinib, pazopanib and tivozanib to be the same as the OS for avelumab+axitinib	[redacted]									£36,391	+£27,170
R1+R2	[redacted]									**£73,554**	**+£64,334**
R1+R3	[redacted]									**£131,167**	**+£121,947**
R1+R2, R4:R6	[redacted]									**£1,309,868**	**+£1,300,647**
R1+R3, R4:R6	[redacted]									**£2,497,318**	**+£2,488,098**

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year
* Confidential prices applied

Table 43 ERG adjustments to company base case: avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population)

Scenario/ERG amendment	Avelumab+axitinib*			Cabozantinib			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***Dominant***	-
R1. Remove stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£240,668	-
R2. Remove treatment waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9	-
R3. Apply treatment waning effect to all patients treated with avelumab+axitinib who are alive at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	
R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£172,657***	-
R1+R3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£795,993***	-

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
* Confidential prices applied

5.5 Conclusions of the cost effectiveness section

The company's cost effectiveness results show that, at a willingness to pay threshold of £30,000 per QALY gained, treatment with avelumab+axitinib is cost effective versus sunitinib, pazopanib, tivozanib and cabozantinib. This result is driven by how the company has modelled treatment with avelumab+axitinib. The company has implemented a treatment stopping rule and assumed that, for one third of patients alive at 2 years who had received avelumab+axitinib, the benefits of treatment wane, and the survival hazards become equal to the survival hazards of patients who had received the comparator.

In the company base case, the primary driver of QALY gain in the model results from differential representations of OS (for example, 93% of the QALY gain for avelumab+axitinib versus sunitinib arises from an improvement in OS with avelumab+axitinib). However, OS data from the JAVELIN Renal 101 trial do not show a statistically significant improvement in OS for avelumab+axitinib compared to sunitinib. This may be due to data immaturity, which means that OS projections are uncertain which, in turn, leads to a wide range of potential ICERs per QALY gained being generated.

6 END OF LIFE CRITERIA

The company has not presented evidence to support treatment with avelumab+axitinib being considered as a NICE 'End of Life' treatment.

The ERG does not consider that treatment with avelumab+axitinib meets the NICE End of Life criterion that the treatment should be indicated for patients with a short life expectancy, normally less than 12 months. The ERG highlights that results from the company base case show that, for patients receiving current NHS standard of care, mean OS is at least 5 years and median OS is at least 3 years, even for the IMDC intermediate/poor risk status population.

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8 APPENDICES

8.1 Appendix 1: Safety data

8.1.1 Treatment-related adverse events

It is reported in the CS that the profiles of treatment-related AEs (TRAEs) and all-causality adverse events (AEs) were similar in the JAVELIN 101 trial. The Evidence Review Group (ERG) has therefore only focussed on TRAEs in this section.

TRAEs where there was a >5% higher frequency of TRAEs in the avelumab+axitinib arm than the sunitinib arm are summarised in Table 44 of this ERG report (a >5% difference being described by the company as being "clinically relevant" (company submission [CS], Section B.2.10.3.1, p86).

Table 44 TRAEs* occurring at a >5% higher frequency with avelumab+axitinib versus sunitinib in the JAVELIN Renal 101 trial

Adverse event	Avelumab+axitinib (N=434)		Sunitinib (N=439)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Diarrhoea (1)	235 (54.1)	22 (5.1)	196 (44.6)	11 (2.5)
Hypertension (2)	208 (47.9)	106 (24.4)	142 (32.3)	67 (15.3)
Dysphonia	116 (26.7)	2 (0.5)	12 (2.7)	0
Hypothyroidism (1)	105 (24.2)	1 (0.2)	59 (13.4)	1 (0.2)
Chills	62 (14.3)	1 (0.2)	16 (3.6)	0
Alanine aminotransferase increased (1)	57 (13.1)	21 (4.8)	43 (9.8)	9 (2.1)
Dyspnoea	53 (12.2)	6 (1.4)	24 (5.5)	1 (0.2)
Pruritus	53 (12.2)	0	19 (4.3)	0
Infusion-related reaction	52 (12.0)	7 (1.6)	n/a	n/a
Arthralgia	52 (12.0)	1 (0.2)	24 (5.5)	0
Weight decreased	49 (11.3)	7 (1.6)	17 (3.9)	1 (0.2)

* TRAEs n ≥10% patients with any grade or ≥5% patients with Grade ≥3
n/a=not applicable (1) A known adverse drug reaction for both avelumab and axitinib (CS, Section B.2.10.3.1, p87) (2) A known adverse drug reaction for axitinib (CS, Section B.2.10.3.1, p87)
Source: CS, extracted from Section B.2.10.3.1 Table B.2.29 (p91)

TRAEs where there was a >5% higher frequency of TRAEs in the avelumab+axitinib arm than the sunitinib arm included diarrhoea and hypertension which were reported by just over and just under half of all patients, respectively, in the avelumab+axitinib arm. The former is noted by the company to be a known adverse drug reaction for both avelumab and axitinib and the latter a known adverse drug reaction for axitinib (CS, Section B.2.10.3.1, p87). Approximately 5% of patients experienced Grade ≥3 diarrhoea and increased alanine aminotransferase in the avelumab+axitinib arm but a higher proportion still hypertension (24.4%). Hypertension was also the most common Grade ≥3 TRAE in the sunitinib arm in the trial (15.3%). The company have highlighted that the frequencies of diarrhoea, hypertension, hypothyroidism

and increased alanine aminotransferase were all reported at higher frequencies in the avelumab+axitinib arm than previously observed with the single agents (CS, Section B.2.10.4, p99).

TRAEs where there was a >5% higher frequency in the sunitinib arm than the avelumab+axitinib arm are summarised in Table 45 of this ERG report.

Table 45 TRAEs* occurring at a >5% higher frequency with sunitinib versus avelumab+axitinib in the JAVELIN Renal 101 trial

Adverse event	Avelumab+axitinib (N=434)		Sunitinib (N=439)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Nausea	107 (24.7)	3 (0.7)	148 (33.7)	5 (1.1)
Dysgeusia	56 (12.9)	0	141 (32.1)	0
Decreased appetite	86 (19.8)	7 (1.6)	115 (26.2)	4 (0.9)
Neutropenia	6 (1.4)	1 (0.2)	79 (18.0)	34 (7.7)
Thrombocytopenia	12 (2.8)	1 (0.2)	78 (17.8)	24 (5.5)
Dyspepsia	24 (5.5)	0	74 (16.9)	0
Anaemia	9 (2.1)	1 (0.2)	73 (16.6)	22 (5.0)
Vomiting	42 (9.7)	1 (0.2)	68 (15.5)	7 (1.6)
Platelet count decreased	7 (1.6)	0	61 (13.9)	22 (5.0)
Neutrophil count decreased	1 (0.2)	0	44 (10.0)	25 (5.7)

* TRAEs n ≥10% patients with any grade or ≥5% patients with Grade ≥3
Source: CS, extracted from Section B.2.10.3.1 Table B.2.29 (p91)

At least a quarter of patients treated with sunitinib experienced nausea, dysgeusia and decreased appetite. However, Grade ≥3 occurrences of these TRAEs were relatively uncommon (<2%). Grade ≥3 neutropenia was the most common TRAE that occurred more frequently with sunitinib than avelumab+axitinib (7.7% versus 0.2%, respectively) with occurrences of Grade ≥3 thrombocytopenia, anaemia, decreased platelet count and decreased neutrophil count being approximately 5% in the sunitinib arm.

TRAEs that occurred at similar frequencies of patients in both arms of the JAVELIN 101 Renal trial are reported in Table 46 of this ERG report.

Table 46 TRAEs* occurring at a similar frequency in the avelumab+axitinib and sunitinib arms in the JAVELIN Renal 101 trial

Adverse event	Avelumab+axitinib (N=434)		Sunitinib (N=439)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Fatigue	156 (35.9)	13 (3.0)	159 (36.2)	16 (3.6)
Palmar-plantar erythrodysaesthesia	144 (33.2)	25 (5.8)	148 (33.7)	19 (4.3)
Stomatitis	96 (22.1)	8 (1.8)	100 (22.8)	4 (0.9)
Mucosal inflammation	58 (13.4)	5 (1.2)	60 (13.7)	4 (0.9)
Rash	54 (12.4)	2 (0.5)	42 (9.6)	2 (0.5)
Aspartate aminotransferase increased	49 (11.3)	12 (2.8)	48 (10.9)	6 (1.4)
Asthenia	41 (9.4)	5 (1.2)	54 (12.3)	8 (1.8)

* TRAEs n ≥10% patients with any grade or ≥5% patients with Grade ≥3
Source: CS, extracted from Section B.2.10.3.1 Table B.2.29 (p91)

Any grade fatigue and palmar-plantar erythrodysaesthesia occurred in approximately a third of all patients and Grade ≥3 events were reported by between 3% and 6% of patients. The frequencies of five other types of TRAEs was also similar between arms.

8.1.2 Serious adverse events

In the JAVELIN Renal 101 trial, more patients in the avelumab+axitinib arm reported treatment-emergent and treatment-related serious adverse events (SAEs) compared with the sunitinib arm. Only three types of treatment-emergent SAE were reported by ≥2% of patients in either treatment arm: diarrhoea [redacted], abdominal pain [redacted] and anaemia [redacted]. No treatment-related SAEs occurred in ≥2% of patients in either treatment arm of JAVELIN Renal 101.

8.1.3 Fatal adverse events

The frequency of deaths from treatment related AEs were <2% in the avelumab+axitinib arm (1.2%) and the sunitinib arm (0.2%) of the JAVELIN Renal 101 trial. It is reported in the CS (Section B.2.10.3.3, pp92-93) that fatal AEs were predominantly of cardiovascular nature in the avelumab+axitinib arm (see also Section 8.1.4 of this ERG report) and the cause of death in the sunitinib arm was intestinal perforation.

8.1.4 Adverse events of special interest

As highlighted by the company (CS, Section B.2.10.3.7, p98), cardiovascular events have been reported in patients treated with vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine kinase inhibitor (TKI) agents. In JAVELIN Renal 101, cardiac AEs were reported for [redacted] of patients in the avelumab+axitinib arm and [redacted] of patients in the sunitinib arm. Grade ≥3 cardiac AEs were [redacted] and [redacted] respectively (Clinical Study

Report [CSR] of interim analysis 1 [IA1], Section 12.2.2.4.3, p198) and summarised in Table 47 of this ERG report.

Table 47 Summary of Grade ≥3 cardiac AEs reported in >1 patient in the JAVELIN Renal 101 trial

Cardiac event	Avelumab+axitinib (N=434)	Sunitinib (N=439)
Treatment emergent, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Treatment-related, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: CS, Section B.2.10.3.7, p98 and CSR of IA1, Section 12.2.2.4.3

Grade ≥3 cardiac AEs included [redacted] Grade 5 AEs, i.e. fatal AEs: [redacted].

Unsurprisingly, given avelumab' s mechanism of action and mode of administration, immune-related and infusion-related reactions were more common in the avelumab+axitinib arm than in the sunitinib arm of the JAVELIN 101 trial (Table 48 of the ERG report). The ERG notes that it is important to detect immune-related reactions at an early stage as they can become irreversible, severe and life-threatening if inappropriately treated.[104,105]

Table 48 Summary of adverse events of special interest in the JAVELIN Renal 101 trial

Adverse event of special interest	Avelumab+axitinib (N=434)	Sunitinib (N=439)
Immune-related reaction		
- Any grade	166 (38.2)	[redacted]
- Grade ≥3	38 (9.0)	[redacted]
Infusion-related reaction		
- Any grade	121 (27.9)	n/a
- Grade ≥3	7 (1.6)	n/a

Source: CS, Section B.2.10.3.1, p86

In the avelumab+axitinib arm, the most common type of any grade immune-related reactions were those categorised as [redacted], most commonly [redacted] ([redacted]

of all patients in the avelumab+axitinib arm) (CSR of IA1, Section 12.2.2.4.1, p190). Immune-related reactions categorised as [redacted] were the most common Grade ≥3 immune-related reactions [redacted] (CS, Table B.2.34, p97). It is reported in the CSR of IA1 (Section 12.2.2.4.1, pp190-191) that [redacted] of patients treated with avelumab+axitinib had serious immune-related reactions and that [redacted] of patients treated with avelumab+axitinib had fatal immune-related reactions [redacted].

8.1.5 Adverse events associated with dose modification

Dose modifications were not permitted for avelumab although it is reported that [redacted] in the JAVELIN Renal 101 trial did have a dose reduction (following Grade 1 hypersensitivity) (CS, Section B.2.10.3.5, p95). Proportionately [redacted] patients treated with axitinib had dose reductions but proportionately [redacted] had dose interruptions in comparison to patients treated with sunitinib ([redacted] versus [redacted] and [redacted] versus [redacted], respectively) (CS, Table B.2.33). The proportion of patients who had both a dose reduction and interruption was [redacted] with axitinib versus [redacted] with sunitinib.

Reasons given for dose modification provided in the CS have only been provided for the pooled population of patients treated with avelumab+axitinib, not only patients in the JAVELIN Renal 101 trial. In summary:

- The most common reason for axitinib and sunitinib dose reductions was [redacted]. Avelumab dose reductions were not permitted.
- The most common reasons for dose interruptions for patients treated with axitinib and sunitinib were [redacted]. The most frequent AEs leading to interruption of avelumab were [redacted].
- The most frequent AE leading to both interruption and dose reduction was [redacted] for patients treated with axitinib and [redacted] for patients treated with sunitinib.

8.1.6 Treatment discontinuation resulting from adverse events

The proportion of patients who discontinued avelumab+axitinib due to treatment-emergent AEs (TEAEs) [redacted] was higher in the avelumab+axitinib arm than in the sunitinib arm (Table 49 of this ERG report). [redacted]

Table 49 Treatment discontinuations in the JAVELIN Renal 101 trial

Adverse event	Avelumab+axitinib (N=434)	Sunitinib (N=439)
Treatment emergent, n (%)		
- Discontinuation of any study drug	[redacted]	[redacted]
- Discontinuation of all study drugs	33 (7.6)	59 (13.4)
- Discontinuation of avelumab	[redacted]	n/a
- Discontinuation of axitinib	[redacted]	n/a
- Discontinuation of sunitinib	n/a	[redacted]
Treatment-related, n (%)		
- Discontinuation of any study drug	[redacted]	[redacted]
- Discontinuation of all study drugs	15 (3.5)	35 (8.0)
- Discontinuation of avelumab	[redacted]	n/a
- Discontinuation of axitinib	[redacted]	n/a
- Discontinuation of sunitinib	n/a	[redacted]

n/a=not applicable
Source: CS, Section B.2.10.3.4, Table B.2.32

The types of TEAEs leading to discontinuation of any study drug in >2% of patients in either treatment arm were [redacted] Approximately [redacted] of these TEAEs leading to treatment discontinuation were considered to be immune-related reactions in the avelumab+axitinib arm (i.e. [redacted] (CSR of IA1, Section 12.2.2.4.1, p191).

8.1.7 Safety data reported for other comparators

No safety data versus comparators other than sunitinib are presented in the main CS document (Document B). However, there are data for some AEs (hereafter referred to as 'select AEs') for other comparators in Appendix D, Section 2.5.6, Tables B.5.11 and B.5.12. The select AEs are anaemia, decreased appetite, diarrhoea, fatigue, hand-foot syndrome (palmar-plantar erythrodysaesthesia), hypertension, neutropenia, rash, stomatitis/ mucositis, thrombocytopenia. Data are also reported for withdrawal of study drug due to AEs and/or withdrawal due to any cause.

Generally, the ERG notes frequencies of any grade and Grade ≥3 anaemia, neutropenia and thrombocytopenia were lower in the avelumab+axitinib arm of the JAVELIN Renal 101 trial than in the sunitinib arms. Frequencies of anaemia, neutropenia and thrombocytopenia were also lower in the avelumab+axitinib arm of the JAVELIN Renal 101 trial than in any of the other treatment arms of the other trials.[22,27,67] While diarrhoea and hypertension were the most common any grade AEs reported by patients in the avelumab+axitinib arm of the JAVELIN Renal 101 trial, incidences of these AEs reported in the arms of other trials were similar (Table 50 of this ERG report).

Table 50 Comparison of most common TEAEs with avelumab+axitinib and withdrawals due to AEs with other comparators

Adverse event	AVE+AXI (%)	SUN* (%)	PAZ (%)	TIVO (%)	CABO** (%)
Any grade TEAE					
- Diarrhoea	62	23-57	63	22	73
- Hypertension	50	32-45	46	40	67
Grade ≥3 TEAE					
- Diarrhoea	7	3-11	9	2	10
- Hypertension	26	12-21	15	25	28
Withdrawals	[redacted]	[redacted]-22	24	12	21

TEAE=treatment-emergent AE
*Range from 5 different trials, including patients with only IMDC intermediate/poor risk status in the CABOSUN trial
**Only includes patients with IMDC intermediate/poor risk status
Source: Data from the JAVELIN Renal 101 trial, COMPARZ trial,[27] TIVO-1 trial[22] and CABOSUN trial,[67] as reported in the CS, extracted from Appendix D, Section 2.5.6, Tables B.5.11 and B.5.12, except for withdrawal data taken from CS, Table B.2.32

However, when interpreting the data presented by the company (and also that summarised by the ERG above), the ERG highlights the following:

- Frequencies of the select AEs were typically lower in the sunitinib arm of the JAVELIN Renal 101 trial than in the sunitinib arms of either the COMPARZ trial[27] or CABOSUN trial, although the CABOSUN trial[27] did only include patients with IMDC intermediate/poor risk status of aRCC. Most notably, incidence of any grade thrombocytopenia was reported to be 78% and Grade ≥3 thrombocytopenia was reported to be 31% in the sunitinib arm of the COMPARZ trial[27] compared to 19% and 6% respectively in the sunitinib arm of the JAVELIN Renal 101 trial.

- Frequencies of the select AEs experienced by patients treated with pazopanib in the COMPARZ trial[27] were generally lower than reported for those treated with sunitinib in the same trial. However the frequencies of all select any grade AEs in the pazopanib arm of the COMPARZ trial[27] were higher than all equivalent AEs in the sunitinib arm of the JAVELIN Renal 101 trial.

- Frequencies of withdrawals due to AEs were higher in the pazopanib arm of the COMPARZ trial[27] than either arm of the JAVELIN Renal 101 trial, TIVO-1 trial[22] or CABOSUN trial.[67] However, withdrawals due to AEs in the sunitinib arm of the COMPARZ trial[27] and CABOSUN trial[67] were also markedly higher than reported in the sunitinib arm of the JAVELIN Renal 101 trial.

- The data reported by the company also include data for axitinib monotherapy from the trial by Hutson et al 2015.[10] The ERG notes that for any grade anaemia and thrombocytopenia, frequencies reported for avelumab+axitinib in the JAVELIN 101 Renal trial (6% and 4% respectively) were markedly lower than reported for axitinib monotherapy in the trial by Hutson et al 2015[10] (21% and 10% respectively).

The differences across trials highlighted above suggest heterogeneity exists and for this reason, it is difficult to make any comparison of how avelumab+axitinib may compare to pazopanib, tivozinib or cabozantinib, either using statistical methods or by simply naively comparing the data.

8.1.8 Safety conclusions

The ERG notes that the company concludes that in the JAVELIN Renal 101 trial, avelumab+axitinib was generally well tolerated as AEs were typically manageable and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies (CS, Section B.2.10.4, p99). Given the known potential cardiovascular events associated with VEGFR-targeted TKI agents such as axitinib and sunitinib, clinical advice to the ERG is that immune-related reactions are perhaps AEs to be most concerned about with regard to treatment with avelumab+axitinib since immune-related reactions can be irreversible, severe and life-threatening. In the avelumab+axitinib arm of the JAVELIN Renal 101 trial, it is not reported if any immune-related reactions were reversible or irreversible. However, the proportion of patients with severe (Grade ≥3) immune-related reactions was 9.0% and the proportion of patients with fatal immune-related reactions was [redacted].

8.2 Appendix 2: Microsoft Excel revisions made by the ERG to the company's model

All revisions are activated by the company's switch and the ERG's logic switch. ERG's Logic switches are indicated by named range variables Mod_*letter* where *letter* = A or B. A menu of revisions and Mod names appears below and on the 'ERG switches' worksheet in the ERG amended model.

Instructions for modifying the updated company model

Note: It may be necessary to force a full calculation in the model to update array formulas after making amendments: CTRL+ALT+F9

1. Paste the following table into a new sheet named 'ERG switches', and name the switches R5 and R6 with the modification names

Table 51 Menu of ERG revisions and switches for revisions

Revision #	Name	Switch	Description	Instructions
R1	-	Yes	Include stopping rule for avelumab and axitinib (base case= yes)	Use company switch (Yes, No): Controls!F121 Controls!F123
R2	-	Yes	Include waning effect for avelumab and axitinib (base case= yes)	Use company switch (Yes, No) Controls! F125
R3	-	33%	Apply waning to 100% of people receiving avelumab+axitinib	Use company switch
R4	-	Log-Logistic	Select choice of parametric function for extrapolating OS for avelumab+axitinib and comparators	Use company switches (dropdown list)
R5	Mod_B	0	Use the same OS and PFS for avelumab+axitinib regardless of comparator	Use switch (0,1): **for tivozanib only**
R6	Mod_A	0	Remove the OS benefit for avelumab+axitinib versus comparators	Use switch (0,1)

2. To implement the switches appropriately, the ERG has manually separated stopping rule from treatment waning effect (R0) as shown in Table 52
3. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

Table 52 Log for implementing ERG revisions

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R0: Separate waning effect from stopping rule	-	Controls	I125	=IF(c_include_waning="yes",1,0)
		Efficacy Summary	AY15:AY2132	=IF(c_include_waning="No",0,(IF(AS15>p_c_Treat_eff_end+p_c_SR_avel_dur,1*p_c_prop_waning,IF(AW15=0,0,AY14+AW15*(1/SUM($AW$15:$AW$2132))*p_c_prop_waning))))
		Efficacy Summary	BK15:BK2132	=IF(c_include_waning="No",0,(IF(BE15>p_c_Treat_eff_end+p_c_SR_avel_dur,1*p_c_prop_waning,IF(BI15=0,0,BK14+BI15*(1/SUM($BI$15:$BI$2132))*p_c_prop_waning))))
R1 Remove stopping rule for avelumab and axitinib	-	Controls	F121	=" No"
	-	Controls	F123	=" No"
R2 Remove Waning effect	-	Controls	F125	=" No"
R3 Apply waning to 100%	-	Controls	J125	=100%
R4 Use exponential function to extrapolate OS for avelumab+axitinib	-	Controls	F62	="Exponential"
R4 Use exponential function to extrapolate OS for Sunitinib	-	Controls	F69	="Exponential"
R4 Use exponential function to extrapolate OS for tivozanib	-	Controls	F60	="JAVELIN"
	-	Controls	F62	="Exponential"

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R5 Use the same OS and PFS for avelumab+axitinib regardless of comparator	Mod_B	Efficacy Summary	L14:L2132	=IF(Mod_B=0, IF(c_OS_avel_ITC_opt="JAVELIN",'Stratified curves - Avel+axt'!G41,IF(AND(c_OS_ITC_opt="PH ITC",c_PatientGroup="JAVELIN Renal 101 population"),'Stratified curves - Sunitinib'!AS41^'PH ITC'!$G$18,IF(AND(c_OS_ITC_opt="PH ITC",c_PatientGroup="Poor/Intermediate risk"),'Stratified curves - Sunitinib'!AS41^'PH ITC'!$G$35,IF(c_PatientGroup="JAVELIN Renal 101 population",'Non-PH ITC'!EI29,IF(c_PatientGroup="Poor/Intermediate risk",'Non-PH ITC'!FU29,"Error"))))), 'Stratified curves - Avel+axt'!G41)

	Mod_B	Efficacy Summary	M14:M2132	=IF(Mod_B=0,
				IF(Mod_A=0,
				IF(c_PatientGroup=Lists!$M$7,IF(c_OS_ITC_opt="PH ITC",'Stratified curves - Sunitinib'!G41,'Non-PH ITC'!CW29),IF(c_OS_ITC_opt="PH ITC",'Stratified curves - Sunitinib'!G41,'Non-PH ITC'!EV29)),
				L14), IF(Mod_A=0, 'Stratified curves - Sunitinib'!G41,L14))

	Mod_B	Efficacy Summary	G14:G2132	=IF(Mod_B=0, IF(c_PFS_avel_ITC_opt="JAVELIN",'Stratified curves - Avel+axt'!F41,IF(AND(c_PFS_ITC_opt="PH ITC",c_PatientGroup="JAVELIN Renal 101 population"),'Stratified curves - Sunitinib'!V41^'PH ITC'!$G$12,IF(AND(c_PFS_ITC_opt="PH ITC",c_PatientGroup="Poor/Intermediate risk"),'Stratified curves - Sunitinib'!V41^'PH ITC'!$G$30,IF(c_PatientGroup="JAVELIN Renal 101 population",'Non-PH ITC'!AX29,IF(c_PatientGroup="Poor/Intermediate risk",'Non-PH ITC'!CI29))))), 'Stratified curves - Avel+axt'!F41)
	Mod_B -	Efficacy Summary	H14:H2132	=IF(Mod_B=0, IF(c_PatientGroup=Lists!$M$7,IF(c_PFS_ITC_opt="PH ITC",'Stratified curves - Sunitinib'!F41,'Non-PH ITC'!L29),IF(c_PFS_ITC_opt="PH ITC",'Stratified curves - Sunitinib'!F41,'Non-PH ITC'!BJ29)), 'Stratified curves - Sunitinib'!F41)
R6 Remove avelumab+axitinib OS benefit: versus pazopanib	Mod_A	Efficacy Summary	N14:N2132	=IF(Mod_A=0, IF(c_OS_ITC_opt="Non-PH ITC",'Non-PH ITC'!DK29,'Stratified curves - Sunitinib'!AS41^'PH ITC'!$G$20), L14)
R6 Remove avelumab+axitinib OS benefit: versus tivozanib	Mod_A	Efficacy Summary	O14:O2132	=IF(Mod_A=0, IF(c_OS_ITC_opt="Non-PH ITC",'Non-PH ITC'!DW29,'Stratified curves - Sunitinib'!AS41^'PH ITC'!$G$19), L14)
		PF - Tivozanib	N14:N2132	=IF(Mod_A=0,'Efficacy Summary'!AL14,'PF - Avel+axit'!N14)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R6 Remove avelumab+axitinib OS benefit: versus cabozantinib	Mod_A	Efficacy Summary	P14:P2132	= IF(Mod_A=0, IF(c_OS_ITC_opt="PH ITC",'Stratified curves - Sunitinib'!G41^'PH ITC'!G$36,'Non-PH ITC'!FH29), L14)

Note: It may be necessary to force a full calculation in the model to update array formulas after making amendments: CTRL+ALT+F

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]

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, Monday 30 September 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 **Overall Survival assumption**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
R6 exploratory and sensitivity analyses undertaken by the ERG for all risk and intermediate/ poor risk P88: The ERG report states "*…the OS results from the JAVELIN Renal 101 trial are immature at IA1 (as used in the model) and although the HR result favours treatment with avelumab+axitinib over sunitinib at IA1 (HR=0.78; 95% CI: 0.55 to 1.08), this difference is not statistically significant. Even if IA2 data were used, the data would still be immature (and again, there is no statistically significant difference between arms* [redacted]. *Until the OS data from the JAVELIN Renal 101 trial are more mature, it will not be possible to determine whether the lack of statistical significance is due to the immaturity of the OS data or to an absence of difference in comparative effectiveness. For the purposes of economic modelling, the ERG considers that the correct approach at this stage is to assume equivalent OS* [to comparators in the ITT population]." Whilst the immaturity of the OS data in the JAVELIN Renal 101 is acknowledged, the ERG's assumption of equivalent OS between avelumab+axitinib and its comparators in the ITT population ignores standard practice of exploring uncertainty around survival gains which are not yet	The ERG adjustments to company base case for the avelumab+axitinib and sunitinib OS should reflect the survival data reported in the JAVELIN Renal 101 trial.	For balanced representation of the available evidence in line with current practice of exploring uncertainty of clinical data.	This is not a matter of factual accuracy. No change made to the ERG report. The ERG reiterates that the comparator in the JAVELIN 101 trial is sunitinib first line followed by nivolumab second line. The ERG is unaware of any evidence outside of the JAVELIN Renal 101 trial describing the impact on OS of avelumab+axitinib vs sunitinib 1st line, nivolumab 2nd line in patients with RCC. If the parameters in a model have been reliably specified, then PSA offers a framework for quantifying the uncertainty around the magnitude of effect of several model parameters simultaneously. PSA is not designed for incorporating statistically insignificant clinical effectiveness evidence into an economic model.

statistically significant. For example, one common method of reflecting the impact of uncertainty around an immature survival gain is probabilistic sensitivity analysis (PSA), which allows for the full range of uncertainty as expressed in the confidence interval around a hazard ratio (HR). Assuming no survival gain for avelumab+axitinib versus sunitinib in the JAVELIN Renal 101 trial based on IA2 data which shows a [redacted] rather than varying the HR through PSA and evaluating the mean ICERs across the PSA simulations results in overly pessimistic clinical and health economic outcomes and ignores the available clinical data reported in the clinical trial. Furthermore, it ignores expert clinical opinion, recognition of avelumab + axitinib PIM designation and EAMS positive scientific opinion. Finally, IO combinations for first line advanced RCC have been established with evidence of a statistically significant survival gain demonstrated in an IO:TKI combination.			

Issue 2 **Treatment Waning**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
R1 exploratory and sensitivity analyses undertaken by the ERG for all risk and intermediate/ poor risk P94: The ERG report states "*The ERG disabled the 2-year avelumab+axitinib treatment stopping rule and assumed that all patients who had received, or were still receiving, avelumab+axitinib at this time point, would, over the subsequent 2 years, gradually lose their accumulated PFS and OS advantage so that, at 4 years, the PFS and OS hazard rates for patients treated with avelumab+axitinib and those treated with the comparator treatment would converge.*" This exploratory analysis is extremely conservative and unsubstantiated. There is no evidence to support the assumption that the treatment effect would wane in the absence of stopping treatment, nor is there precedent to do so in other IO submissions where, in contrast, a flattening out of the survival curve is typically realised. The implementation of a treatment effect waning in the CS was included specifically to reflect the uncertainty of outcomes for patients who were progression-free at 2 years *and* who would stop treatment according to the assumption of a 2-year stopping rule. This functionality should not be used independently from the application of a stopping rule and there is no rationale to do so.	This assumption should be either supported with evidence or removed from the ERG adjustments to the company base case	Assumptions in economic models should be justified by available evidence or clinical opinion, and this assumption by the ERG is supported by neither.	This is not a matter of factual accuracy. No change made to the ERG report. As stated in the ERG report, waning and a stopping rule should be considered separately rather than together. As neither waning nor a lifetime effect of treatment with avelumab+axitinib on PFS and OS is supported by evidence, the ERG considers it is appropriate to model treatment waning in a scenario analysis.

Issue 3 **Commercial Access Scheme**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P31: The ERG report states: "*Avelumab is only available to NHS patients via a CDF managed access scheme (for the treatment of metastatic Merkel cell carcinoma).*" This is only partially correct. Avelumab is available to NHS patients via a CDF managed access scheme for first-line treatment of metastatic Merkel cell carcinoma only. Avelumab for second-line treatment of metastatic Merkel cell carcinoma is available to NHS patients through baseline commissioning.	It should be stated within the ERG report that: Avelumab is available to NHS patients via a CDF managed access scheme for first-line treatment of metastatic Merkel cell carcinoma. Avelumab is also available to NHS patients through baseline commissioning for second-line treatment of metastatic Merkel cell carcinoma.	To provide the full and correct NICE recommendation (TA 517) and reimbursement status of avelumab for metastatic Merkel cell carcinoma in the NHS.	Thank you for highlighting this error which the ERG has corrected using the company's suggested wording.

Issue 4 **Oversight of clarification provided in the company response to ERG clarification questions**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P51: The ERG report states: "*The ERG assumes that the OS data reported in the Eichelberg et al 2015 publication have been used in the NMAs, this is not stated within the company response to the clarification letter*." However, Table 1 (row corresponding to Eichelberg et al 2015 study) of the company response to ERG clarification question A1 clearly states: "*Published HRs (and KMs) and associated variability for OS and 1L progression-free survival incorporated into the ITCs.*" The ERG does not need to assume that OS data reported in the Eichelberg *et al* 2015 publication has been used in the NMA's given that it has been clearly stated that Eichelberg 2015 is the source of OS data.	OS data reported in the Eichelberg *et al* 2015 publication have been used in the NMA as stated in the company's response to the ERGs clarification questions.	The ERG report has overlooked information submitted within the response to their clarification questions.	The ERG was confused by the company's clarification response as it is also stated in Table 1 that OS data are NR (not reported). Hence the ERG's uncertainty regarding the source of the OS data used within the NMAs for this study. Thank you for clarifiying the source of the OS data used within the NMAs for the Eichelberg et al 2015 study. The ERG has therefore removed the following bullet point from page 51 (and the same text from footnote d of Table 12) of the ERG report *The ERG assumes that the OS data reported in the Eichelberg et al 2015 publication[61] have been used in the NMAs, this is not stated within the company response to the clarification letter.*

Issue 5 **Clarification to data from TA512 used in the NMAs**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P51: The ERG report states "*For the TIVO-1 trial, the company states in response to question A1 of the clarification letter that OS data from NICE TA512 was incorporated into its NMAs. However, the ERG is unsure whether OS data for the previously untreated population or for the whole population has been included in the NMAs (and whether the OS data adjusted for treatment crossover or unadjusted OS data were used).*" The company acknowledges the ambiguity of this point and wishes to clarify that the core ITCs used data unadjusted for crossover as follows: PH ITC: From p23 (slide 21) of the TA512 submission documents 'Treatment-naive subgroup, unadjusted for crossover, July 2013 data cut' https://www.nice.org.uk/guidance/ta512/documents/committee-papers Non-PH ITC: The KM presented on page 377 ('Figure 34 OS analysis for treatment-naïve population') for the treatment naïve subgroup Crossover-adjusted data were considered in ITC scenarios but were not presented in the model.	The proposed amendment would reflect the aforementioned data sources.	To more accurately report the ITC data sources.	Thank you for providing clarification of the source of the OS data used within the NMAs for the TIVO-1 trial. The ERG has therefore removed the following bullet point from page 51 (and the same text from footnote d of Table 12) of the ERG report: *"For the TIVO-1 trial,[22] the company states in response to question A1 of the clarification letter that OS data from NICE TA512[19] was incorporated into its NMAs. However, the ERG is unsure whether OS data for the previously untreated population or for the whole population has been included in the NMAs (and whether the OS data adjusted for treatment crossover or unadjusted OS data were used). "* The ERG has clarified within footnote b of Table 12 of the ERG report that: *"…OS data for the previously untreated subgroup, unadjusted for treatment cross-over from NICE TA512[19] was incorporated into its NMAs"*

Issue 6 Emphasis on the survival expectations for sunitinib in the CABOSUN trial survival as reflective of outcomes for patients with intermediate/poor risk

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P53: The ERG report states: *"In the CABOSUN trial, median PFS and OS were lower in the sunitinib arm compared to the sunitinib arms of the JAVELIN Renal 101 trial (median PFS 5.3 months and median OS 21.2 months); the ERG considers that this reflects survival expectations for the recruited population (IMDC intermediate/poor risk status and the only trial which recruited >1% of participants with ECOG PS 2 [13%])."* The ERG ignores the larger Checkmate 214 trial mentioned on p167 of the CS and referenced within NICE TA542 of cabozantinib in 1L aRCC. By doing so, it fails to compare the baseline characteristics of the CABOSUN trial population to those of the Checkmate 214 trial, which do not support the statement that the outcomes observed in CABOSUN reflect survival expectations for the IMDC intermediate/poor risk status patients: Whilst the proportion of patients with ECOG PS2 is not reported in the Checkmate 214 trial, a similar proportion of patients in the sunitinib arm (21% of n = 422) were classified as poor-risk status, as compared with 19.2% (of n=78) of patients classified as poor-risk in the Phase 2 CABOSUN trial. In the sunitinib arm of the Checkmate 214 trial, median PFS was 8.4 months and median OS 26.0 months.	The ERG report should acknowledge the full range evidence available to assess the generalisability of the performance of the sunitinib arm in the CABOSUN trial, as cited in the CS and previous NICE technology appraisals in aRCC. The statement "the ERG considers that this reflects survival expectations for the recruited population" should be amended to recognise the underperformance of the sunitinib in the CABOSUN trial compared to recent larger trials in the IMDC intermediate/poor risk	For balanced representation of the available evidence, which highlights the CABOSUN trial as a source of uncertainty in the subgroup analysis of the intermediate and poor-risk population.	The ERG is aware of the CheckMate 214 trial and that the median PFS reported for sunitinib in this trial was higher than the median PFS reported in the sunitinib arm of the CABOSUN trial. In the ERG report, the ERG observed that the median PFS was lower in the CABOSUN trial than the median PFS in the JAVELIN Renal 101 trial and highlighted that, unlike the JAVELIN Renal 101 trial, the CABOSUN trial **only** included patients with intermediate/poor status and also, unlike the JAVELIN Renal 101 trial, included 13% of patients with ECOG PS 2. However, the ERG should have stated: *"the ERG considers that this **may** reflect survival expectations for the recruited population"* The ERG has therefore amended the text accordingly.

In the sunitinib arm of the CABOSUN trial, median PFS was 5.3 months and median OS 21.2 months. In light of this evidence and in addition to the outcomes in the intermediate and poor-risk subpopulation in JAVELIN Renal 101 cited on p167 of the CS, it is clear that the sunitinib arm of the CABOSUN has underperformed in terms of PFS and OS compared to larger trials in the same population.	population.		

Issue 7 **Clarification to PFS data included within the updated PH NMA**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P51: The ERG report states: "*For the Hutson et al 2013 trial, the company included different PFS data within the updated PH NMA provided in response to question A1 of the clarification letter (median PFS axitinib=11.1 months; sorafenib=7.4 months; HR=0.77 [95% CI 0.57 to 1.04]) which the ERG has identified as being published within an abstract of updated OS data published in 2015.74 However, the ERG is unclear why these PFS data differ from the PFS data reported in papers published earlier (2013) and later (2017) which are identical (median PFS axitinib=10.1 months; sorafenib=6.5 months; HR=0.77 [95% CI 0.56 to 1.05])*." Table 2 of the company response to ERG clarification indicates that the updated PFS data used to calculate updated HR's reflected independent review PFS. The previous PFS estimate reflected investigator-assessed PFS, which was not explicitly stated in the company response to ERG clarification questions.	The updated PFS estimate from Hutson et al 2013 should be described as detailed in Table 2 of the company response to ERG clarification questions.	To reflect the information included within the company response to ERG clarification question.	Thank you for providing clarification of the source of the reason for the difference in the PFS data for the Hutson et al 2013 trial. The ERG has removed the following text from page 51 of the ERG report: *"For the Hutson et al 2013 trial,[10] the company included different PFS data within the updated PH NMA provided in response to question A1 of the clarification letter (median PFS axitinib=11.1 months; sorafenib=7.4 months; HR=0.77 [95% CI 0.57 to 1.04]) which the ERG has identified as being published within an abstract of updated OS data published in 2015.[74] However, the ERG is unclear why these PFS data differ from the PFS data reported in papers published earlier (2013)[10] and later (2017)[76] which are identical (median PFS axitinib=10.1 months; sorafenib=6.5 months; HR=0.77 [95% CI 0.56 to 1.05])[10,76]"* The ERG has added the following text to footnote a of Table 12 of the ERG report: *"The company clarified during the factual accuracy check that this PFS data reflects independent review PFS while PFS data*

			reported in papers published earlier (2013)[10] and later (2017)[76] reflects investigator assessed PFS (median PFS axitinib=10.1 months; sorafenib=6.5 months; HR=0.77 [95% CI 0.56 to 1.05])[10,76] "

Issue 8 **Incorrect reflection of the OS benefit for the combination from the non-PH NMA**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P12: The ERG Report states "*Results from the company's non-PHS NMAs found PFS probabilities in the all risk status population to be generally higher for avelumab+axitinib compared to all of the comparators at 1, 2 and 10 years. For OS, a difference favouring avelumab+axitinib was only observed at 10 years.*" Regarding the ERG's statement that the non-PH ITC only showed an OS benefit after 10 years, is untrue. Figure B.2.18 in the CS clear shows a difference in the OS estimate for avelumab+axitinib vs all comparators included in the ITC at all timepoints. Furthermore, Table B.3.22 and B.3.23 reporting OS landmark estimate for tivozanib and avelumab+axitinib, respectively. clearly indicate a survival benefit at the first reported timepoint of 6 months. Tables B.3.18 and B.3.19 further show an OS benefit for avelumab+axitinib vs sunitinib, respectively, at all time points.	The ERG's statement should be revised to accurately reflect the timing of the first observed OS benefit of avelumab+axitinib in the non-PH NMA. "*Results from the company's non-PHS NMAs found PFS and OS probabilities in the all risk status population to be generally higher for avelumab+axitinib compared to all of the comparators at 1, 2 and 10 years.*"	To accurately report the data presented in the CS.	The ERG has amended the sentence on p12 of the ERG report to more accurately reflect the ERG's interpretation of the landmark survival estimates: "*Estimated OS probabilities are similar across all treatments at 1 and 2 years, and a slightly higher OS probability is estimated for avelumab+axitinib compared to all of the comparators at 10 years."*

Issue 9 **Misinterpretation of information provided in the context of subgroup analysis**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P16: The ERG Report states: "*The ERG considers the most important issue is the immaturity of the IA1 JAVELIN Renal 101 trial OS results. The company highlights that the results from this trial are so uncertain for the IMDC intermediate/poor risk status population that definitive conclusions about relative effectiveness (OS) cannot be drawn for this population (CS, Appendix E, p1). The ERG considers that using uncertain clinical effectiveness results as the basis for a cost effectiveness analysis will lead to uncertain cost effectiveness results. The ERG also highlights that approximately 80% of patients recruited to the JAVELIN Renal 101 trial were of IMDC intermediate/poor risk status and, therefore, it is difficult to have confidence in any of the cost effectiveness results generated by the company or the ERG.*" The company notes that the statement *"definitive conclusions about relative effectiveness (OS) cannot be drawn for [the IMDC intermediate/poor risk status] population"* was made in the context of subgroup analysis for OS conducted on trial data, referring to the absence of forest plots presented for OS for the FAS from JAVELIN Renal 101. The company recognises that the data is maturing but does not agree that statement or data used in the context of subgroup analysis should discredit the relative effectiveness data from the clinical trial and in turn the cost-effectiveness results for the IMDC intermediate/ poor risk which make up a significant proportion of the total patient population.	The statement casting doubt on the reliability of the overall OS benefit in JAVELIN Renal 101 linked to the proportion of patients comprising a subgroup which hasn't yet demonstrated a statistically significant OS benefit should be removed.	To more accurately reflect the trial data which has demonstrated a numerical OS benefit at its first two interim analyses.	This ERG has amended the paragraph to say: *The ERG considers the most important issue is the immaturity of the IA1 JAVELIN Renal 101 trial OS results. For the IMDC intermediate/poor risk status population, the data are so uncertain that the company considers that definitive conclusions about relative effectiveness (on OS) cannot be drawn for this population (CS, Appendix E, p1). The ERG considers that incorporating uncertain clinical effectiveness evidence into the economic model means that it is difficult to have confidence in any of the cost effectiveness results generated by the company or the ERG.*

Issue 10 **Proportion of patients receiving subsequent treatment**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
P77: The ERG Report states: *"Thereafter, the company then explicitly assumed that only people who experienced a PFS event (avelumab+axitinib=180; sunitinib=216) would receive a subsequent therapy. Therefore, the number of subsequent therapies (reweighted) was expressed as a proportion of those who had experienced a PFS event (avelumab+axitinib=67.8% [122/180]; sunitinib=116.4% [252/216]). A noteworthy point is that the actual proportion of people with a PFS event who received at least a subsequent therapy in the JAVELIN Renal 101 trial were 51% (92/180) and 81% (174/216) in the avelumab+axitinib arm and sunitinib arm respectively"* The 92 and 174 patients who received subsequent treatment following avelumab + axitinib and sunitinib respectively, are quoted from Table 9 in the CSR report. The figures reflected in Table 9 of the CSR are not based on patients that have had a PFS event but applies to any patient who received a subsequent treatment. Some patients in the trial who received subsequent therapy before a PFS event (28 instances for avelumab and 55 in the sunitinib arm). These figures were adjusted in the company submission to account for these instances and therefore explains the difference in proportions of patients who received subsequent therapy.	No amendment needed other than a recognition of this clarification of how the proportions of patients receiving subsequent treatment was calculated.	The proportion of patients receiving subsequent treatment stated in the ERG report does not accurately reflect the clinical data from JAVELIN Renal 101 and excludes patients who received subsequent treatment prior to progression.	No changes made to the ERG report.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

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:

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	Amerah Amin
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Merck**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with sunitinib?	The company acknowledges the feedback in the Technical Engagement report regarding the immaturity of the overall survival data - 25.8% and 44.4% of the 535 deaths required for final OS analysis (Interim analysis 1 (IA1) and Interim analysis 2 (IA2), respectively). As the data approaches median OS, the company would like to draw the committee towards the strength of the clinical effectiveness data demonstrated so far. Table B.2.17 Summary of OS (FAS; IA2) from the company submission (CS) is reproduced below. The figures in the table shows consistently higher OS for avelumab+axitinib at each time point from 6 to 30 months.

Endpoint	**Avelumab+axitinib (N=442)**	**Sunitinib (N=444)**
Median follow-up time (95% CI), months	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]
Median OS (95% CI), months	NE ([redacted], NE)	NE ([redacted], NE)
HR (95% CI)	[redacted]	
One-sided p-value	[redacted]	
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]

Abbreviations: CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA2 = second interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; OS = overall survival

The JAVELIN Renal 101 data from IA1 also shows a doubling of the Objective Response Rate (ORR) in the avelumab+axitinib arm compared with sunitinib (51.4% and 25.7%, respectively) resulting in a clinically meaningful and statistically significant median PFS improvement of 5.4 months (HR=0.69; 95% CI: 0.56, 0.84). These results remain consistent in IA2 data with even more precision and certainty, demonstrated by a narrowing of the 95% confidence intervals.

At the time of median study follow-up (11.4 months for IA1 and [redacted] months for IA2) avelumab+axitinib is showing a survival advantage with a HR of [redacted] (95% CI: [redacted] to [redacted]) to [redacted] (95% CI: [redacted] to [redacted]) for IA1 and IA2, respectively. The additional 7.8 months of follow-up data has led to a narrowing of the confidence intervals around the OS hazard ratio (HR) trending towards significance (with the upper confidence interval (CI) very close to 1.0).

The data so far (which has resonated well with clinicians both at an advisory board in March and October 2019 as well as well as-to-one discussions with UK oncologists) offers a promising indication of a meaningful OS benefit for avelumab+axitinib as data matures.

The alternative to accepting that the trend is evidence of an OS benefit is to assume that the addition of avelumab, an immune-oncology (IO) drug, has no added benefit to tyrosine kinase inhibitor (TKI) monotherapy. This is inconsistent with previous NICE appraisals which have recognised the overall survival benefit of an IO in the second line (2L) advanced renal cell carcinoma (aRCC) setting[1] and more recently an IO combination in the 1L setting.[2] The very foundation of this acceptance recognises that such drugs are efficacious in the treatment of renal cancer and therefore failure to acknowledge this would be paradoxical.

Importantly, the Company wishes to highlight that the trial results that were utilised in the base case analysis had not been adjusted for the confounding effects of the imbalance in subsequent anti-cancer treatments between trial arms. The underestimation of relative OS benefit that results

	in ITT analyses in these scenarios is already well described and the consequences of adjusting for this bias have been rehearsed in several prior NICE appraisals. Data from the Systematic Anti-Cancer Therapy (SACT) database (from January 2013 to March 2018) has shown that only [redacted]% of patients are treated beyond the first-line setting.[3] Among these patients, [redacted]% are treated with an IO in second line, [redacted]% in third line and [redacted]% in fourth line or higher. Overall, [redacted]% of patients are treated with subsequent IO therapy, the majority of which are treated with nivolumab. There were high rates of programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors use in 2L among patients in the sunitinib arm of JAVELIN Renal 101. This contributed to higher survival outcomes in this arm than the historic benchmark in England. Fewer patients in the avelumab+axitinib arm than in the sunitinib arm received subsequent anti-cancer therapy; [redacted] ([redacted]%) patients compared with [redacted] ([redacted]%) patients, respectively. A total of [redacted] ([redacted]%) patients in the avelumab+axitinib arm were treated with any subsequent PD-1 or PD-L1 inhibitor compared with [redacted] ([redacted]%) patients in the sunitinib arm. Nivolumab was the most commonly administered subsequent PD-1 inhibitor in both arms; [redacted] ([redacted]%) patients in the avelumab+axitinib arm and [redacted] ([redacted]%) patients in the sunitinib arm, respectively. The Company recognises that nivolumab is a recommended 2L therapy in the UK, however, the proportion of sunitinib-treated patients receiving PD-1/PD-L1 inhibitors reported in the JAVELIN Renal 101 trial is higher than in UK clinical practice and would therefore overestimate survival for patients treated with the sunitinib arm clinical pathway. The Public Health England data therefore suggests that survival of sunitinib treated patients from the JAVELIN Renal 101 trial is greater than that observed in real practice. A rank preserving structural failure time (RPSFT) analysis has therefore been undertaken to explore the impact of imbalance between arms in subsequent therapy use on OS. Rank preserving structural failure time models (RPSFTM) can be used to adjust for the contribution of 2L treatment to OS. Traditionally, the RPSFTM method is used to adjust for the confounding effects of crossover within the trial (i.e. patients in the comparator arm crossing over to the experimental treatment upon progression) and when used in this way assumes that post-progression anti-cancer

	therapies, other than those permitted by treatment crossover, represent routine clinical practice. However, the JAVELIN Renal 101 study did not permit study crossover and the application of the RPSFTM in this context balances counter-factual event times (that would be observed if no treatment were received later) between treatment groups. RPSFTM results can be thought of as an estimate of the expected results under ideal conditions (i.e. what we predict would have happened if we had double-blinded study in which the subsequent PD-1/PD-L1 use was similar for both the avelumab+axitinib and sunitinib arms). The Company acknowledges that subsequent use of PD-1/PD-L1 is not formal crossover, however, this supporting investigation aims to provide a clean comparison of avelumab+axitinib compared with sunitinib without the influence of subsequent treatment, whilst acknowledging that this adjusts sunitinib downwards rather than adjusting avelumab+axitinib upwards based on higher use of nivolumab in 2L in the sunitinib arm. The RPSFTM was used to adjust for the subsequent use of PD-1 or PD-L1 inhibitors in the sunitinib arm in the JAVELIN Renal 101 trial. Re-censoring was implemented to obtain an unbiased estimate of the treatment effect. Adjusted OS data were assessed using the Cox proportional hazard model, stratified according to the pre-specified stratification variables. Based on the exploratory RPSFT analysis to adjust for subsequent use of any PD-1 or PD-L1 inhibitor in the sunitinib arm, a [redacted]% reduction in the rate of death would have been expected in the overall population (HR [redacted] [bootstrap 95% CI [redacted]–[redacted]]). The RPSFTM-based analysis is not a replacement for clinical trial data. However, by reducing the confounding effect of 2L treatment with PD-1/PD-L1 inhibitors on OS, the RPSFTM allows a less biased assessment of the OS benefit attributable to avelumab+axitinib compared with sunitinib and adds to the clinical evidence towards the plausibility of a survival benefit for avelumab+axitinib.
Should the statistically non-significant overall survival results from the JAVELIN Renal 101 trial be	The Company considers this question closely linked to issue 1 regarding data maturity addressed above.

used to model an overall survival difference between treatments in the economic model?	In addition to the points raised, it would be exceedingly conservative to assume that avelumab+axitinib has no added benefit to sunitinib because the trial data has not yet demonstrated statistical significance. There are prior examples where NICE (including committee B) have accepted the use of immature survival data with non-significant OS HR's for economic modelling. A recent technology appraisal in untreated aRCC (TA542 of cabozantinib) allowed the use of a non-statistically significant overall survival benefit (HR = 0.80, 95% CI 0.53, 1.21) to model an OS difference in favour of cabozantinib in the economic analysis. In this example, cabozantinib had an OS HR with a wider confidence interval than the OS HR for avelumab+axitinib and an upper CI of 1.21 versus 1.08, respectively. Furthermore, in comparison to JAVELIN Renal 101, the CABOSUN trial was a phase 2 trial with a small sample size (n=157). Equivalent survival efficacy for cabozantinib and sunitinib was never assumed by the ERG or the committee and the methods used to model the OS data based on the actual Kaplan-Meier (KM) data reported in the phase 2 trial were accepted. Given the considerable size of the patient population in the Phase 3 JAVELIN Renal 101 trial, borderline significance in the OS HR with a narrowing of the confidence intervals from IA1 to IA2 (demonstrating greater precision in the point estimate), and the superior ORR and median PFS of avelumab+axitinib, modelling an OS benefit using the available data represents an approach which recognises the evidence generated so far and is consistent with recent appraisals in aRCC.
Issue 2: Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with cabozantinib?	Data from the JAVELIN Renal 101 trial has demonstrated efficacy across all three risk groups. The IMDC intermediate- and poor-risk subgroup accounts for a majority ([redacted]%) of the ITT population in the JAVELIN Renal 101 trial and, as such, the Company's response to the questions within Issue 1 are also considered relevant for Issue 2. Looking at the IMDC poor-risk subgroup alone (n=95/886), the OS HR from the IA2 data cut shows a statistically significant survival advantage (HR: [redacted] [95% CI: [redacted], [redacted]) for the combination compared

	to sunitinib monotherapy. It is reasonable to assume that patients with the poorest risk will reach an event at a faster rate than those with more favourable risk profiles. Consequently, the IMDC poor-risk group will typically show the earliest signs of treatment benefit. As data continues to mature, we expect to see a similar trend towards significant survival advantages for avelumab+axitinib across the intermediate and favourable risk groups. The comparative clinical evidence for cabozantinib can help to draw conclusions regarding the OS benefit of avelumab+axitinib compared with cabozantinib. In the phase 2 CABOSUN trial in US patients, the OS KM curves for cabozantinib and sunitinib crossed multiple times before the end of follow-up. Whereas, in the JAVELIN Renal 101 trial the OS KM curves for the intermediate- and poor-risk subgroup for avelumab+axitinib sits consistently above the OS KM curve for sunitinib. Furthermore, the data from the subject trial is based on 343 patients as opposed to 79 patients for cabozantinib in CABOSUN. As described in the response to Issue 1, the CIs around the OS HR in JAVELIN Renal 101 (upper CI of [redacted]), while not yet statistically significant, are narrower than the CI's around the OS HR for cabozantinib (upper CI of 1.21). Considering the comparative data to cabozantinib and the consistent and emerging trend observed between IA1 and IA2 data from JAVELIN Renal 101, the clinical effectiveness of avelumab+axitinib strongly suggests more favourable OS compared with cabozantinib. As the data matures, clinical uncertainty will further diminish.
Should the statistically non-significant overall survival results in the intermediate/poor risk subgroup from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	The Company wishes to highlight that the overall survival results in the IMDC intermediate- and poor-risk subgroup from the JAVELIN Renal 101 trial should be used to model an overall survival difference between treatments in the economic model. As mentioned in the response directly above, the IMDC intermediate- and poor-risk subgroup comprises [redacted]% of the ITT population in the JAVELIN Renal 101 trial. Borderline significance of the survival data and a narrowing of the 95% CI's between IA1 and IA2, reflect a statistically significant OS advantage for the IMDC poor-risk subgroup. As such, the

	favourable OS trend seen in the ITT population can reasonably be applied as representative of this large subgroup. Given the above, the data so far demonstrates that the immaturity of the trial data is the primary cause of 'statistically non-significant overall survival results' rather than a lack of efficacy in the considered treatment combination.
Should overall survival estimates for cabozantinib be assumed to be non-inferior to the overall survival estimates for avelumab+axitinib?	None of the data supports the assumption implicit in this question. Similar to issue 1, this unsubstantiated assumption implies that the addition of avelumab to a TKI has no added survival benefit to TKI monotherapy. Such assumptions not only disregard the trial data but are also inconsistent from a clinical point of view as confirmed through clinical advice received during submission development.
Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust	
Is the company's all-risk status overall survival network meta-analysis sufficiently robust to enable a comparison with tivozanib?	Whilst the Company acknowledges the limitations of the network meta-analysis (NMA) due to differences in the trial design (namely the allowance of cross-over from the comparator arm to the experimental arm) of one study included in the network, the use of the NMA is still considered appropriate. The impact of crossover in TIVO-1 on the results of the NMA was explored in a sensitivity analysis which used crossover-adjusted overall survival outcomes for the TIVO study as included in TA512. The RPSFT adjusted OS results for TIVO-1, based on the ERGs (BMJ-TAG) preferred approach (the stratified log rank test) was incorporated into sensitivity analyses for both the proportional hazards (PH) and non-PH approach.[4] A crossover adjusted HR was estimated for inclusion in the PH ITCs leading to a hazard ratio of 1.29 (95% CrI 0.85, 1,98, fixed effects) for tivozanib versus sunitinib which is similar to the ITT ITC estimate 1.25 (95% CrI 0.84, 1.88 , fixed effects). Similarly, when incorporating the crossover adjusted data into the non-PH ITCs, estimated survival for tivozanib remained relatively consistent with the ITT analyses (Table 1). This is also consistent with

the ERGs observation that the RPSFT adjustment led to a similar benefit for sorafenib as shown in the unadjusted analysis.

Table 1: Estimated tivozanib survival for including ITT or crossover adjusted data

Treatment	Time*	ITT TIVO-1			Using TIVO-1 adjusted for crossover		
		Estimated survival probability (95% CI)			Estimated survival probability (95% CI)		
		Generalised gamma	Log normal	Log logistic	Generalised gamma	Log normal	Log logistic
Tivozanib	1 year	0.82 (0.70, 0.90)	0.83 (0.71, 0.91)	0.81 (0.70, 0.90)	0.81 (0.67, 0.91)	0.82 (0.67, 0.91)	0.80 (0.67, 0.90)
	2 years	0.64 (0.46, 0.76)	0.66 (0.48, 0.78)	0.62 (0.43, 0.75)	0.61 (0.37, 0.76)	0.62 (0.39, 0.77)	0.59 (0.37, 0.74)
	10 years	0.14 (0.01, 0.32)	0.19 (0.04, 0.36)	0.15 (0.04, 0.31)	0.11 (0.00, 0.30)	0.14 (0.01, 0.33)	0.11 (0.02, 0.29)

The company also acknowledge the limitation of incorporating the crossover trials that compare sunitinib to sorafenib (SWITCH and CROSS-J-RCC), however this was an unavoidable issue to allow the relative treatment comparisons to tivozanib. To explore the impact of this limitation, the company conducted a sensitivity analyses which assumed that sorafenib had equivalent survival to sunitinib. This assumption was considered plausible given the similarity in PFS between the treatments when given in the first line setting. In addition, this assumption avoids the use of crossover impacted information. The outcome produced similar results; a HR of 0.63 (95% CrI 0.40, 1.00, fixed effects) for avelumab+axitinib vs tivozanib compared to 0.62 (95% CrI 0.37 to 1.05, fixed effects) when the observed HR information was used for sunitinib vs sorafenib. Given the limited difference in the HR, it seems most appropriate to use the observed relative efficacy of sunitinib and sorafenib which allows for the incorporation of variability around the estimate.

Despite the limitations highlighted in the NICE technical report, the Company considers the results of the NMA sufficiently robust to enable a comparison with tivozanib.

Should tivozanib be considered equivalent to sunitinib in terms of overall survival? Is this seen in clinical practice?	The Company acknowledges the perception among clinicians that tivozanib has similar but not necessarily equivalent efficacy to sunitinib and other recommended TKI's used in the treatment of 1L aRCC. Furthermore, the NICE guidance for TA512 also recognised that tivozanib is likely to be less effective than sunitinib and pazopanib.[4] Given prior NICE consensus and clinical perception, it would be unreasonable to assume that tivozanib is equivalent to sunitinib.
Issue 4: The overall survival and progression-free survival associated with avelumab+axitinib is modelled differently when compared to different comparators	
Should different representations of overall survival and progression-free survival for avelumab+axitinib be used depending on the comparator?	The Company acknowledges the methodological concerns of the NICE technical team around using different representations of overall survival. As such, the Company accepts the use of OS and PFS estimates associated with avelumab+axitinib from JAVELIN Renal 101 trial. The resulting ICER when implementing the trial-based estimates for avelumab+axitinib and the NMA results for tivozanib decreases to £8,398 per QALY from £9,220 per QALY in the base case.
Issue 5: Intervention overall survival extrapolations	
Should the exponential distribution be used to extrapolate JAVELIN Renal 101 trial overall survival data?	The Company disagrees with the approach of using the same extrapolation for both avelumab+axitinib and sunitinib, given the expectation that avelumab+axitinib will produce a durable response and substantially extend OS for a proportion of patients compared with TKI monotherapy. Clinical advice to the Company indicates that the exponential distribution is an inappropriate choice for the modelling of OS for an IO-based treatment given it features a constant mortality hazard over time that does not allow for decreasing mortality hazard at the right-hand tail of the OS curve. The recommendation to use the exponential distribution to extrapolate OS does not appear to have been informed nor validated by clinical experts. The ERG's primary criticism against using the log-logistic distribution (which was the 'best-fitting' extrapolation) was the fact that at 18 years from t=0 it predicted lower mortality rates than seen in the general population. Two key points counter this concern. Firstly, the Company accounted for the comparison with the general population by

	capping mortality rates in the economic model at the level seen in the general population (i.e. they could never fall below). Secondly, the use of the exponential distribution (as recommended by the ERG) does not solve this issue, as projected mortality rates still fall below those of the general population at t=30 years. All consulting oncologists whose feedback was sought for this submission indicated that a flattening of the OS curve could be expected and preferred the use of the log-logistic distribution to extrapolate OS based on visual inspection and the accuracy of PFS and survival predictions. Recommendations from the NICE Decision Support Unit (DSU) highlights clinical validation as one of the three key aspects to testing model fit and plausibility, along with goodness-of-fit measures (AIC and BIC) and visual inspection. All three of these recommendations were considered in the choice of OS extrapolation.
In clinical practice, what proportion of patients would be expected to be alive after 5 and 10 years, if treated with avelumab+axitinib (10%, 20%, 40%, 60%?)?	The Company refers to its company submission (CS) reporting the survival estimates at 5 and 10 years using the log-logistic distribution to extrapolate OS for avelumab+axitinib, which estimated 5-year and 10-year survival to be [redacted]% and [redacted]%, respectively. These survival estimates were validated by UK clinicians.
Issue 6: ***Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect***	
Should a stopping rule be implemented in the model? If so, at what point?	The ERG and NICE technical team have cited the lack of a stopping rule within JAVELIN Renal 101 as the rationale for excluding a stopping rule from the base case. However, to exclude a stopping rule from the economic model is to disregard the emerging clinical recognition that two years is a natural time point when treatment is reassessed. Feedback from clinicians is that responding patients at 2 years are likely to stop treatment prior to progression whilst continuing to benefit. NICE has published guidance in 13 appraisals in the past 3 years for IO treatments including nivolumab (squamous cell carcinoma of the head and neck, squamous and non-squamous non-small-cell lung cancer), pembrolizumab (untreated metastatic squamous non-small-cell lung cancer, untreated, metastatic, non-squamous non-small-cell lung cancer, relapsed or

	refractory classical Hodgkin lymphoma, untreated PD-L1-positive metastatic non-small-cell lung cancer, untreated PD-L1-positive locally advanced or metastatic urothelial cancer, locally advanced or metastatic urothelial carcinoma, ovarian, fallopian tube and peritoneal cancer), and atezolizumab (metastatic non-squamous non-small-cell lung cancer, locally advanced or metastatic urothelial carcinoma) in which a 2-year stopping rule was included as part of the NICE recommendations. Regarding the absence of a stopping rule in the protocol of JAVELIN Renal 101, the Company wishes to highlight recent NICE appraisals where a stopping rule has been accepted by the committee when one was not included in the pivotal clinical trial. Across different IO agents, the following recent NICE appraisals have published guidance contingent on a stopping rule without a fixed treatment duration included in the trial protocol: 1) Nivolumab for previously treated non-squamous non-small-cell lung cancer. [TA484]; 2) Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520]; 3) Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525]; 4) Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [TA490]. In each of the above, a stopping rule was included at 2 years as part of NICE recommendations. As detailed in the CS, the use of a 2-year stopping rule in these appraisals was supported by the Cancer Drugs Fund Clinical Lead who considered it to be acceptable to both patients and clinicians and could be practically applied in NHS practice. Similar advice was sought by the company through an Office of Market Access meeting and an NHSE surgery where a stopping rule was discussed for the subject combination. In both instances the use and practicality of a stopping rule was unanimously affirmed.

	Feedback from consulting oncologists in the UK indicates that they would advise stopping avelumab+axitinib at 2 years for patients still progression-free and believe benefits will continue in most cases.[5] It is unclear the basis by which the ERG can refute the appropriateness of a stopping rule. Given the evidence cited above and stipulated practice, the use of a stopping rule should be considered for the base case analysis.
Should the benefit of treatment be modelled to continue after the treatment has stopped? And if so, should there be any waning of the treatment effect?	It is now well accepted that some patients treated with an IO (and by extension an IO in combination) will receive lasting benefits from their therapy. Previous NICE appraisals have accepted the premise and in the absence of empirical data have accepted assumptions around the proportion of patients to which this applies. In TA428 (pembrolizumab for the treatment of PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy),[6] the assumption of continued treatment benefit for a full 3 years beyond treatment discontinuation at 2 years was deemed clinically plausible by the NICE committee. The ERG's conservative assumption that therapeutic benefits abates when treatment is discontinued is not consistent with our current understanding of the biological and clinical realities of IO therapies. Whilst the Company acknowledges that uncertainty remains regarding the continued treatment benefit beyond stopping, clinical advice suggests that it is reasonable to assume that up to one third of patients will not continue to realise the same long-term benefits beyond cessation of therapy. Following the NICE technical engagement meeting on the 12th November, the Company consulted five additional clinicians on the base case treatment effect waning assumption. During these one-on-one discussions, clinicians were asked to estimate the proportion of patients who would remain progression-free at 12- and 24-months following treatment cessation at 2 years. The clinician responses are presented below in Table 2. Responses form clinicians show that they would expect an estimated 20-25% of patients to progress within 12 months of stopping treatment. This proportion would marginally increase to 30% within 24 months.

Table 2: Survey responses from consulting oncologists in the UK: estimated proportion of patients in PFS and stopping treatment at 2 years who progress at 12- and 24-months

	Estimated proportion progressing by 12 months post stopping	Estimated proportion progressing by 24 months post stopping
Clinician 1 (Bristol)	20%	30%
Clinician 2 (Ipswich)	25%	NR
Clinician 3 (Mount Vernon)	20%	30%
Clinician 4 (Leeds)	5%	10%
Clinician 5 (Royal Free)	60%	80%

In the company's base case, 33% of patients experience gradual treatment effect waning over the first two years following treatment stop, the proportion of patients progression-free at 2 years who stop treatment and are estimated to progress within the next 12 and 24 months in the economic model (Table 3) is aligned with the clinician feedback collected in the survey presented above. At 12 months post stopping, the modelled estimate (22%) is consistent with clinician estimates (20-25%). The estimated proportion of patients who experience a progression event at 24 months in the economic model (38%) is also consistent with clinicians' expectations (~30%), with the model reflecting the more conservative outcome.

Table 3: Estimated proportion of patients in PFS and stopping treatment at 2 years who progress at 12- and 24-months in the economic model

Time point	Proportion in PFS as modelled using base case assumptions on treatment effect waning	Proportion of those patients in PFS who stop treatment at 2 years who later progress
2-years (at treatment stop)	37%	-
12 months post-stop	29%	22%

	<table><tr><td>24 months post-stop</td><td>23%</td><td>38%</td></tr></table> In view of the above, the company's base case assumption around treatment effect waning is consistent with the expectation of clinicians and in the long-term errs on the conservative.
Issue 7: Source of clinical parameters used in the economic model	
Should data from the second interim analysis be used to inform the cost effectiveness model where available?	The ERG has indicated in its report (and reiterated during the NICE technical engagement meeting on 12 November 2019) that the use of data from IA2 in the economic model would not reduce uncertainty surrounding the overall survival benefit of avelumab+axitinib. In principle, the company agrees with this position and would like to highlight some key details. IA2 is not an event-driven analysis, rather it was triggered 6 months following IA1. An economic model based upon IA2 data would necessarily also incorporate IA1 data (i.e. for safety and time-on-treatment) as not all relevant outcomes were reported at IA2. The PFS and OS HRs for IA2 are broadly similar to those of IA1. As the data matures, OS is expected to improve moving from borderline significance to statistical significance. In the meantime, the Company considers that the availability of avelumab+axitinib via the CDF whilst the trial data are maturing is the most appropriate outcome for patients and the NHS.
Issue 8: External validity of the JAVELIN Renal 101 trial results	
Are the trial results generalisable to NHS practice or people with poor performance status?	The baseline characteristics of the patients who entered into the JAVELIN Renal 101 trial reflect clinical practise globally and in the UK. The ratio of males:females and the proportion of patients in each risk group are similar to UK statistics as confirmed at an advisory board by consulting oncologists in the UK.**Error! Bookmark not defined.**

	As part of the clinical study, only patients with a performance status of 0-1 were enrolled however, there is no reason to believe that patients with an ECOG score greater than 1 would not benefit from treatment. This is consistent with the current understanding of the EMA licence. The safety profile for avelumab+axitinib in the JAVELIN Renal 101 was similar to that seen for the individual assets.[10] Furthermore, both avelumab and axitinib have been used in clinical practise in patients with performance status >2 with no additional burden and similar efficacy results.[7] The Company therefore believes that the study results are generalisable to NHS practice.
What is the likely impact on clinical effectiveness of the dose being different in the trial to that which will be used in clinical practice?	The EMA and MHRA (as part of EAMS assessment) assessed the potential change in clinical efficacy with a change in the dosing regimen from weight based to flat dosing and were satisfied that the change was acceptable.[8] Modelling and simulation-based analyses were performed to simulate PK exposure and consequent efficacy and safety responses for the 10 mg/kg Q2W and the flat 800 mg Q2W dosing regimens. Similar predicted PK exposure (with less variability for flat dosing) provided the pivotal evidence for changing to a flat dosing regimen. Additional justification for the flat dose regimen was obtained from the similarity in the predicted efficacy and safety profiles for the flat versus weight-based dosing regimens. These analyses were provided to both the EMA and MHRA. A flat dosing regimen provides more consistent dosing across body weights, minimises drug wastage, facilitate preparation and administration, and reduce pharmacy errors. The use of flat dosing is consistent with NHSE's proposed avelumab dose banding table.[9] Based on the mean weight of patients in the JAVELIN Renal 101 trial (83.06kg), a flat dose of 800mg would be recommended according to the recommended dosing table. For more information on the PK analysis please refer to the EPAR and EAMS scientific opinion.[8]
In clinical practice, what would be the difference in expected treatment effect between those with clear	The EMA has approved the use of avelumab in combination with axitinib for all advanced RCC patients.[10]

and non-clear cell RCC? Is it appropriate to extrapolate the results to non-clear RCC?	The JAVELIN Renal 101 trial included patients with a clear cell component, this means that patients recruited could still have a heterogenous tumour with non-clear cell components. Non-clear cell RCC (nccRCC) is characterised by a mixture of tumour types of different histologies - two major histological subtypes are papillary (10-14%) and chromophobe (5%), they also include collecting duct, translocation carcinoma, medullary carcinoma, and unclassified RCC.[11] Although individually these diverse tumours are relatively rare, the total nccRCC population make up around 20% of the total RCC population. NICE has approved sunitinib for all advanced and/ or metastatic RCC patients (TA169) based on a study looking at patients with clear cell RCC.[12] As avelumab in combination with axitinib has shown clinical benefit over sunitinib in a similar cohort of patients, the Company believes that the combination should also be available to nccRCC patients. Despite the fact that nccRCC effects a relatively small population of patients, it is imperative to provide these patients with treatment options. Based on the above evidence, we cannot say that avelumab+axitnib has no benefit in patients with a non-clear cell component (as they have been accounted for in JAVELIN Renal study and the occurrence of clear cell and non-clear cell is not mutually exclusive).
Issue 9: Consideration for the Cancer drugs Fund	
Will the ongoing data collection in JAVELIN 101 be sufficient to address uncertainties in the effectiveness of avelumab+axitinib?	Yes, by 2023 the JAVELIN Renal 101 study will have 5 years of follow-up data, limiting the clinical uncertainty with respect to the long-term benefits of the avelumab+axitinib combination.
Are any data other than overall survival required to inform the effectiveness of avelumab+axitinib?	The Company welcomes a discussion on the inclusion of additional data during the development of the Data Collection Agreement.
Based on current modelling, does the treatment have a potential to be cost effective?	Yes, aveluamb+axitinib can be cost-effective if the trial data is used to model OS and the committee acknowledge that most patients are not treated with IO combinations until progression.

Errors identified in the NICE technical report to be amended in the updated report

1. Table on page 5 of the technical report incorrectly states the number of patients in the overall population rather than those in the PD-L1 positive population. Avelumab+axitinib N=442 should be N=270 and sunitinib N=444 should be N=290.
2. In the 'Background/ description of issue' section of Issue 5 (below), the 47.5% of patients alive is for the exponential at **5** years. Excluded from the paragraph is **22.5%** which is the OS landmark estimate at 10 years for the exponential.

Issue 5 – Intervention overall survival extrapolations

Background/description of issue	The company used extrapolations (parametric distributions) of the overall survival data observed in the JAVELIN Renal 101 trial, in order to inform the economic model given the lifetime horizon. The selection of parametric distributions was determined using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, visual inspection to assess how closely the chosen parametric curves fitted the JAVELIN Renal 101 trial data, and expert clinical opinion on expected outcomes based on their experience. **The ERG** noted that the survival estimates vary widely depending on the choice of extrapolation curve. For example, in the company model, at the 5-year time point, the proportion of patients alive treated with avelumab+axitinib could be [redacted]% using a Gompertz function or [redacted]% using a log-normal function. It also noted that using either the log-normal function or the log-logistic function generates clinically implausible overall survival extrapolations as it results in mortality rates for patients treated with avelumab+axitinib falling below (that is, surviving longer than) those of the general population. Given the uncertainty of the long-term effectiveness of the intervention, the ERG used the exponential distribution to extrapolate JAVELIN Renal 101 trial OS K-M data, because this function generates the most optimistic cost effectiveness results for the company (**[redacted]% of patients treated with avelumab+axitinib alive after 5 and 10 years**), after excluding the log-normal and log-logistic functions.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

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.

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Thank you for your time.

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- 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	xxxxxxxxxxxxxxxxx
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Kidney Cancer Support Network
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with sunitinib?	One of the most important benefits of treatment for patients with metastatic renal cell carcinoma (mRCC) is survival; patients would like to live a long time with good quality life. In the multicentre, randomised, open-label, phase III JAVELIN Renal 101 trial, the avelumab plus axitinib combination (442 patients) was compared with sunitinib (444 patients) as a first-line treatment in patients with previously untreated advanced clear cell RCC. The primary endpoint was progression-free survival (PFS) among patients with PD-L1–positive tumours. In this patient population, median PFS was significantly longer with avelumab plus axitinib (13.8 months) than with sunitinib (7.2 months). In the overall population, PFS was also significantly longer with avelumab plus axitinib (median, 13.8 months) than with sunitinib (8.4 months). The frequency of adverse events of grade 3 or higher was 71.2% with the combination and 71.5% with sunitinib. However, overall survival (OS) data are still immature, and median OS for both the PD-L1-positive tumours and the overall patient population is yet to be reached. Therefore, no confident conclusions can be drawn regarding OS.
Should the statistically non-significant overall survival results from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	There is almost 12 months of follow-up data available from the JAVELIN Renal 101 trial, and, although not statistically significant, the combination is showing an OS survival benefit over single agent sunitinib. In addition, the data clearly show a statistically significant PFS benefit for the combination over single agent VEGF-TKI therapy. If the PFS data can be extrapolated and used as a surrogate for OS, this could give an indication of the OS benefit expected in this study.

Issue 2: Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with cabozantinib?	Since the OS data from JAVELIN Renal 101 are immature, no confident conclusions can be drawn regarding the OS benefit of avelumab plus axitinib compared with cabozantinib in intermediate-/poor-risk mRCC patients. However, the avelumab plus axitinib combination compares well with nivolumab plus ipilimumab in this group of patients, which makes up about 80% of the clinical trial data and the majority of patients with mRCC. The PFS data could be extrapolated to make a comparison with the survival data for cabozantinib in this group of patients.
Should the statistically non-significant overall survival results in the intermediate/poor risk subgroup from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	
Should overall survival estimates for cabozantinib be assumed to be non-inferior to the overall survival estimates for avelumab+axitinib?	
Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust	
Is the company's all-risk status overall survival network meta-analysis sufficiently robust to enable a comparison with tivozanib?	
Should tivozanib be considered equivalent to sunitinib in terms of overall survival? Is this seen in clinical practice?	In our opinion, tivozanib should not be considered equivalent to sunitinib in terms of overall survival; this has not been proven. Extrapolation of the tivozanib versus sorafenib data showed tivozanib not to be equivalent to sunitinib in terms of OS.
Issue 4: The overall survival and progression-free survival associated with avelumab+axitinib is modelled differently when compared to different comparators	
Should different representations of overall survival and progression-free survival for avelumab+axitinib	

be used depending on the comparator?	
Issue 5: Intervention overall survival extrapolations	
Should the exponential distribution be used to extrapolate JAVELIN Renal 101 trial overall survival data?	
In clinical practice, what proportion of patients would be expected to be alive after 5 and 10 years, if treated with avelumab+axitinib (10%, 20%, 40%, 60%?)?	
Issue 6: Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect	
Should a stopping rule be implemented in the model? If so, at what point?	A stopping rule wasn't incorporated into the JAVELIN Renal 101 clinical trial and there is, therefore, no clinical evidence to support the implementation of a stopping rule in the model. Clinician and patient perspectives are needed to determine a stopping rule, since there are a number of unanswered questions regarding this issue, for example: Will patients stop treatment before 2 years? What is the benefit to patients after 2 years? Will patients continue with treatment until they are unable to tolerate the drugs? Will patients benefit from treatment breaks?
Should the benefit of treatment be modelled to continue after the treatment has stopped? And if so, should there be any waning of the treatment effect?	Again, there is no clinical evidence for this because a stopping rule wasn't incorporated into JAVELIN Renal 101.
Issue 7: Source of clinical parameters used in the economic model	
Should data from the second interim analysis be used to inform the cost effectiveness model where available?	Yes
Issue 8: External validity of the JAVELIN Renal 101 trial results	
Are the trial results generalisable to NHS practice or people with poor performance status?	The trial results are generalisable to NHS clinical practice, but not patients with poor performance

	status.
What is the likely impact on clinical effectiveness of the dose being different in the trial to that which will be used in clinical practice?	Unknown
In clinical practice, what would be the difference in expected treatment effect between those with clear and non-clear cell RCC? Is it appropriate to extrapolate the results to non-clear RCC?	Non-clear cell RCC is a constellation of biologically distinct diseases, which differ in behaviour and treatment. It is, therefore, not appropriate to extrapolate the JAVELIN Renal 101 results to non-clear cell RCC. However, there were some patients with a sarcomatoid element to their clear cell RCC included in JAVELIN Renal 101, and these patients showed a PFS benefit versus sarcomatoid patients on sunitinib.
Issue 9: Consideration for the Cancer drugs Fund	
Will the ongoing data collection in JAVELIN 101 be sufficient to address uncertainties in the effectiveness of avelumab+axitinib?	As the OS data from JAVELIN Renal 101 matures and ongoing data collection from the Early Access to Medicine Scheme (EAMS) continues, we are confident that this will be sufficient to show an OS benefit for mRCC patients on avelumab plus axitinib.
Are any data other than overall survival required to inform the effectiveness of avelumab+axitinib?	More mature OS data are needed.
Based on current modelling, does the treatment have a potential to be cost effective?	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

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- Do not use abbreviations.
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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)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

Questions for engagement

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with sunitinib?	Whilst the OS advantage over sunitinib is not yet statistically significant, there is a trend. Given the mode of action of the combination it is likely that the data is currently too immature to reach significance. This does not mean that it is reasonable or indeed sensible to assume that the axi-avelumab OS is equivalent to all TKI OS. This does not take into account the MoA of immunotherapy for RCC (we know that checkpoint inhibitors are active in the 1st and 2nd line settings for this disease). Also note that the PFS and OS curves for axi-avelumab superimpose with the axi-pembro curves which, with longer follow up have reached statistical significance. It is therefore very unlikely that Axi-Avelumab will have the same OS as single agent TKI therapy.
Should the statistically non-significant overall survival results from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	Yes – see above.
Issue 2: Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with cabozantinib?	No
Should the statistically non-significant overall survival results in the intermediate/poor risk subgroup from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	Yes

Should overall survival estimates for cabozantinib be assumed to be non-inferior to the overall survival estimates for avelumab+axitinib?	Our experts believe there is insufficient data to instruct this analysis. The CaboSun dataset is small.
Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust	
Is the company's all-risk status overall survival network meta-analysis sufficiently robust to enable a comparison with tivozanib?	
Should tivozanib be considered equivalent to sunitinib in terms of overall survival? Is this seen in clinical practice?	Our experts believe that in the absence of head to head data this can only be based upon clinical experience and professional opinion. It is unlikely that there are clinically meaningful differences in activity between sunitinib and tivozanib.
Issue 4: The overall survival and progression-free survival associated with avelumab+axitinib is modelled differently when compared to different comparators	
Should different representations of overall survival and progression-free survival for avelumab+axitinib be used depending on the comparator?	Our experts believe it reasonable to model axi-avelumab against all first line single agent TKIs combined rather than individually. The greatest variation in outcome will not be with which TKI is used first line but on the prognostic category of the patient. Axi-avulemab should be modelled separately vs ipi-nivo.
Issue 5: Intervention overall survival extrapolations	
Should the exponential distribution be used to extrapolate JAVELIN Renal 101 trial overall survival data?	
In clinical practice, what proportion of patients would be expected to be alive after 5 and 10 years, if treated with avelumab+axitinib (10%, 20%, 40%,	Our experts believe that at 5 years 20% of patients will be alive and at 10 years 15%

60%?)?	
Issue 6: ***Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect***	
Should a stopping rule be implemented in the model? If so, at what point?	A stopping rule at 2 years would be reasonable assuming that patients who relapse after stopping would be able to re-access the combination upon relapse.
Should the benefit of treatment be modelled to continue after the treatment has stopped? And if so, should there be any waning of the treatment effect?	Yes. There will be 2 groups of patients, those who never relapse after stopping and those who do. There is no data our experts are aware of to instruct the proportions of these two groups. It would in my opinion be reasonable and conservative to assume a 50:50 split.
Issue 7: Source of clinical parameters used in the economic model	
Should data from the second interim analysis be used to inform the cost effectiveness model where available?	yes
Issue 8: External validity of the JAVELIN Renal 101 trial results	
Are the trial results generalisable to NHS practice or people with poor performance status?	Yes
What is the likely impact on clinical effectiveness of the dose being different in the trial to that which will be used in clinical practice?	No impact. The flat dose will be equally active to the weight adjusted dose. There is abundant precedent with immune checkpoint inhibitors for this.
In clinical practice, what would be the difference in expected treatment effect between those with clear and non-clear cell RCC? Is it appropriate to extrapolate the results to non-clear RCC?	The activity in non-clear cell patients is unknown. Our experts would not assume equivalent activity. This is however an area of significant clinical need. It would be helpful and refreshing if, were there to be a CDF approval for the axi-avelumab combo, that non-clear cell patients were allowed to be recruited and outcomes audited.

Issue 9: Consideration for the Cancer drugs Fund	
Will the ongoing data collection in JAVELIN 101 be sufficient to address uncertainties in the effectiveness of avelumab+axitinib?	Yes.
Are any data other than overall survival required to inform the effectiveness of avelumab+axitinib?	See non-clear answer above.
Based on current modelling, does the treatment have a potential to be cost effective?	Our experts believe the current modelling is highly flawed if it is only based on assumptions of equivalent OS between TKIs and Axi-Avelumab. More realistic modelling would demonstrate potential for cost-effectivenes.

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

ERG critique of the company technical engagement response form

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 129584

Completed 17 December 2019

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

In response to a request from NICE, the ERG has provided a critique of the additional information provided by the company in the company's response to the Technical Engagement report. The company's response and ERG critique are presented below.

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with sunitinib?	The company acknowledges the feedback in the Technical Engagement report regarding the immaturity of the overall survival data - 25.8% and 44.4% of the 535 deaths required for final OS analysis (Interim analysis 1 (IA1) and Interim analysis 2 (IA2), respectively). As the data approaches median OS, the company would like to draw the committee towards the strength of the clinical effectiveness data demonstrated so far. Table B.2.17 Summary of OS (FAS; IA2) from the company submission (CS) is reproduced below. The figures in the table shows consistently higher OS for avelumab+axitinib at each time point from 6 to 30 months.

Endpoint	**Avelumab+axitinib (N=442)**	**Sunitinib (N=444)**
Median follow-up time (95% CI), months	[redacted]	[redacted]
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]
Median OS (95% CI), months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
One-sided p-value	[redacted]	
Probability (95% CI) of being event-free at:		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
Abbreviations: CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IA2 = second interim analysis; n = number of patients in the category; N = number of patients evaluable; NE = not estimable; OS = overall survival		

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
	The JAVELIN Renal 101 data from IA1 also shows a doubling of the Objective Response Rate (ORR) in the avelumab+axitinib arm compared with sunitinib (51.4% and 25.7%, respectively) resulting in a clinically meaningful and statistically significant median PFS improvement of 5.4 months (HR=0.69; 95% CI: 0.56, 0.84). These results remain consistent in IA2 data with even more precision and certainty, demonstrated by a narrowing of the 95% confidence intervals. At the time of median study follow-up (11.4 months for IA1 and 19.3 months for IA2) avelumab+axitinib is showing a survival advantage with a HR of 0.78 (95% CI: 0.55 to 1.08) to 0.80 (95% CI: 0.62 to 1.03) for IA1 and IA2, respectively. The additional 7.8 months of follow-up data has led to a narrowing of the confidence intervals around the OS hazard ratio (HR) trending towards significance (with the upper confidence interval (CI) very close to 1.0). The data so far (which has resonated well with clinicians both at an advisory board in March and October 2019 as well as well as-to-one discussions with UK oncologists) offers a promising indication of a meaningful OS benefit for avelumab+axitinib as data matures. The alternative to accepting that the trend is evidence of an OS benefit is to assume that the addition of avelumab, an immune-oncology (IO) drug, has no added benefit to tyrosine kinase inhibitor (TKI) monotherapy. This is inconsistent with previous NICE appraisals which have recognised the overall survival benefit of an IO in the second line (2L) advanced renal cell carcinoma (aRCC) setting[i] and more recently an IO combination in the 1L setting.[ii] The very foundation of this acceptance recognises that such drugs are efficacious in the treatment of renal cancer and therefore failure to acknowledge this would be paradoxical.
ERG critique	The ERG disagrees with the company. Accepting the 'trend' of OS benefit is not the only alternative to assuming that treatment with avelumab has 'no added benefit to TKI monotherapy.' Another alternative to accepting the 'trend' is to conclude that there is substantial uncertainty around the OS results due to the

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
	immature JAVELIN Renal 101 trial data and to accept, as acknowledged by the company, that as the data mature, clinical uncertainty will further diminish (see also below).
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with sunitinib? [continued]	Importantly, the Company wishes to highlight that the trial results that were utilised in the base case analysis had not been adjusted for the confounding effects of the imbalance in subsequent anti-cancer treatments between trial arms. The underestimation of relative OS benefit that results in ITT analyses in these scenarios is already well described and the consequences of adjusting for this bias have been rehearsed in several prior NICE appraisals. Data from the Systematic Anti-Cancer Therapy (SACT) database (from January 2013 to March 2018) has shown that only [redacted]% of patients are treated beyond the first-line setting.[iii] Among these patients, [redacted]% are treated with an IO in second line, [redacted]% in third line and [redacted]% in fourth line or higher. Overall, [redacted]% of patients are treated with subsequent IO therapy, the majority of which are treated with nivolumab. There were high rates of programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors use in 2L among patients in the sunitinib arm of JAVELIN Renal 101. This contributed to higher survival outcomes in this arm than the historic benchmark in England. Fewer patients in the avelumab+axitinib arm than in the sunitinib arm received subsequent anti-cancer therapy; [redacted] ([redacted]%) patients compared with [redacted] ([redacted]%) patients, respectively. A total of [redacted] ([redacted]%) patients in the avelumab+axitinib arm were treated with any subsequent PD-1 or PD-L1 inhibitor compared with [redacted] ([redacted]%) patients in the sunitinib arm. Nivolumab was the most commonly administered subsequent PD-1 inhibitor in both arms; [redacted] ([redacted]%) patients in the avelumab+axitinib arm and [redacted] ([redacted]%) patients in the sunitinib arm, respectively. The Company recognises that nivolumab is a recommended 2L therapy in the UK, however, the proportion of sunitinib-treated patients receiving PD-1/PD-L1 inhibitors reported in the JAVELIN Renal 101 trial is higher than in UK clinical practice and would therefore overestimate survival for patients treated with the sunitinib arm clinical pathway. The Public Health England data therefore suggests that survival of sunitinib treated patients from the JAVELIN Renal 101 trial is greater than that observed in real practice.

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
	A rank preserving structural failure time (RPSFT) analysis has therefore been undertaken to explore the impact of imbalance between arms in subsequent therapy use on OS. Rank preserving structural failure time models (RPSFTM) can be used to adjust for the contribution of 2L treatment to OS. Traditionally, the RPSFTM method is used to adjust for the confounding effects of crossover within the trial (i.e. patients in the comparator arm crossing over to the experimental treatment upon progression) and when used in this way assumes that post-progression anti-cancer therapies, other than those permitted by treatment crossover, represent routine clinical practice. However, the JAVELIN Renal 101 study did not permit study crossover and the application of the RPSFTM in this context balances counter-factual event times (that would be observed if no treatment were received later) between treatment groups. RPSFTM results can be thought of as an estimate of the expected results under ideal conditions (i.e. what we predict would have happened if we had double-blinded study in which the subsequent PD-1/PD-L1 use was similar for both the avelumab+axitinib and sunitinib arms). The Company acknowledges that subsequent use of PD-1/PD-L1 is not formal crossover, however, this supporting investigation aims to provide a clean comparison of avelumab+axitinib compared with sunitinib without the influence of subsequent treatment, whilst acknowledging that this adjusts sunitinib downwards rather than adjusting avelumab+axitinib upwards based on higher use of nivolumab in 2L in the sunitinib arm. The RPSFTM was used to adjust for the subsequent use of PD-1 or PD-L1 inhibitors in the sunitinib arm in the JAVELIN Renal 101 trial. Re-censoring was implemented to obtain an unbiased estimate of the treatment effect. Adjusted OS data were assessed using the Cox proportional hazard model, stratified according to the pre-specified stratification variables. Based on the exploratory RPSFT analysis to adjust for subsequent use of any PD-1 or PD-L1 inhibitor in the sunitinib arm, a [redacted]% reduction in the rate of death would have been expected in the overall population (HR [redacted] [bootstrap 95% CI [redacted]-[redacted]]).

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
	The RPSFTM-based analysis is not a replacement for clinical trial data. However, by reducing the confounding effect of 2L treatment with PD-1/PD-L1 inhibitors on OS, the RPSFTM allows a less biased assessment of the OS benefit attributable to avelumab+axitinib compared with sunitinib and adds to the clinical evidence towards the plausibility of a survival benefit for avelumab+axitinib.
ERG critique	The methods used by the company to carry out the RPSFTM-based analysis have not been provided. The RPSFTM is an approach that can be used to take into account the effect of treatment switching (i.e., when participants switch from their randomised treatment to the other trial treatment during the trial follow-up). The ERG considers that the RPSFTM should not be used to adjust for the effect of other subsequent therapies (i.e., treatments that were not trial interventions).
Should the statistically non-significant overall survival results from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	The Company considers this question closely linked to issue 1 regarding data maturity addressed above. In addition to the points raised, it would be exceedingly conservative to assume that avelumab+axitinib has no added benefit to sunitinib because the trial data has not yet demonstrated statistical significance. There are prior examples where NICE (including committee B) have accepted the use of immature survival data with non-significant OS HR's for economic modelling. A recent technology appraisal in untreated aRCC (TA542 of cabozantinib) allowed the use of a non-statistically significant overall survival benefit (HR = 0.80, 95% CI 0.53, 1.21) to model an OS difference in favour of cabozantinib in the economic analysis. In this example, cabozantinib had an OS HR with a wider confidence interval than the OS HR for avelumab+axitinib and an upper CI of 1.21 versus 1.08, respectively. Furthermore, in comparison to JAVELIN Renal 101, the CABOSUN trial was a phase 2 trial with a small sample size (n=157). Equivalent survival efficacy for cabozantinib and sunitinib was never assumed by the ERG or the committee and the methods used to model the OS data based on the actual Kaplan-Meier (KM) data reported in the phase 2 trial were accepted.

Issue 1: Immature JAVELIN Renal 101 trial overall survival results in the overall population	
	Given the considerable size of the patient population in the Phase 3 JAVELIN Renal 101 trial, borderline significance in the OS HR with a narrowing of the confidence intervals from IA1 to IA2 (demonstrating greater precision in the point estimate), and the superior ORR and median PFS of avelumab+axitinib, modelling an OS benefit using the available data represents an approach which recognises the evidence generated so far and is consistent with recent appraisals in aRCC.
ERG critique	The ERG agrees that as the data from the JAVELIN Renal 101 trial become more mature, the evidence relating to the effectiveness of treatments on OS will become more robust. Increased data will also allow the uncertainty surrounding long term OS projections to be reduced which, in turn, will reduce the uncertainty around the cost effectiveness of treatment with avelumab+axitinib versus sunitinib.

Issue 2: Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup	
Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with cabozantinib?	Data from the JAVELIN Renal 101 trial has demonstrated efficacy across all three risk groups. The IMDC intermediate- and poor-risk subgroup accounts for a majority ([redacted]%) of the ITT population in the JAVELIN Renal 101 trial and, as such, the Company's response to the questions within Issue 1 are also considered relevant for Issue 2. Looking at the IMDC poor-risk subgroup alone (n=95/886), the OS HR from the IA2 data cut shows a statistically significant survival advantage (HR: [redacted] [95% CI: [redacted], [redacted]) for the combination compared to sunitinib monotherapy. It is reasonable to assume that patients with the poorest risk will reach an event at a faster rate than those with more favourable risk profiles. Consequently, the IMDC poor-risk group will typically show the earliest signs of treatment benefit. As data continues to mature, we expect to see a similar trend towards significant survival advantages for avelumab+axitinib across the intermediate and favourable risk groups.

Issue 2: Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup	
	The comparative clinical evidence for cabozantinib can help to draw conclusions regarding the OS benefit of avelumab+axitinib compared with cabozantinib. In the phase 2 CABOSUN trial in US patients, the OS KM curves for cabozantinib and sunitinib crossed multiple times before the end of follow-up. Whereas, in the JAVELIN Renal 101 trial the OS KM curves for the intermediate- and poor-risk subgroup for avelumab+axitinib sits consistently above the OS KM curve for sunitinib. Furthermore, the data from the subject trial is based on 343 patients as opposed to 79 patients for cabozantinib in CABOSUN. As described in the response to Issue 1, the CIs around the OS HR in JAVELIN Renal 101 (upper CI of [redacted]), while not yet statistically significant, are narrower than the CI's around the OS HR for cabozantinib (upper CI of 1.21). Considering the comparative data to cabozantinib and the consistent and emerging trend observed between IA1 and IA2 data from JAVELIN Renal 101, the clinical effectiveness of avelumab+axitinib strongly suggests more favourable OS compared with cabozantinib. As the data matures, clinical uncertainty will further diminish.
ERG critique	The ERG considers that generalising this result to the IMDC intermediate- and poor-risk group is inappropriate and misleading.
Should the statistically non-significant overall survival results in the intermediate/poor risk subgroup from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?	The Company wishes to highlight that the overall survival results in the IMDC intermediate- and poor-risk subgroup from the JAVELIN Renal 101 trial should be used to model an overall survival difference between treatments in the economic model. As mentioned in the response directly above, the IMDC intermediate- and poor-risk subgroup comprises [redacted]% of the ITT population in the JAVELIN Renal 101 trial. Borderline significance of the survival data and a narrowing of the 95% CI's between IA1 and IA2, reflect a statistically significant OS advantage for the IMDC poor-risk subgroup. As such, the favourable OS trend seen in the ITT population can reasonably be applied as representative of this large subgroup.

Issue 2: Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup	
	Given the above, the data so far demonstrates that the immaturity of the trial data is the primary cause of 'statistically non-significant overall survival results' rather than a lack of efficacy in the considered treatment combination.
ERG critique	The ERG reiterates that generalising results from the IMDC poor-risk group to the IMDC intermediate- and poor-risk group is inappropriate and misleading.
Should overall survival estimates for cabozantinib be assumed to be non-inferior to the overall survival estimates for avelumab+axitinib?	None of the data supports the assumption implicit in this question. Similar to issue 1, this unsubstantiated assumption implies that the addition of avelumab to a TKI has no added survival benefit to TKI monotherapy. Such assumptions not only disregard the trial data but are also inconsistent from a clinical point of view as confirmed through clinical advice received during submission development.
ERG critique	The ERG notes that an assumption of 'non-inferiority' is associated with certain statistical assumptions which were not included in the design of the JAVELIN Renal 101 and CABOSUN trials (both trials included within the network). Therefore, the ERG considers that it is not appropriate to explore whether cabozantinib estimates are 'non-inferior' to avelumab+axitinib. Instead, the question should be whether OS for patients treated with cabozantinib is no worse than OS for patients treated with avelumab+axitinib.

Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust	
Is the company's all-risk status overall survival network meta-analysis sufficiently robust to	Whilst the Company acknowledges the limitations of the network meta-analysis (NMA) due to differences in the trial design (namely the allowance of cross-over from the comparator arm to the experimental arm) of one study included in the network, the use of the NMA is still considered appropriate.

Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust

enable a comparison with tivozanib?

The impact of crossover in TIVO-1 on the results of the NMA was explored in a sensitivity analysis which used crossover-adjusted overall survival outcomes for the TIVO study as included in TA512. The RPSFT adjusted OS results for TIVO-1, based on the ERGs (BMJ-TAG) preferred approach (the stratified log rank test) was incorporated into sensitivity analyses for both the proportional hazards (PH) and non-PH approach.[iv] A crossover adjusted HR was estimated for inclusion in the PH ITCs leading to a hazard ratio of 1.29 (95% CrI 0.85, 1,98, fixed effects) for tivozanib versus sunitinib which is similar to the ITT ITC estimate 1.25 (95% CrI 0.84, 1.88 , fixed effects). Similarly, when incorporating the crossover adjusted data into the non-PH ITCs, estimated survival for tivozanib remained relatively consistent with the ITT analyses (Table 1). This is also consistent with the ERGs observation that the RPSFT adjustment led to a similar benefit for sorafenib as shown in the unadjusted analysis.

Table 1: Estimated tivozanib survival for including ITT or crossover adjusted data

Treatment	Time*	ITT TIVO-1			Using TIVO-1 adjusted for crossover		
		Estimated survival probability (95% CI)			Estimated survival probability (95% CI)		
		Generalised gamma	Log normal	Log logistic	Generalised gamma	Log normal	Log logistic
Tivozanib	1 year	0.82 (0.70, 0.90)	0.83 (0.71, 0.91)	0.81 (0.70, 0.90)	0.81 (0.67, 0.91)	0.82 (0.67, 0.91)	0.80 (0.67, 0.90)
	2 years	0.64 (0.46, 0.76)	0.66 (0.48, 0.78)	0.62 (0.43, 0.75)	0.61 (0.37, 0.76)	0.62 (0.39, 0.77)	0.59 (0.37, 0.74)
	10 years	0.14 (0.01, 0.32)	0.19 (0.04, 0.36)	0.15 (0.04, 0.31)	0.11 (0.00, 0.30)	0.14 (0.01, 0.33)	0.11 (0.02, 0.29)

Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust	
	The company also acknowledge the limitation of incorporating the crossover trials that compare sunitinib to sorafenib (SWITCH and CROSS-J-RCC), however this was an unavoidable issue to allow the relative treatment comparisons to tivozanib. To explore the impact of this limitation, the company conducted a sensitivity analyses which assumed that sorafenib had equivalent survival to sunitinib. This assumption was considered plausible given the similarity in PFS between the treatments when given in the first line setting. In addition, this assumption avoids the use of crossover impacted information. The outcome produced similar results; a HR of 0.63 (95% CrI 0.40, 1.00, fixed effects) for avelumab+axitinib vs tivozanib compared to 0.62 (95% CrI 0.37 to 1.05, fixed effects) when the observed HR information was used for sunitinib vs sorafenib. Given the limited difference in the HR, it seems most appropriate to use the observed relative efficacy of sunitinib and sorafenib which allows for the incorporation of variability around the estimate. Despite the limitations highlighted in the NICE technical report, the Company considers the results of the NMA sufficiently robust to enable a comparison with tivozanib.
ERG critique	The ERG acknowledges that when using TIVO-1 data adjusted for crossover, NMA results presented by the company are consistent with TIVO-1 results for the ITT TIVO-1. However, the most important limitation is that the entire network for OS in the all-risk status population is invalidated due to the inclusion of the SWITCH and CROSS-J-RCC trials (see ERG report, Section 4.7.1).
Should tivozanib be considered equivalent to sunitinib in terms of overall survival? Is this seen in clinical practice?	The Company acknowledges the perception among clinicians that tivozanib has similar but not necessarily equivalent efficacy to sunitinib and other recommended TKI's used in the treatment of 1L aRCC. Furthermore, the NICE guidance for TA512 also recognised that tivozanib is likely to be less effective than sunitinib and pazopanib.[iv] Given prior NICE consensus and clinical perception, it would be unreasonable to assume that tivozanib is equivalent to sunitinib.

Issue 3: Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust	
ERG critique	No additional information has been presented by the company. The ERG's rationale for assuming equivalence is presented in the ERG report (Section 5.3.3).

Issue 4: The overall survival and progression-free survival associated with avelumab+axitinib is modelled differently when compared to different comparators	
Should different representations of overall survival and progression-free survival for avelumab+axitinib be used depending on the comparator?	The Company acknowledges the methodological concerns of the NICE technical team around using different representations of overall survival. As such, the Company accepts the use of OS and PFS estimates associated with avelumab+axitinib from JAVELIN Renal 101 trial. The resulting ICER when implementing the trial-based estimates for avelumab+axitinib and the NMA results for tivozanib decreases to £8,398 per QALY from £9,220 per QALY in the base case.
ERG critique	No additional information has been presented by the company. The ICER per QALY gained quoted by the company matches that reported by the ERG in its report (Table 42, R5).

Issue 5: Intervention overall survival extrapolations	
Should the exponential distribution be used to extrapolate JAVELIN Renal 101 trial overall survival data?	The Company disagrees with the approach of using the same extrapolation for both avelumab+axitinib and sunitinib, given the expectation that avelumab+axitinib will produce a durable response and substantially extend OS for a proportion of patients compared with TKI monotherapy. Clinical advice to the Company indicates that the exponential distribution is an inappropriate choice for the modelling of OS for an IO-based treatment given it features a constant mortality hazard over time that does not allow for decreasing mortality hazard at the right-hand tail of the OS curve.

Issue 5: Intervention overall survival extrapolations	
	The recommendation to use the exponential distribution to extrapolate OS does not appear to have been informed nor validated by clinical experts. The ERG's primary criticism against using the log-logistic distribution (which was the 'best-fitting' extrapolation) was the fact that at 18 years from t=0 it predicted lower mortality rates than seen in the general population. Two key points counter this concern. Firstly, the Company accounted for the comparison with the general population by capping mortality rates in the economic model at the level seen in the general population (i.e. they could never fall below). Secondly, the use of the exponential distribution (as recommended by the ERG) does not solve this issue, as projected mortality rates still fall below those of the general population at t=30 years. All consulting oncologists whose feedback was sought for this submission indicated that a flattening of the OS curve could be expected and preferred the use of the log-logistic distribution to extrapolate OS based on visual inspection and the accuracy of PFS and survival predictions. Recommendations from the NICE Decision Support Unit (DSU) highlights clinical validation as one of the three key aspects to testing model fit and plausibility, along with goodness-of-fit measures (AIC and BIC) and visual inspection. All three of these recommendations were considered in the choice of OS extrapolation.
ERG critique	No additional information has been presented by the company. Please see Section 5.3.3 for justification of the ERG's approach.
In clinical practice, what proportion of patients would be expected to be alive after 5 and 10 years, if treated with avelumab+axitinib (10%, 20%, 40%, 60%?)?	The Company refers to its company submission (CS) reporting the survival estimates at 5 and 10 years using the log-logistic distribution to extrapolate OS for avelumab+axitinib, which estimated 5-year and 10-year survival to be [redacted]% and [redacted]%, respectively. These survival estimates were validated by UK clinicians.
ERG critique	No additional information has been presented by the company.

Issue 6: ***Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect***	
Should a stopping rule be implemented in the model? If so, at what point?	The ERG and NICE technical team have cited the lack of a stopping rule within JAVELIN Renal 101 as the rationale for excluding a stopping rule from the base case. However, to exclude a stopping rule from the economic model is to disregard the emerging clinical recognition that two years is a natural time point when treatment is reassessed. Feedback from clinicians is that responding patients at 2 years are likely to stop treatment prior to progression whilst continuing to benefit. NICE has published guidance in 13 appraisals in the past 3 years for IO treatments including nivolumab (squamous cell carcinoma of the head and neck, squamous and non-squamous non-small-cell lung cancer), pembrolizumab (untreated metastatic squamous non-small-cell lung cancer, untreated, metastatic, non-squamous non-small-cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, untreated PD-L1-positive metastatic non-small-cell lung cancer, untreated PD-L1-positive locally advanced or metastatic urothelial cancer, locally advanced or metastatic urothelial carcinoma, ovarian, fallopian tube and peritoneal cancer), and atezolizumab (metastatic non-squamous non-small-cell lung cancer, locally advanced or metastatic urothelial carcinoma) in which a 2-year stopping rule was included as part of the NICE recommendations. Regarding the absence of a stopping rule in the protocol of JAVELIN Renal 101, the Company wishes to highlight recent NICE appraisals where a stopping rule has been accepted by the committee when one was not included in the pivotal clinical trial. Across different IO agents, the following recent NICE appraisals have published guidance contingent on a stopping rule without a fixed treatment duration included in the trial protocol: 1) Nivolumab for previously treated non-squamous non-small-cell lung cancer. [TA484]; 2) Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520]; 3) Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [TA525]; 4) Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [TA490]. In each of the above, a stopping rule was included at 2 years as part of NICE recommendations. As detailed in the CS, the use of a 2-year stopping rule in these appraisals was supported by the Cancer

Issue 6: ***Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect***	
	Drugs Fund Clinical Lead who considered it to be acceptable to both patients and clinicians and could be practically applied in NHS practice. Similar advice was sought by the company through an Office of Market Access meeting and an NHSE surgery where a stopping rule was discussed for the subject combination. In both instances the use and practicality of a stopping rule was unanimously affirmed. Feedback from consulting oncologists in the UK indicates that they would advise stopping avelumab+axitinib at 2 years for patients still progression-free and believe benefits will continue in most cases.[v] It is unclear the basis by which the ERG can refute the appropriateness of a stopping rule. Given the evidence cited above and stipulated practice, the use of a stopping rule should be considered for the base case analysis.
ERG critique	The ERG maintains that it considers that a stopping rule that is not included within a trial should be explored in scenario analyses, and not in the base case (see Section 5.3.3 of the ERG report).
Should the benefit of treatment be modelled to continue after the treatment has stopped? And if so, should there be any waning of the treatment effect?	It is now well accepted that some patients treated with an IO (and by extension an IO in combination) will receive lasting benefits from their therapy. Previous NICE appraisals have accepted the premise and in the absence of empirical data have accepted assumptions around the proportion of patients to which this applies. In TA428 (pembrolizumab for the treatment of PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy),[vi] the assumption of continued treatment benefit for a full 3 years beyond treatment discontinuation at 2 years was deemed clinically plausible by the NICE committee. The ERG's conservative assumption that therapeutic benefits abates when treatment is discontinued is not consistent with our current understanding of the biological and clinical realities of IO therapies. Whilst the Company acknowledges that uncertainty remains regarding the continued treatment benefit beyond stopping, clinical advice suggests that it is reasonable to assume that up to one third of patients will not continue to realise the same long-term benefits beyond cessation of therapy.

Issue 6: ***Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect***

Following the NICE technical engagement meeting on the 12th November, the Company consulted five additional clinicians on the base case treatment effect waning assumption. During these one-on-one discussions, clinicians were asked to estimate the proportion of patients who would remain progression-free at 12- and 24-months following treatment cessation at 2 years. The clinician responses are presented below in Table 2. Responses form clinicians show that they would expect an estimated 20-25% of patients to progress within 12 months of stopping treatment. This proportion would marginally increase to 30% within 24 months.

Table 2: Survey responses from consulting oncologists in the UK: estimated proportion of patients in PFS and stopping treatment at 2 years who progress at 12- and 24-months

	Estimated proportion progressing by 12 months post stopping	Estimated proportion progressing by 24 months post stopping
Clinician 1 (Bristol)	20%	30%
Clinician 2 (Ipswich)	25%	NR
Clinician 3 (Mount Vernon)	20%	30%
Clinician 4 (Leeds)	5%	10%
Clinician 5 (Royal Free)	60%	80%

In the company's base case, 33% of patients experience gradual treatment effect waning over the first two years following treatment stop, the proportion of patients progression-free at 2 years who stop treatment and are estimated to progress within the next 12 and 24 months in the economic model (Table **3**) is aligned with the clinician feedback collected in the survey presented above. At 12 months post stopping, the modelled estimate (22%) is consistent with clinician estimates (20-25%). The estimated proportion of patients who experience a progression event at 24 months in the economic model (38%) is also consistent with clinicians' expectations (~30%), with the model reflecting the more conservative outcome.

<table>
<tr><th colspan="2">Issue 6: Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect</th></tr>
<tr><td></td><td>Table 3: Estimated proportion of patients in PFS and stopping treatment at 2 years who progress at 12- and 24-months in the economic model
<table>
<tr><th>Time point</th><th>Proportion in PFS as modelled using base case assumptions on treatment effect waning</th><th>Proportion of those patients in PFS who stop treatment at 2 years who later progress</th></tr>
<tr><td>2-years (at treatment stop)</td><td>37%</td><td>-</td></tr>
<tr><td>12 months post-stop</td><td>29%</td><td>22%</td></tr>
<tr><td>24 months post-stop</td><td>23%</td><td>38%</td></tr>
</table>

In view of the above, the company’s base case assumption around treatment effect waning is consistent with the expectation of clinicians and in the long-term errs on the conservative.</td></tr>
<tr><td>ERG critique</td><td>The ERG reiterates the position outlined in the ERG report (Section 5.3.1, Table 37) that the concept of an IO effect and the modelling of that effect remains a matter of conjecture.

The areas of uncertainty around the IO effect can be summarised as follows:

• The definition of the IO effect in previous appraisals is varied and the preferred definition in this appraisal is unclear.

• There is a lack of clarity on whether all immunotherapies exhibit an IO effect and to what extent the size of the IO effect depends on the site of the cancer that is being treated.</td></tr>
</table>

Issue 6: ***Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect***	
	• Both the characteristics and the proportion of patients that will benefit from an IO effect is also unknown. • The impact of an IO effect on PFS, OS and treatment duration is unclear. • It is unclear whether the extent of the IO effect differs in patients that are naïve to immunotherapy compared to those that have been previously treated with an immunotherapy. • There is a lack of evidence as to when a patient would begin to experience an IO effect and when the IO effect would end. The ERG notes that the clinician responses presented in Table 2 above, in which the estimated proportion of patients who may benefit from an IO effect varies considerably, highlights the uncertainty amongst clinicians regarding any potential IO effect.

Issue 7: Source of clinical parameters used in the economic model	
Should data from the second interim analysis be used to inform the cost effectiveness model where available?	The ERG has indicated in its report (and reiterated during the NICE technical engagement meeting on 12 November 2019) that the use of data from IA2 in the economic model would not reduce uncertainty surrounding the overall survival benefit of avelumab+axitinib. In principle, the company agrees with this position and would like to highlight some key details. IA2 is not an event-driven analysis, rather it was triggered 6 months following IA1. An economic model based upon IA2 data would necessarily also incorporate IA1 data (i.e. for safety and time-on-treatment) as not all relevant outcomes were reported at IA2. The PFS and OS HRs for IA2 are broadly similar to those of IA1. As the data matures, OS is expected to improve moving from borderline significance to statistical significance. In the meantime, the Company considers that the availability of avelumab+axitinib via the CDF whilst the trial data are maturing is the most appropriate outcome for patients and the NHS.
ERG critique	No additional information has been presented by the company. However, the ERG agrees that as data from the JAVELIN Renal 101 trial mature, the evidence on the effect of treatment on OS will become more robust. Increased data will also allow the uncertainty around long term OS projections to be reduced, which will reduce the uncertainty around the cost effectiveness of avelumab+axitinib versus sunitinib.

Issue 8: External validity of the JAVELIN Renal 101 trial results	
Are the trial results generalisable to NHS practice or people with poor performance status?	The baseline characteristics of the patients who entered into the JAVELIN Renal 101 trial reflect clinical practise globally and in the UK. The ratio of males:females and the proportion of patients in each risk group are similar to UK statistics as confirmed at an advisory board by consulting oncologists in the UK.**Error! Bookmark not defined.** As part of the clinical study, only patients with a performance status of 0-1 were enrolled however, there is no reason to believe that patients with an ECOG score greater than 1 would not benefit from treatment. This is consistent with the current understanding of the EMA licence. The safety profile for avelumab+axitinib in the JAVELIN Renal 101 was similar to that seen for the individual assets.[x] Furthermore, both avelumab and axitinib have been used in clinical practise in patients with performance status >2 with no additional burden and similar efficacy results.[vii] The Company therefore believes that the study results are generalisable to NHS practice.
What is the likely impact on clinical effectiveness of the dose being different in the trial to that which will be used in clinical practice?	The EMA and MHRA (as part of EAMS assessment) assessed the potential change in clinical efficacy with a change in the dosing regimen from weight based to flat dosing and were satisfied that the change was acceptable.[viii] Modelling and simulation-based analyses were performed to simulate PK exposure and consequent efficacy and safety responses for the 10 mg/kg Q2W and the flat 800 mg Q2W dosing regimens. Similar predicted PK exposure (with less variability for flat dosing) provided the pivotal evidence for changing to a flat dosing regimen. Additional justification for the flat dose regimen was obtained from the similarity in the predicted efficacy and safety profiles for the flat versus weight-based dosing regimens. These analyses were provided to both the EMA and MHRA. A flat dosing regimen provides more consistent dosing across body weights, minimises drug wastage, facilitate preparation and administration, and reduce pharmacy errors.

Issue 8: External validity of the JAVELIN Renal 101 trial results	
	The use of flat dosing is consistent with NHSE's proposed avelumab dose banding table.[ix] Based on the mean weight of patients in the JAVELIN Renal 101 trial (83.06kg), a flat dose of 800mg would be recommended according to the recommended dosing table. For more information on the PK analysis please refer to the EPAR and EAMS scientific opinion.[viii]
In clinical practice, what would be the difference in expected treatment effect between those with clear and non-clear cell RCC? Is it appropriate to extrapolate the results to non-clear RCC?	The EMA has approved the use of avelumab in combination with axitinib for all advanced RCC patients.[x] The JAVELIN Renal 101 trial included patients with a clear cell component, this means that patients recruited could still have a heterogenous tumour with non-clear cell components. Non-clear cell RCC (nccRCC) is characterised by a mixture of tumour types of different histologies - two major histological subtypes are papillary (10-14%) and chromophobe (5%), they also include collecting duct, translocation carcinoma, medullary carcinoma, and unclassified RCC.[xi] Although individually these diverse tumours are relatively rare, the total nccRCC population make up around 20% of the total RCC population. NICE has approved sunitinib for all advanced and/ or metastatic RCC patients (TA169) based on a study looking at patients with clear cell RCC.[xii] As avelumab in combination with axitinib has shown clinical benefit over sunitinib in a similar cohort of patients, the Company believes that the combination should also be available to nccRCC patients. Despite the fact that nccRCC effects a relatively small population of patients, it is imperative to provide these patients with treatment options. Based on the above evidence, we cannot say that avelumab+axitnib has no benefit in patients with a non-clear cell component (as they have been accounted for in JAVELIN Renal study and the occurrence of clear cell and non-clear cell is not mutually exclusive).

Issue 8: External validity of the JAVELIN Renal 101 trial results	
ERG critique	The ERG considers the company's interpretation of the information presented above to be reasonable.

Issue 9: Consideration for the Cancer drugs Fund	
Will the ongoing data collection in JAVELIN 101 be sufficient to address uncertainties in the effectiveness of avelumab+axitinib?	Yes, by 2023 the JAVELIN Renal 101 study will have 5 years of follow-up data, limiting the clinical uncertainty with respect to the long-term benefits of the avelumab+axitinib combination.
Are any data other than overall survival required to inform the effectiveness of avelumab+axitinib?	The Company welcomes a discussion on the inclusion of additional data during the development of the Data Collection Agreement.
Based on current modelling, does the treatment have a potential to be cost effective?	Yes, aveluamb+axitinib can be cost-effective if the trial data is used to model OS and the committee acknowledge that most patients are not treated with IO combinations until progression.
ERG critique	The ERG considers that longer-term follow-up data will reduce the uncertainty around the cost effectiveness analysis which is currently highly uncertain.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Avelumab in combination with axitinib for advanced renal cell carcinoma [ID1547]

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:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key 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: November 2019

1. Topic background

Advanced or metastatic Renal Cell Carcinoma (RCC) Disease Background

- Company define 'advanced' RCC as Stage III and IV in the submission, which includes both locally advanced and metastatic RCC.
- Mortality is associated with stage at diagnosis. 1 and 5-year survival rates by stage of diagnosis are:
  - Stage III: 90% and 67% respectively
  - Stage IV: 37% and 11% respectively
- Risk scores to predict survival which are commonly used to categorise patients into favourable-, intermediate- and poor-risk include:
  - International Metastatic Renal Cell Carcinoma Database (IMDC) or
  - Memorial Sloan Kettering Cancer Center (MKSCC) classification systems

  Both use multiple prognostic factors e.g. Karnofsky performance status, time from diagnosis to treatment, haemoglobin level and corrected calcium concentration

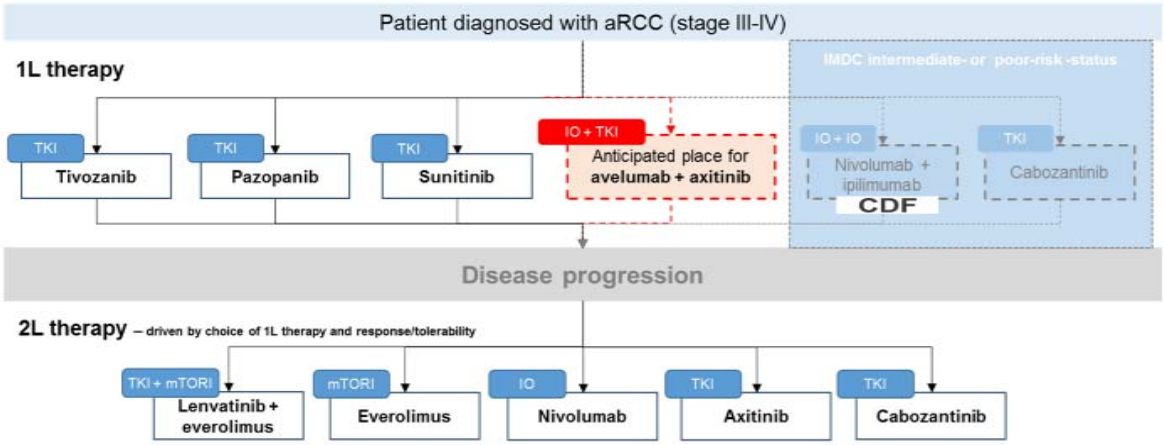
Decision Problem

	Final scope issued by NICE	Company submission and ERG comments
Population	Adults with untreated advanced or metastatic renal cell carcinoma	As per scope (**but** JAVELIN Renal 101 trial population limited to clear cell aRCC).
Intervention	Avelumab with axitinib	As per scope
Comparator	• Pazopanib • Sunitinib • Tivozanib • Cabozantinib (only for intermediate/poor risk status disease as defined in International Metastatic Renal Cell Carcinoma Database Consortium criteria)	As per scope. ERG noted avelumab+axitinib effectiveness vs: • sunitinib derived from JAVELIN Renal 101 trial. • pazopanib assumed same as sunitinib (accepted in TA512, TA581) • tivozanib and vs cabozantinib derived from network meta-analyses
Outcomes	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	As per scope. Company only included overall survival and progression-free survival in network meta-analyses
Subgroups	None specified	Avelumab+axitinib vs cabozantinib is restricted to subgroup with advanced renal cell carcinoma of intermediate/poor risk status (as per the cabozantinib licence)

Avelumab and axitinib for untreated advanced RCC

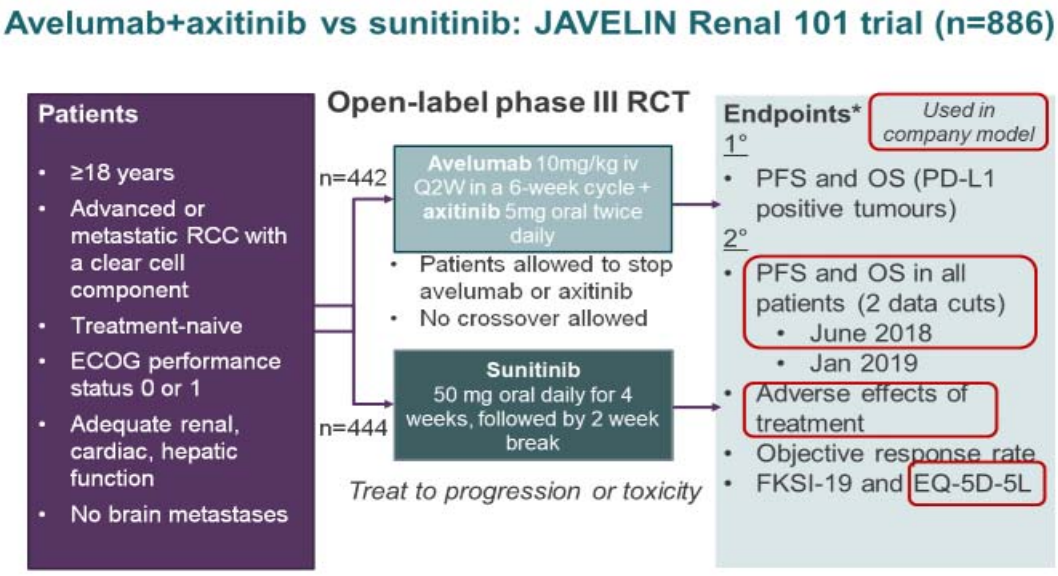
Mechanism of action	• Avelumab: human immunoglobulin G1 monoclonal antibody directed against the programmed cell death-ligand-1 (PD-L1) protein • Axitinib: tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3
Market Authorisation	• Positive CHMP opinion (Sept. 2019): '*Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC)'*
Administration and dose	• Company anticipates flat dosing schedule for avelumab of 800mg every 2 weeks (Q2W), and uses this in cost-effectiveness analyses • ERG note that dosing schedule was different in trial evidence therefore there is no clinical evidence using this dosing schedule. In JAVELIN Renal 101 trial dosing was as follows: • - Avelumab: 10mg/kg of body weight as 1-hour intravenous infusion Q2W (dose reductions not permitted but doses could be skipped if toxic effect) • - Axitinib orally 5mg twice daily (could be increased/decreased) • - No stopping rule
List price	• Avelumab: £768.00 per 200 mg vial • Axitinib: £3,517.00 for the 5 mg strength (pack of 56 tablets)
Other recommendations	• Axitinib for 2nd line or later option for advanced RCC (TA333) • Avelumab for metastatic Merkel cell carcinoma (CDF) (TA517)

Treatment Pathway



Abbreviations: 1L=first-line; 2L=second-line; aRCC=advanced renal cell carcinoma; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IO=immuno-oncology; mTORI=mammalian target of rapamycin inhibitor; TKI= tyrosine kinase inhibitor

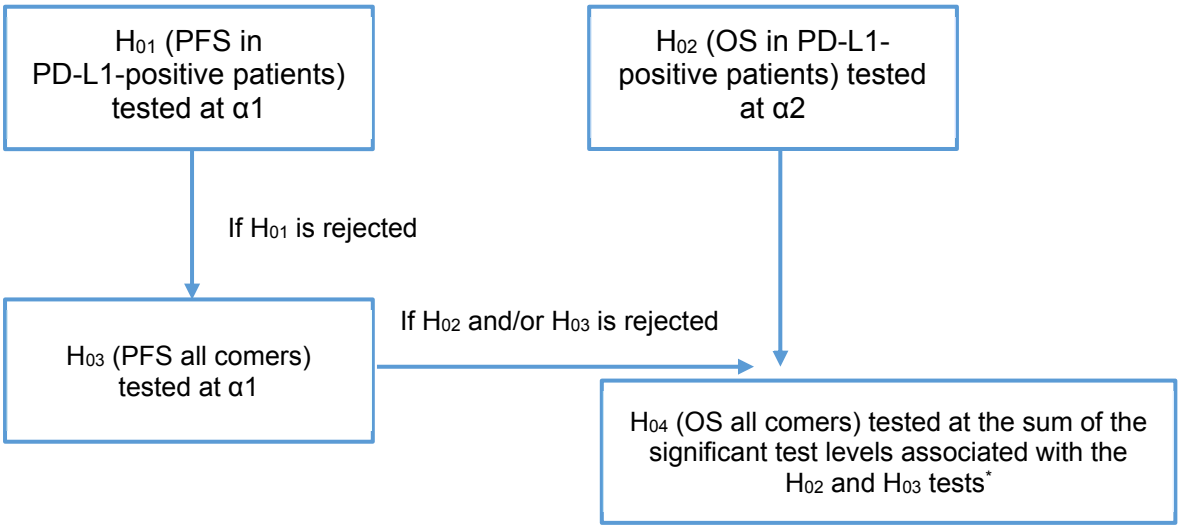
Clinical evidence



Abbreviations: RCC=renal cell carcinoma, Q2W: every two weeks, EQ-5D-5L=EuroQol 5-Dimension 5-Level, FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index-19, PFS=progression free survival, OS=overall survival, ECOG=Eastern Cooperative Oncology Group

Clinical evidence

- Overall type I-error was maintained below one-sided 0.025 by allocating α=0.004 (α1) to the PFS comparison in the PD L1 positive population and by allocating α=0.021 (α2) to the OS comparison in the PD L1 positive populations. Group sequential design taken into account.
- A gatekeeping procedure was used to allow further testing of PFS and OS in the overall trial population irrespective of PD L1 expression.
- Primary analysis of PFS in patients with PD L1-positive tumours: 336 events would provide 90% power to detect a HR of 0.65 at a significance level of 0.004
- Primary analysis of OS in patients with PD L1 positive tumours: 368 events would provide 90% power to detect a HR of 0.70 at a significance level of 0.021



α level for H04 will be α1 + α2 if both H02 and H03 are rejected; α2 if H02 is rejected and H03 is not rejected; α1 if H02 is not rejected and H03 is rejected

Primary Analysis Key Results (JAVELIN Renal 101)

Overall Survival (PD-L1 positive tumour population)	IA1 (data cut-off 20 June 2018)		Progression-free survival (PD-L1 positive tumour population, RECIST 1.1, BICR)	IA1 (data cut-off 20 June 2018)	
	Avelumab+ axitinib (N=270)	Sunitinib (N=290)		Avelumab+ axitinib (N=270)	Sunitinib (N=290)
Median follow-up time (95% CI), months	11.6 [redacted]	10.7 [redacted]	Median follow-up time (95% CI), months	9.9 (9.7, 11.1)	8.4 (8.1, 9.7)
Events, n (%)	37 (13.7)	44 (15.2)	Events, n (%) [disease progression or death]	[redacted]	[redacted]
Censored*, n (%)	[redacted]	[redacted]	Censored*, n (%)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]	Ongoing without event, n (%)	[redacted]	[redacted]
Median OS (95% CI), months	[redacted]	[redacted]	Median PFS (95% CI), months	13.8 (11.1, NE)	7.2 (5.7, 9.7)
HR (95% CI)	0.82 (0.53, 1.28)		HR (95% CI)	[redacted]	

*patients who have not experienced an event inc. being alive (i.e. ongoing without event), lost to follow up, withdrawal of consent

Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors.

Full Analysis Set Key Results (JAVELIN Renal 101) overall survival (overall population)

Overall Survival (overall population)	IA1 (data cut-off 20 June 2018)		IA2 (data cut-off 28 Jan 2019)	
	Avelumab+ axitinib (N=442)	Sunitinib (N=444)	Avelumab+ axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI) months	12.0 [redacted]	11.5 [redacted]	[redacted]	[redacted]
Events, n (%)	63 (14.3)	75 (16.9)	109 (24.7)	129 (29.1)
Censored*, n (%)	379 (85.7)	369 (83.1)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (95% CI), months	NE [redacted]	NE [redacted]	NE (30.0 to NE)	NE (27.4 to NE)
HR (95% CI)	**0.78 (0.55 to 1.08)**		0.80 (0.62 to 1.03)	

Note: Immature OS data: 25.8% and [redacted] of the 535 deaths required for final OS analysis (IA1 and IA2 respectively).

*patients who have not experienced an event inc. being alive (i.e. ongoing without event), lost to follow up, withdrawal of consent
Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors.

Full Analysis Set Key Results (JAVELIN Renal 101) progression free survival (overall population)

	1st data cut off 20 June 2018		2nd data cut-off 28 Jan 2019	
	Avelumab+ axitinib (N=442)	Sunitinib (N=444)	Avelumab+ axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI), months	10.8 [redacted]	8.6 [redacted]	[redacted]	[redacted]
Events, n (%) [disease progression or death]	180 (40.7)	216 (48.6)	229 (51.8)	258 (58.1)
Censored*, n (%)	262 (59.3)	228 (51.4)	[redacted]	[redacted]
Ongoing without disease progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (95% CI), months	13.8 (11.1 to NE)	8.4 (6.9 to 11.1)	13.3 (11.1 to 15.3)	8.0 (6.7 to 9.8)
HR (95% CI)	0.69 (0.56 to 0.84)		0.69 (0.57 to 0.83)	

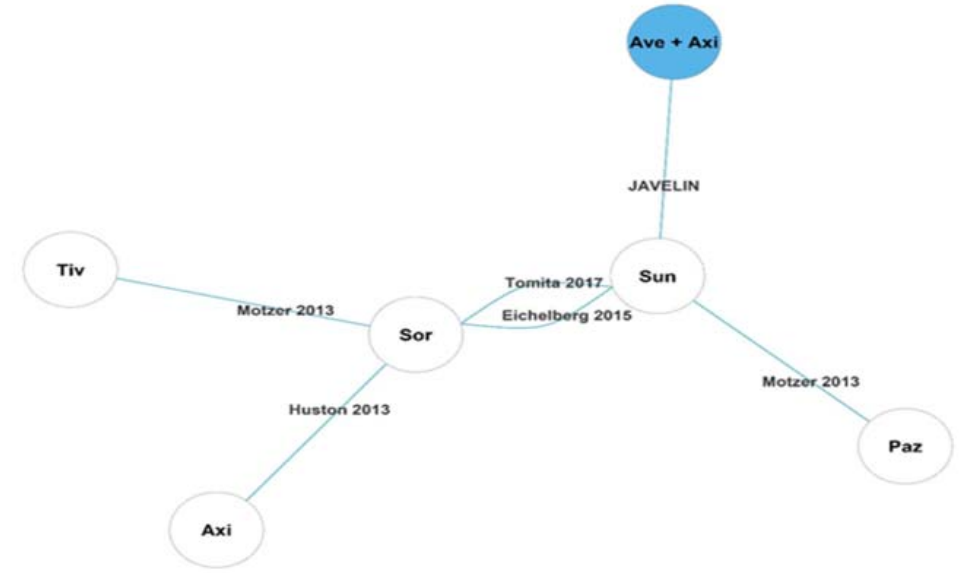
*patients whose disease has not progressed, lost to follow up, withdrawal of consent, no adequate baseline assessment, start of new anti-cancer therapy
Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors.

Full Analysis Set Key Results (JAVELIN Renal 101) objective response (overall population)

Objective response (overall population, RECIST 1.1, BICR)	IA1 (data cut-off 20 June 2018)		IA2 (data cut-off 28 Jan 2019)	
	Avelumab+ axitinib (N=442)	Sunitinib (N=444)	Avelumab+ axitinib (N=442)	Sunitinib (N=444)
Objective response, n (%)	227 (51.4)	114 (25.7)	[redacted]	[redacted]
CR, n (%)	15 (3.4)	8 (1.8)	[redacted]	[redacted]
PR, n (%)	212 (48.0)	106 (23.9)	[redacted]	[redacted]
ORR (%) (95% CI)	51.4 (46.6 to 56.1)	25.7 (21.7 to 30.0)	[redacted]	[redacted]
OR (95% CI)	3.10 (2.30 to 4.15)		[redacted]	

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; FAS=full analysis set; IA1=first interim analysis; IA2=second interim analysis; PR=partial response; OR=odds ratio; ORR=objective response rate, RECIST=Response Evaluation Criteria in Solid Tumors.

Network meta-analysis (PFS and OS in all-risk status population)



Ave=avelumab; Axi=axitinib; Paz=pazopanib; OS=overall survival; PFS=progression-free survival; Sor=sorafenib; Sun=sunitinib; Tiv=tivozanib

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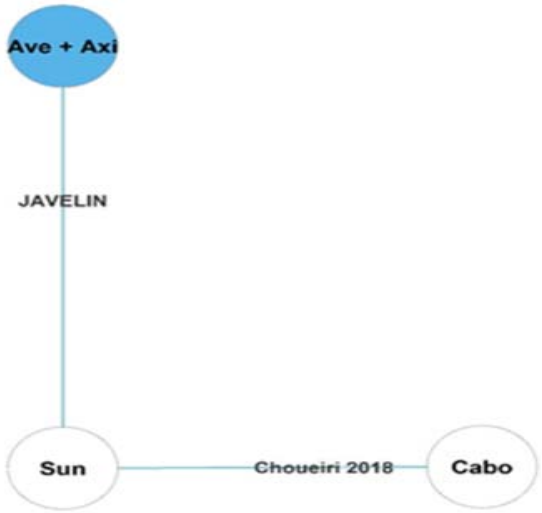
Network meta-analysis (PFS and OS in all-risk status population) results

Estimated survival probabilities			
Time	Treatment	PFS (95% CI)	OS (95% CI)
		Generalised Gamma	Generalised Gamma
1 year	Avelumab+axitinib	0.53 (0.48 to 0.58)	0.86 (0.82 to 0.89)
	Sunitinib	0.38 (0.33 to 0.43)	0.83 (0.78 to 0.86)
	Pazopanib	0.35 (0.26 to 0.43)	0.84 (0.79 to 0.89)
	Tivozanib	0.41 (0.29 to 0.51)	0.82 (0.70 to 0.90)
2 years	Avelumab+axitinib	0.36 (0.31 to 0.42)	0.74 (0.66 to 0.80)
	Sunitinib	0.21 (0.17 to 0.26)	0.67 (0.59 to 0.72)
	Pazopanib	0.17 (0.11 to 0.24)	0.69 (0.60 to 0.76)
	Tivozanib	0.24 (0.13 to 0.35)	0.64 (0.46 to 0.76)
10 years	Avelumab+axitinib	0.10 (0.06 to 0.15)	0.34 (0.16 to 0.47)
	Sunitinib	0.03 (0.02 to 0.05)	0.20 (0.09 to 0.33)
	Pazopanib	0.02 (0.01 to 0.04)	0.21 (0.08 to 0.35)
	Tivozanib	0.04 (0.01 to 0.12)	0.14 (0.01 to 0.32)

Network meta-analysis (PFS and OS in IMDC intermediate/ poor risk status population)



Ave=avelumab; Axi=axitinib; Cabo=cabozantinib; IMDC=International Metastatic RCC Database Consortium; OS=overall survival; PFS=progression-free survival; RCC=renal cell carcinoma; Sun=sunitinib

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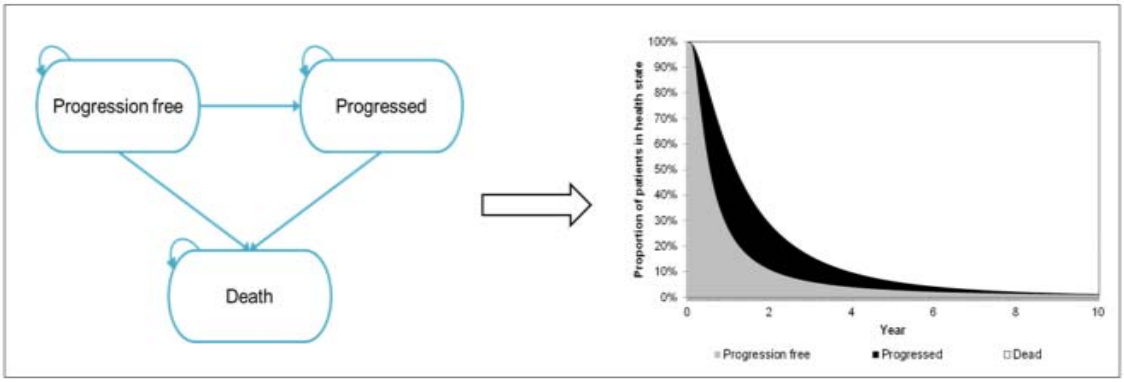
Network meta-analysis (progression free survival and overall survival in IMDC intermediate/ poor risk status population) results

Estimated survival probabilities			
Time	Treatment	PFS (95% CI)	OS (95% CI)
		Generalised Gamma	Log logistic
1 year	Avelumab+axitinib	[redacted]	[redacted]
	Cabozantinib	[redacted]	[redacted]
2 years	Avelumab+axitinib	[redacted]	[redacted]
	Cabozantinib	[redacted]	[redacted]
10 years	Avelumab+axitinib	[redacted]	[redacted]
	Cabozantinib	[redacted]	[redacted]

Company's model structure



- Partitioned-survival model
- Estimated proportions in each health state based on parametric survival curves fitted to clinical trial data for PFS and OS
- Time horizon: 40 years
- Cycle length: 1 week

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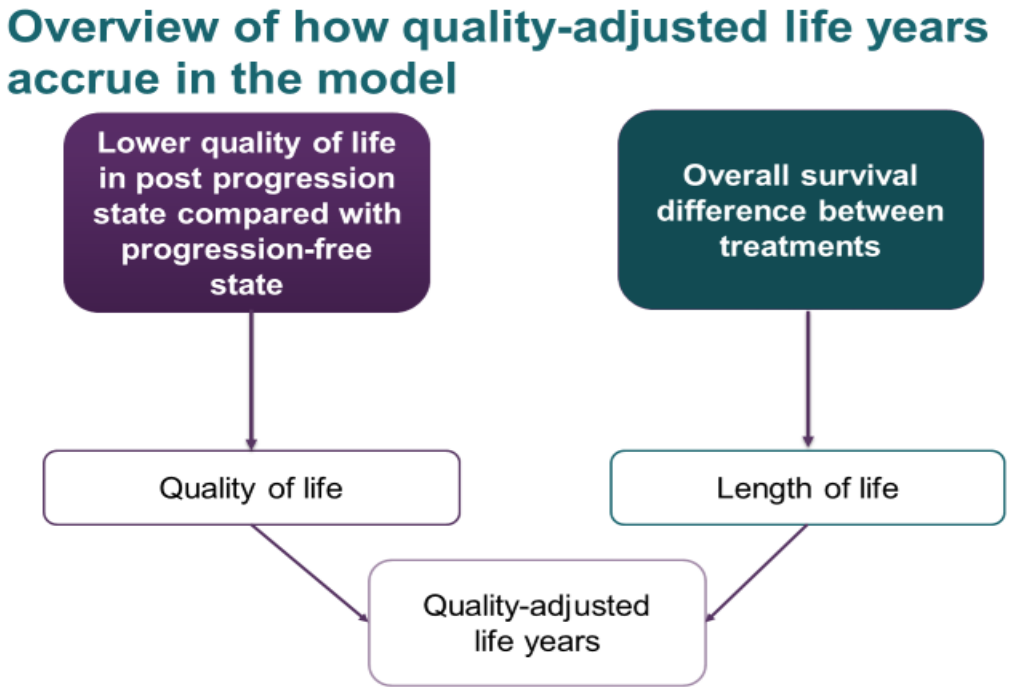
Company's model and assumptions

- Two populations:
  - all risk status (vs sunitinib, pazopanib and tivozanib)
  - IMDC intermediate/poor risk status (vs cabozantinib, as per its licence)
- OS, PFS and time on treatment (ToT) experience were represented using parametric distributions
- OS, PFS and ToT estimates for sunitinib used also for pazopanib (in line with TA581).
- Data from JAVELIN Renal 101 trial used for comparison vs sunitinib and pazopanib
- Data from network meta-analyses used for comparisons vs tivozanib and cabozantinib
  - This means that data sources and parametric models for avelumab+axitinib differ depending on the comparator
- 2-year stopping rule applied for avelumab and axitinib
- Treatment waning: after stopping treatment 33% of patients will adopt the PFS and OS hazards associated with treatment with sunitinib within a two-year period

Overview of how quality-adjusted life years accrue in the model



2. Summary of the technical report

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.

2.1 In summary, the technical team considered the following:

Issue 1 **The technical team took into account the additional analysis results submitted by the company and noted that the methods employed for this analysis were not provided. It further noted that rank preserving structural failure time (RPSFT) analysis is used to adjust for cross-over and not for imbalances in subsequent therapies, as is the case here. Therefore, the technical team considers the results are not**

	relevant for addressing the current issue. The technical team acknowledged that the data as a whole for treatment benefit are promising, but given the lack of statistical significance and the immaturity of overall survival data in the first and the second interim analyses of the JAVELIN Renal 101 trial, there is uncertainty about whether there is or there is not an overall survival benefit of avelumab+axitinib over sunitinib. Given this uncertainty, results modelling both an overall survival benefit and no benefit should be presented to the Appraisal Committee to allow assessment of the impact of this uncertainty on the cost-effectiveness estimates.
Issue 2	**The technical team took into account the statistically significant result in the IMDC poor-risk subgroup alone at interim analysis 2. It noted that this result cannot be generalised to the IMDC intermediate/poor risk subgroup. It also noted that selectively reporting interim analyses subgroup results that reach statistical significance runs the risk of multiplicity (that is increases the risk of a false positive result). The technical team considers that given the lack of statistical significance and the immaturity of overall survival data in the overall population and the IMDC intermediate- and poor-risk subgroup of the JAVELIN Renal 101 trial, there is uncertainty about the overall survival benefit of avelumab+axitinib over sunitinib in this subgroup. This adds to the uncertainty of the indirect comparison of avelumab+axitinib with cabozantinib in the IMDC intermediate- and poor-risk population. Scenario analysis results modelling both an overall survival benefit and no benefit should be presented to the Appraisal Committee to allow assessment of the impact of this uncertainty on the cost-effectiveness estimates.**

Issue 3 The technical team took into account the limitations of the overall survival NMA network, the company sensitivity analyses, the clinical input and the TA512 Committee discussion that '*at best tivozanib may have a similar effect to sunitinib or pazopanib*'. It also took into account the fact that the network for overall survival is invalidated due to the limitation of the 2 trials comparing sunitinib with sorafenib (Eichelberg et al, 2015 and Tomita et al, 2017) as described above. Therefore, the technical team considers that alternative approaches should be explored such as an alternative network or assuming that the overall survival associated with tivozanib and sunitinib are the same.

Issue 4 The same representations of overall survival for avelumab+axitinib should be used for the same population irrespective of comparator. Therefore, for the comparison with tivozanib, the PFS and OS estimates for avelumab+axitinib should be set to be the same as the PFS and OS estimates used for avelumab+axitinib in the comparison with sunitinib and pazopanib (that is, modelled on data from the JAVELIN Renal 101 trial).

Issue 5 The technical team, taking into account the discrepancy between the clinical input and the survival estimates using either the exponential or the log-logistic function, considers that a range of survival extrapolations should be considered. The overall survival extrapolations should be clinically plausible and incorporate expert opinion as well as the best available evidence.

Issue 6 **The technical team notes the absence of clinical evidence for avelumab+axitinib, for both a lifetime treatment benefit despite stopping treatment at 2 years, and for the treatment waning effect as modelled by the company. The technical team notes that no previous NICE appraisal in aRCC have accepted a stopping rule and a continued treatment benefit.**

It also notes the wide range of estimates (10%-80%) in the clinical input on the proportion of patients expected to progress after stopping treatment. The technical team is also unclear about the rationale of stopping axitinib at 2 years. It notes that in the case of the KEYNOTE-426 trial (pembrolizumab+axitinib vs sunitib) (Rini et al, 2019), there is a protocol specified stopping rule at 2 years which applies only to pembrolizumab. The technical team considers that the inclusion of a stopping rule and the assumptions of continued treatment benefit in the absence of any evidence add to the uncertainty on the long-term effectiveness of the intervention as modelled by the company. Relevant scenario analyses factoring in the stopping rule and the treatment effect waning or not should be presented to the Appraisal Committee to allow assessment of the impact of this uncertainty on the cost-effectiveness estimates.

Issue 7 The company should present analyses using the latest data cuts from JAVELIN Renal 101.

Issue 8 The technical team notes the evidence provided and published in the EPAR and EAMS scientific opinion and the clinical input. It notes that there is precedent for similar changes in dosing regimens in checkpoint inhibitors (eg nivolumab). The technical team notes the uncertainty on the effectiveness of the combination on patients with non-clear cell RCC and the need for evidence generation in this patient population.

Issue 9 Ongoing data collection in the Javelin 101 trial would address a key uncertainty in this appraisal.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The risk of bias associated with the open label design of the JAVELIN Renal 101 trial

2.3 The cost-effectiveness results include a commercial arrangement for axitinib and avelumab. Taking these aspects into account, some of the technical team's scenario analyses result in increases in incremental cost-effectiveness ratios (ICER) of more than £30,000 per QALY gained versus sunitinib, pazopanib and tivozanib and cabozantinib (see table 1 and 2). These estimates do not include the commercial arrangements for tivozanib, cabozantinib and subsequent treatments (nivolumab, lenvatinib and everolimus), because these are confidential and cannot be reported here. Estimates that included these commercial arrangements would be higher than those reported above.

2.4 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Immature JAVELIN Renal 101 trial overall survival results in the overall population

Background/description of issue	The overall survival results from the JAVELIN Renal 101 trial are immature (only 25.8 and [redacted] of the 535 deaths required for the final analysis have been reported at the first and second interim analyses respectively), and do not show statistically significant differences: • First interim analysis (IA1): hazard ratio (HR) =0.78 (95% confidence interval [CI]: 0.55 to 1.08) • Second interim analysis (IA2): HR=0.80 (95% CI: 0.62 to 1.03) In the health economic modelling **the company** assumed that overall survival was longer with avelumab+axitinib than the comparator. **The ERG** stated that: • Using uncertain clinical effectiveness results as the basis for a cost effectiveness analysis will lead to uncertain cost effectiveness results. • The available trial evidence does not support the company's approach to modelling. The correct approach is to assume equivalent overall survival. The ERG performed a scenario analysis setting overall survival estimates for sunitinib, pazopanib and tivozanib to be the same as the overall survival estimates for avelumab+axitinib (modelled on data from the JAVELIN Renal 101 trial). **The technical team** noted that, given the immaturity of overall survival results in the first and the second interim analyses, there is uncertainty about the effectiveness of avelumab+axitinib compared with sunitinib for overall survival.
Questions for engagement	1. Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with sunitinib? 2. Should the statistically non-significant overall survival results from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model?

Why this issue is important	There is no statistical evidence that avelumab+axitinib extends life. Therefore, assuming an overall survival benefit in the model may overestimate the benefits associated with this new technology and underestimate the ICER.
Technical team preliminary judgement and rationale	Given the immaturity of the overall survival results in the JAVELIN Renal 101 trial, overall survival estimates for sunitinib, pazopanib and tivozanib should be modelled to be equivalent to the OS estimates for avelumab+axitinib.
Summary of comments	**Comments received from company:** - Acknowledges that overall survival data are immature, however the data so far shows a promising indication of survival benefit: o Overall survival has consistently been higher in the avelumab+axitinib arm compared with the sunitinib arm, up to the second interim analysis. o The overall survival hazard ratio of 0.78 (95% CI: 0.55 to 1.08) to 0.80 (95% CI: 0.62 to 1.03) for IA1 and IA2, respectively, shows that, as confidence intervals are narrowing with data maturing, it is trending towards significance. o Progression free survival and objective response rate are statistically significant. - To assume no added benefit of an immune-oncology drug to a tyrosine kinase inhibitor would be paradoxical, "exceedingly conservative", and not in line with a previous appraisal: o Avelumab+axitinib is a combination of an immune-oncology drug and a tyrosine kinase inhibitor and thus it must have a better overall survival over tyrosine kinase inhibitor monotherapy. o In TA542 (Cabozantinib for untreated advanced renal cell carcinoma) a non-statistically significant overall survival benefit (HR = 0.80, 95% CI 0.53, 1.21) was used to model an OS difference in favour of cabozantinib in the economic analysis, on the basis of poorer evidence (the CABOSUN trial was a phase 2 trial with a small sample size [n=157]). - The underpinning OS estimates from JAVELIN Renal 101 may be biased in favour of the comparator, and this has not been adjusted for in the company economic model: o In JAVELIN Renal 101 there was an imbalance in the proportion of patients receiving a checkpoint inhibitor second line between arms. A total of [redacted] ([redacted] %) patients in the avelumab+axitinib arm were treated with any subsequent PD-1 or PD-L1 inhibitor

	compared with [redacted] ([redacted] %) patients in the sunitinib arm. This may have underestimated the overall survival benefit of avelumab+axitinib over sunitinib. o The company performed a rank preserving structural failure time (RPSFT) analysis to explore this. Exploratory analysis results in an adjusted HR of [redacted] (bootstrap 95% CI [redacted]-[redacted]). o Methodologically, RPSFT analysis is used to adjust for crossover, which is not the case here (where it is being used to adjust for the subsequent use of PD-1 or PD-L1 inhibitors in the sunitinib arm in the JAVELIN Renal 101 trial), and this is not a replacement for the clinical data. However, it does support the clinical evidence for a survival benefit being plausible. **Comments received from professional organisations:** - Overall survival benefit is not yet statistically significant, but this is likely to be due to immature data. - Avelumab+axitinib is a combination of an immune-oncology drug and a tyrosine kinase inhibitor. It is therefore likely to have an overall survival benefit over tyrosine kinase inhibitor monotherapy. This is supported by external evidence of a pembrolizumab+axitinib versus sunitinib trial in which the OS benefit of the intervention over the control has reached statistical significance. - The statistically non-significant overall survival results from the JAVELIN Renal 101 trial should be used to model an overall survival difference between treatments in the economic model **Comments received from patient organisations:** - Overall survival with good quality of life matters to patients. No confident conclusions can be drawn regarding OS yet in JAVELIN Renal 101. There is clear evidence of PFS benefit.
Technical team judgement after engagement	Changed. The technical team took into account the additional analysis results submitted by the company and noted that the methods employed for this analysis were not provided. It further noted that rank preserving structural failure time (RPSFT) analysis is used to adjust for cross-over and not for imbalances in subsequent therapies, as is the case here. Therefore, the technical team considers the results are not relevant for addressing the current issue. The technical team acknowledged that the data as a whole for treatment benefit are promising, but given the lack of statistical significance and the immaturity of overall survival data in the first and the second interim

	analyses of the JAVELIN Renal 101 trial, there is uncertainty about whether there is or there is not an overall survival benefit of avelumab+axitinib over sunitinib. Given this uncertainty, results modelling both an overall survival benefit and no benefit should be presented to the Appraisal Committee to allow assessment of the impact of this uncertainty on the cost-effectiveness estimates.

Issue 2 – Immature JAVELIN Renal 101 trial overall survival results in the IMDC intermediate/poor risk subgroup

Background/description of issue	One of the comparators is cabozantinib, which has a narrower licence than the other treatments in this appraisal (its licence restricts it for use in those with intermediate/poor risk status). Therefore, for the indirect comparison with cabozantinib, **the company** took overall survival results for avelumab+axitinib from the *IMDC intermediate/poor risk status subgroup* in JAVELIN Renal 101. However, the company has noted that the overall survival data from the JAVELIN Renal 101 trial for this subgroup are immature and definitive conclusions about relative effectiveness cannot be drawn. In JAVELIN Renal 101, the HR (95% CI) in the intermediate risk group was [redacted] and in the poor risk group [redacted] The company used the OS data from JAVELIN Renal 101 for the indirect treatment comparison with cabozantinib and the results from the indirect treatment comparison (indicating an OS survival benefit of avelumab+axitinib over cabozantinib) to inform the cost-effectiveness model. In the company base case avelumab+axitinib dominates cabozantinib in the IMDC intermediate/poor risk status population. **The ERG** noted that: • If reliable conclusions cannot be drawn from the subgroup overall survival results, then any cost effectiveness results generated using these data will also be unreliable. • The company's *progression-free* survival network meta-analysis suggest that treatment with cabozantinib is superior to avelumab+axitinib (which, if true, could lead to avelumab+axitinib being dominated by cabozantinib). **The technical team** noted the uncertainty in the overall survival results in the IMDC intermediate/poor risk subgroup in the JAVELIN Renal 101 trial.

Questions for engagement	3. Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with cabozantinib? 4. Should the statistically non-significant overall survival results in the intermediate/poor risk subgroup from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model? 5. Should overall survival estimates for cabozantinib be assumed to be no worse to the overall survival estimates for avelumab+axitinib?
Why this issue is important	There is no statistical evidence that avelumumab+axitinib extends life compared with cabozantinib for people with intermediate/poor risk RCC. Therefore, assuming an overall survival benefit in the model may overestimate the benefits associated with this new technology and underestimate the ICER.
Technical team preliminary judgement and rationale	Overall survival estimates for cabozantinib should be assumed to be no worse to the overall survival estimates for avelumab+axitinib, given the immaturity of the overall survival results in the JAVELIN Renal 101 trial for the IMDC intermediate/poor risk status population.
Summary of comments	**Comments received from company:** - The IMDC intermediate- **and** poor-risk subgroup accounts for a majority ([redacted]%) of the ITT population in the JAVELIN Renal 101 trial - In the IMDC **poor-risk subgroup alone** (n=95/886), the OS HR from the IA2 data cut shows a statistically significant survival advantage (HR: [redacted] [95% CI: [redacted], [redacted]). It is reasonable to assume that patients with the poorest risk will reach an event at a faster rate than those with more favourable risk profiles. - The CABOSUN trial (cabozantinib vs sunitinib) is a much smaller trial than JAVELIN Renal 101, where OS KM curves for cabozantinib and sunitinib crossed multiple times before the end of follow-up. This is not the case in JAVELIN Renal 101. In addition, the confidence intervals around the OS hazard ratio in JAVELIN Renal 101 for the **whole** population (upper CI of [redacted]), while not yet statistically significant, are narrower than the CI's around the OS HR for cabozantinib (upper CI of 1.21). **Comments received from clinician:**

	- Does the clinical effectiveness evidence allow any conclusions to be drawn about the overall survival benefit of avelumab+axitinib compared with cabozantinib? o No. - Should the statistically non-significant overall survival results in the intermediate/poor risk subgroup from the JAVELIN Renal 101 trial be used to model an overall survival difference between treatments in the economic model? o Yes. - Should overall survival estimates for cabozantinib be assumed to be non-inferior to the overall survival estimates for avelumab+axitinib? o Our experts believe there is insufficient data to instruct this analysis. The CaboSun dataset is small. **Comments received from patient organisations:** - Since the OS data from JAVELIN Renal 101 are immature, no confident conclusions can be drawn regarding the OS benefit of avelumab plus axitinib compared with cabozantinib in intermediate-/poor-risk mRCC patients. - The PFS data could be extrapolated to make a comparison with the survival data for cabozantinib in this group of patients.
Technical team judgement after engagement	Changed. The technical team took into account the statistically significant result in the IMDC poor-risk subgroup alone at interim analysis 2. It noted that this result cannot be generalised to the IMDC intermediate/poor risk subgroup. It also noted that selectively reporting interim analyses subgroup results that reach statistical significance runs the risk of multiplicity (that is increases the risk of a false positive result). The technical team considers that given the lack of statistical significance and the immaturity of overall survival data in the overall population and the IMDC intermediate- and poor-risk subgroup of the JAVELIN Renal 101 trial, there is uncertainty about the overall survival benefit of avelumab+axitinib over sunitinib in this subgroup. This adds to the uncertainty of the indirect comparison of avelumab+axitinib with cabozantinib in the IMDC intermediate- and poor-risk population. Scenario analysis results modelling both an overall survival benefit and no benefit should be presented to the Appraisal Committee to allow assessment of the impact of this uncertainty on the cost-effectiveness estimates.

Issue 3 – Overall survival assumptions derived from the network meta-analysis for avelumab+axitinib compared with tivozanib are not robust

Background/description of issue	**The company** had direct trial evidence available for avelumab+axitinib compared with sunitinib. Indirect evidence from network meta-analyses was required to compare avelumab+axitinib with pazopanib and tivozanib in the all-risk status population, and with cabozantinib in the intermediate/poor risk status population. To compare avelumab+axitinib with tivozanib, the company used sunitinib and sorafenib as links in the all-risk status overall survival network. Sorafenib is not a comparator for this topic, but was used to indirectly compare sunitinib with tivozanib (see section 1.3 above). There were several challenges with this: • The 2 trials comparing sunitinib with sorafenib (Eichelberg et al, 2015 and Tomita et al, 2017) had a randomised sequential design (that is, patients were randomised to receive sunitinib followed by sorafenib, or sorafenib followed by sunitinib). o **The ERG** noted that overall survival data were only available in these trials at the end of each treatment sequence (i.e. sorafenib followed by sunitinib or sunitinib followed by sorafenib). Therefore, there is no direct comparison of sorafenib versus sunitinib for overall survival in either of these trials. This invalidates the whole network for OS in the all-risk status population. • The trial comparing tivozanib with sorafenib (Motzer et al 2013) allowed crossover from the sorafenib arm to the tivozanib arm (61% of patients who progressed on sorafenib crossed over to tivozanib), and a large proportion of the patients in all of the trials included in the whole network received subsequent treatments after progression. o **The ERG** noted that this would mean that overall survival observed on the trials could not be attributed only to the randomised treatments, but also to those received after progression and thus raise concerns about the validity of the overall survival results in these trials and consequently the network meta-analysis results. Because of the challenges in the network meta-analysis, the ERG's preferred assumption is to assume that the effect of treatment with tivozanib and sunitinib on overall survival are equivalent.

Questions for engagement	6. Is the company's all-risk status overall survival network meta-analysis sufficiently robust to enable a comparison with tivozanib? 7. Should tivozanib be considered equivalent to sunitinib in terms of overall survival? Is this seen in clinical practice?
Why this issue is important	There are no trials that directly compare the length of life with avelumab+axitinib with tivozanib. The structure of the trials available that indirectly compare these 2 treatments do not allow an accurate comparison.
Technical team preliminary judgement and rationale	Alternative approaches should be explored for the indirect comparison of avelumab+axitinib with tivozanib. For example, the company should explore assuming that the overall survival associated with tivozanib and sunitinib are the same
Summary of comments	**Comments received from company:** - The NMA does have limitations, but it is still appropriate after exploring different approaches and finding similar results: o The impact of crossover in TIVO-1 (Motzer et al 2013) on the results of the NMA was explored in a sensitivity analysis which used crossover-adjusted overall survival outcomes for the TIVO study. A crossover adjusted HR was estimated for inclusion in the PH NMA leading to a hazard ratio of 1.29 (95% CrI 0.85, 1,98, fixed effects) for tivozanib versus sunitinib which is similar to the ITT NMA estimate 1.25 (95% CrI 0.84, 1.88 , fixed effects). Similarly, when incorporating the crossover adjusted data into the non-PH NMA, estimated survival for tivozanib remained relatively consistent with the ITT analyses. o The impact of incorporating the crossover trials that compare sunitinib to sorafenib (Eichelberg et al, 2015 and Tomita et al, 2017)) was explored in a sensitivity analysis which assumed that sorafenib had equivalent survival to sunitinib. The outcome produced similar results; a HR of 0.63 (95% CrI 0.40, 1.00, fixed effects) for avelumab+axitinib vs tivozanib compared to 0.62 (95% CrI 0.37 to 1.05, fixed effects) when the observed HR information was used for sunitinib vs sorafenib. - The perception among clinicians is that tivozanib has similar but not necessarily equivalent efficacy to sunitinib. - NICE guidance (TA512) stated that tivozanib is likely to be less effective than sunitinib and pazopanib

	Comments received from clinician: - It is unlikely that there are clinically meaningful differences in activity between sunitinib and tivozanib. **Comments received from patient organisations:** - Tivozanib should not be considered equivalent to sunitinib in terms of overall survival; this has not been proven.
Technical team judgement after engagement	No change. The technical team took into account the limitations of the overall survival NMA network, the company sensitivity analyses, the clinical input and the TA512 Committee discussion that '*at best tivozanib may have a similar effect to sunitinib or pazopanib*'. It also took into account the fact that the network for overall survival is invalidated due to the limitation of the 2 trials comparing sunitinib with sorafenib (Eichelberg et al, 2015 and Tomita et al, 2017) as described above. Therefore, the technical team considers that alternative approaches should be explored such as an alternative network or assuming that the overall survival associated with tivozanib and sunitinib are the same.

Issue 4 – The overall survival and progression-free survival associated with avelumab+axitinib is modelled differently when compared to different comparators

Background/description of issue	When modelling overall survival and progression-free survival for the all-risk status population, **the company** estimates for avelumab+axitinib differ depending on the comparator: estimates were extrapolated from either the generalised gamma and log-logistic function fitted to the JAVELIN Renal 101 *trial data* (versus sunitinib and versus pazopanib) or the generalised gamma function used in company's *network meta-analysis* (versus tivozanib). **The ERG** noted that overall survival and progression-free survival for avelumab+axitinib for a specified population should be the same, irrespective of comparator. The ERG preferred the extrapolations of the JAVELIN Renal 101 trial which were used versus sunitinib and pazopanib, to also be used versus tivozanib.
Questions for engagement	8. Should different representations of overall survival and progression-free survival for avelumab+axitinib be used depending on the comparator?
Why this issue is important	Modelling survival for an intervention can have an impact on cost-effectiveness results. Therefore, when modelling survival, it's important to ensure the underpinning assumptions are valid.

Technical team preliminary judgement and rationale	The same representations of overall survival for avelumab+axitinib should be used for the same population irrespective of comparator.
Summary of comments	**Comments received from company:** - Agree with the technical team's methodological concerns and with avelumab-axitinib extrapolations based on the JAVELIN Renal 101 trial being also used in the comparison versus tivozanib. **Comments received from clinician:** - Reasonable to model avelumab+axitinib against all first line single agent TKIs combined rather than individually
Technical team judgement after engagement	No change. The same representations of overall survival for avelumab+axitinib should be used for the same population irrespective of comparator. Therefore, for the comparison with tivozanib, the PFS and OS estimates for avelumab+axitinib should be set to be the same as the PFS and OS estimates used for avelumab+axitinib in the comparison with sunitinib and pazopanib (that is, modelled on data from the JAVELIN Renal 101 trial).

Issue 5 – Intervention overall survival extrapolations

Background/description of issue	**The company** used extrapolations (parametric distributions) of the overall survival data observed in the JAVELIN Renal 101 trial, in order to inform the economic model given the lifetime horizon. The selection of parametric distributions was determined using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, visual inspection to assess how closely the chosen parametric curves fitted the JAVELIN Renal 101 trial data, and expert clinical opinion on expected outcomes based on their experience. **The ERG** noted that the survival estimates vary widely depending on the choice of extrapolation curve. For example, in the company model, at the 5-year time point, the proportion of patients alive treated with avelumab+axitinib could be 15.7% using a Gompertz function or 57.1% using a log-normal function. It also noted that using either the log-normal function or the log-logistic function generates clinically implausible overall survival extrapolations as it results in mortality rates for patients treated with avelumab+axitinib falling below (that is, surviving longer than) those of the general population.

	Given the uncertainty of the long-term effectiveness of the intervention, the ERG used the exponential distribution to extrapolate JAVELIN Renal 101 trial OS K-M data, because this function generates the most optimistic cost effectiveness results for the company (47.5% and 22.5% of patients treated with avelumab+axitinib alive after 5 and 10 years respectively), after excluding the log-normal and log-logistic functions.
Questions for engagement	9. Should the exponential distribution be used to extrapolate JAVELIN Renal 101 trial overall survival data? 10. In clinical practice, what proportion of patients would be expected to be alive after 5 and 10 years, if treated with avelumab+axitinib (10%, 20%, 40%, 60%?)?
Why this issue is important	Overall survival extrapolations have an impact on the cost-effectiveness estimates. Using the exponential function for OS extrapolation of avelumab+axitinib results in a small decrease of both overall costs and QALYs for avelumab+axitinib (that is, it assumes treatment is given for a shorter period, and length of life is shorter) leading to a moderate increase of the incremental cost effectiveness estimate (ICER).
Technical team preliminary judgement and rationale	Given the uncertainty, a range of survival extrapolations should be taken into account. The overall survival extrapolations considered should be clinically plausible and incorporate expert opinion and the best available evidence. Survival extrapolations (log-normal and log-logistic) which result in mortality rates for patients falling below those of the general population should not be used.
Summary of comments	**Comments received from company:** - Mortality rates derived using the log-logistic curve (company preferred function) were capped in the economic model so that they could never fall below the general population level. Additionally, using the exponential function (ERG preferred function) still produces mortality rates that fall below those of the general population after 30 years. - Clinical input suggests: o the exponential distribution is an inappropriate choice for an IO-based treatment, because the curve has a constant mortality hazard over time, and this does not allow for a decreasing mortality hazard at the right-hand tail of the OS curve. o a flattening of the OS curve could be expected, and the log-logistic distribution was preferable to extrapolate OS based on visual inspection and the accuracy of PFS and survival predictions.

	o The 5-year and 10-year survival estimates produced by the log-logistic function, of 46.4% and 26.9% respectively, appear valid. **Comments received from clinician:** - At 5 years 20% of patients will be alive and at 10 years 15%
Technical team judgement after engagement	No change. The technical team, taking into account the discrepancy between the clinical input and the survival estimates using either the exponential or the log-logistic function, considers that a range of survival extrapolations should be considered. The overall survival extrapolations should be clinically plausible and incorporate expert opinion as well as the best available evidence.

Issue 6 – Stopping rule in the treatment with avelumab and axitinib at 2 years and treatment waning effect

Background/description of issue	**The company** applied a treatment stopping rule which meant that treatment with avelumab+axitinib was stopped at 2 years. The company assumed that this would result in a loss of treatment effectiveness for 33% of patients (treatment waning effect, estimated, by clinicians, to be between 20% and 50%). The company modelled the treatment waning effect by assuming progression and mortality hazards of one third of patients treated with avelumab+axitinib would gradually merge (over 2 to 4 years) with those of the comparator treatment. The remaining two-thirds of patients were assumed to accrue a lifetime treatment benefit from treatment with avelumab+axitinib. **The ERG** noted that there is no trial evidence to support the company's assumptions that treatment with avelumab and axitinib will be stopped at 2 years. There is also no mention of a stopping rule in the protocol for the Early Access to Medicines Scheme for avelumab+axitinib, in the wording of the EMA licence, or in the JAVELIN Renal 101 trial protocol. Furthermore, there is no evidence that, once treatment with avelumab or axitinib is discontinued, the benefits from these treatments (in terms of improved progression-free survival and overall survival) will, for a third of patients, wane. The ERG stated that these assumptions should not be implemented in the company base case because of the lack of evidence. Furthermore, if a treatment waning effect does occur, there is no rationale for restricting the effect to one third of patients. **The technical team** noted that there was an absence of clinical evidence for avelumab+axitinib, for both a lifetime treatment benefit despite stopping treatment at 2 years, and for the treatment waning

	effect as modelled by the company. It also noted that a stopping rule (stop treatment after 5 years) was not accepted in TA581.
Questions for engagement	11. Should a stopping rule be implemented in the model? If so, at what point? 12. Should the benefit of treatment be modelled to continue after the treatment has stopped? And if so, should there be any waning of the treatment effect?
Why this issue is important	In the model, this stopping rule stops the accrual of treatment costs for all patients after 2 years. However, it is assumed that 2/3 of patients will continue to experience the improvements in quality and length of life associated with having the treatment (despite not taking it), for a lifetime. The modelling of the stopping rule therefore underestimates the ICER.
Technical team preliminary judgement and rationale	Neither a stopping rule nor a waning effect should be modelled given the absence of clinical evidence for avelumab+axitinib.
Summary of comments	**Comments received from company:** - Precedent for a 2 year stopping rule: o A 2-year stopping rule was included as part of the NICE recommendations in a number of appraisals in the past 3 years for nivolumab, pembrolizumab and atezolizumab in multiple indications. o Previous NICE appraisals in lung cancer, head and neck cancer and urothelial carcinoma (TA484, TA490, TA520, TA525) in which a 2-year stopping rule was accepted, despite lack of a stopping rule in relevant trials. - Feedback from clinicians: o They would advise stopping avelumab+axitinib at 2 years for patients still progression-free and believe benefits will continue in most cases. o While uncertainty remains regarding the continued treatment benefit beyond stopping, clinical advice suggests that it is reasonable to assume that up to one third of patients will not continue to realise the same long-term benefits beyond cessation of therapy o The company has consulted 5 clinicians whose estimates on the proportion of patients progressing after 1 or 2 years following stopping treatment ranged between 5% and 10% respectively to 60% and 80% respectively. In the company base case

	the modelled estimate of 22% and 38% at 1 year and 2 years post stopping is withing these ranges. **Comments received from clinician:** - A stopping rule at 2 years would be reasonable assuming that patients who relapse after stopping would be able to re-access the combination upon relapse. - Following stopping treatment, there will be 2 groups of patients, those who never relapse after stopping and those who do. There is no data to instruct the proportions of these two groups. It would be reasonable and conservative to assume a 50:50 split. **Comments received from patient organisations:** - A stopping rule wasn't incorporated into the JAVELIN Renal 101 clinical trial and there is, therefore, no clinical evidence to support the implementation of a stopping rule in the model. - there are a number of unanswered questions regarding this issue, for example: Will patients stop treatment before 2 years? What is the benefit to patients after 2 years? Will patients continue with treatment until they are unable to tolerate the drugs? Will patients benefit from treatment breaks?
Technical team judgement after engagement	Changed. The technical team notes the absence of clinical evidence for avelumab+axitinib, for both a lifetime treatment benefit despite stopping treatment at 2 years, and for the treatment waning effect as modelled by the company. The technical team notes that no previous NICE appraisal in aRCC have accepted a stopping rule and a continued treatment benefit. It also notes the wide range of estimates (10%-80%) in the clinical input on the proportion of patients expected to progress after stopping treatment. The technical team is also unclear about the rationale of stopping axitinib at 2 years. It notes that in the case of the KEYNOTE-426 trial (pembrolizumab+axitinib vs sunitib) (Rini et al, 2019), there is a protocol specified stopping rule at 2 years which applies only to pembrolizumab. The technical team considers that the inclusion of a stopping rule and the assumptions of continued treatment benefit in the absence of any evidence add to the uncertainty on the long-term effectiveness of the intervention as modelled by the company. Relevant scenario analyses factoring in the stopping rule and the treatment effect waning or not should be presented to the Appraisal Committee to allow assessment of the impact of this uncertainty on the cost-effectiveness estimates.

Issue 7 – Source of clinical parameters used in the economic model

Background/description of issue	**The company** presented cost-effectiveness estimates primarily based on the results of the first interim analysis (data cut-off date: 20 June 2018). Clinical results of the second interim analysis (data cut-off date: 28 January 2019) are currently available and summaries were presented. **The technical team** noted that one of the major limitations of the cost-effectiveness estimates was the uncertainty due to the immaturity of the JAVELIN Renal 101 survival results. It also noted that the cost-effectiveness estimates should be informed by the latest and most mature evidence.
Questions for engagement	13. Should data from the second interim analysis be used to inform the cost effectiveness model where available?
Why this issue is important	The trial data for this topic are immature, so it's important to use the latest data cuts available.
Technical team preliminary judgement and rationale	The company should present exploratory analyses using the latest data cuts from JAVELIN Renal 101.
Summary of comments	**Comments received from company:** - Interim analysis 2 data would necessarily also incorporate interim analysis 1 data for safety and time-on-treatment - The PFS and OS HR point estimates for interim analysis 2 are broadly similar to those of interim analysis 1 - The use of data from interim analysis 2 in the economic model would not reduce uncertainty surrounding the overall survival benefit of avelumab+axitinib **Comments received from clinician:** - Data from the second interim analysis should be used to inform the cost effectiveness model where available **Comments received from patient organisations:** - Data from the second interim analysis should be used to inform the cost effectiveness model where available
Technical team judgement after engagement	No change, the company should present analyses using the latest data cuts from JAVELIN Renal 101.

Issue 8 – External validity of the JAVELIN Renal 101 trial results

Background/description of issue	In the cost-effectiveness model **the company** modelled the dosing of avelumab+axitinib in line with the licensed dosing regimen; that is, a flat IV dose of 800mg avelumab Q2W and 5mg axitinib twice daily. However, this is different to the dose of avelumab used in the JAVELIN Renal 101 trial, which was calculated based on patient weight (10mg/kg of body weight). Although the company states pharmacology data support this flat dosing schedule, there is no clinical effectiveness evidence provided using the licenced dosing regimen which is going to be used in clinical practice. Additionally, the JAVELIN Renal 101 trial included only patients with clear cell advanced RCC. Although this is the most common form of RCC, the proportion of patients in NHS clinical practice with non-clear cell advanced RCC may be as high as 25%. Furthermore, the JAVELIN Renal 101 trial excluded patients with Eastern Cooperative Oncology Group Performance Status ≥2 and people with some comorbidities who might otherwise be considered for treatment in clinical practice. **The ERG and the technical team** noted that the difference between the licensed dose of avelumab, and that used in the JAVELIN Renal 101 trial may limit the generalisability of the trial results. They also noted that the exclusion of patients with non-clear cell RCC, Eastern Cooperative Oncology Group Performance Status ≥2 and people with some comorbidities may limit the generalisability of the trial results to these patients.
Questions for engagement	14. Are the trial results generalisable to NHS practice or people with poor performance status? 15. What is the likely impact on clinical effectiveness of the dose being different in the trial to that which will be used in clinical practice? 16. In clinical practice, what would be the difference in expected treatment effect between those with clear and non-clear cell RCC? Is it appropriate to extrapolate the results to non-clear RCC?
Why this issue is important	If the trial dose and population is too different to that seen in NHS practice, the benefit of the intervention demonstrated in the trial might not be the same as that seen in clinical practice.
Technical team preliminary judgement and rationale	If available, evidence supporting the equivalence of the dosing regimen used in the trial with the licenced one should be provided. The generalisability of the trial results to NHS practice should be explored.

Summary of comments	**Comments received from company:** - Baseline characteristics of the patients who entered into the JAVELIN Renal 101 trial reflect clinical practice globally and in the UK - ECOG: o There is no reason to believe that patients with an ECOG score greater than 1 would not benefit from treatment in line with the EMA licence o Both avelumab and axitinib have been used in clinical practice in patients with performance status >2 with no additional burden and similar efficacy results - Dosing o Pharmacokinetic modelling and simulation studies showed similar predicted PK exposure with less variability for flat dosing. Additional justification for the flat dose regimen was obtained from the similarity in the predicted efficacy and safety profiles for the flat versus weight-based dosing regimens. o Regulators accepted the change in the dosing regimen from weight based to flat dosing o A flat dosing regimen provides more consistent dosing across body weights, minimises drug wastage, facilitate preparation and administration, and reduce pharmacy errors. - Clear cell RCC o Clear cell and non-clear cell components are not mutually exclusive. JAVELIN Renal 101 trial included patients with a clear cell component. This means that patients recruited could still have a heterogenous tumour with non-clear cell components. o Licence includes all advanced RCC patients o Sunitinib is recommended for all advanced and/ or metastatic RCC patients (TA169) based on a study looking at patients with clear cell RCC. As avelumab in combination with axitinib has shown clinical benefit over sunitinib in a similar cohort of patients, the combination should also be available to nccRCC patients. **Comments received from clinician:** - Trial results are generalisable to NHS practice or people with poor performance status

	- The flat dose will be equally active to the weight adjusted dose. There is abundant precedent with immune checkpoint inhibitors for this. - The activity in patients with non-clear cell RCC is unknown. Our experts would not assume equivalent activity. - Non-clear cell RCC is an area of significant clinical need. It would be helpful if, in the case axitininb-avelumab is approved for used within CDF, patients with non-clear cell RCC are allowed to be recruited and outcomes audited. **Comments received from patient organisations:** - The trial results are generalisable to NHS clinical practice, but not patients with poor performance status. - It is not appropriate to extrapolate the JAVELIN Renal 101 results to non-clear cell RCC. - there were some patients with a sarcomatoid element to their clear cell RCC included in JAVELIN Renal 101, and these patients showed a PFS benefit versus sarcomatoid patients on sunitinib.
Technical team judgement after engagement	No change. The technical team notes the evidence provided and published in the EPAR and EAMS scientific opinion and the clinical input. It notes that there is precedent for similar changes in dosing regimens in checkpoint inhibitors (eg nivolumab). The technical team notes the uncertainty on the effectiveness of the combination on patients with non-clear cell RCC and the need for evidence generation in this patient population.

Issue 9 – Consideration for the Cancer drugs Fund

Background/description of issue	The **company** notes that JAVELIN Renal 101 data for overall survival are immature. It anticipates that data will be sufficiently mature to reassess following the final analysis (date of final analysis is confidential) at which point 535 deaths required for final OS analysis will have occurred. It states that in the interim, including avelumab in combination with axitinib in the Cancer Drugs Fund (CDF) will allow patients access to treatment. The **technical team** note that the key study for this drug is still ongoing, and not enough data are yet available to estimate overall survival.
Questions for engagement	17. Will the ongoing data collection in JAVELIN 101 be sufficient to address uncertainties in the effectiveness of avelumab+axitinib?

	18. Are any data other than overall survival required to inform the effectiveness of avelumab+axitinib? 19. Based on current modelling, does the treatment have a potential to be cost effective?
Why this issue is important	Data are immature, so there is uncertainty about the effectiveness of this drug. A recommendation on the CDF would allow access to the drug whilst the required data is collected. However, the CDF should only be used if the data collection will truly address the uncertainty.
Technical team preliminary judgement and rationale	Ongoing data collection in the Javelin 101 trial would address a key uncertainty in this appraisal.
Summary of comments	**Comments received from company:** - By 2023 the JAVELIN Renal 101 study will have 5 years of follow-up data - Aveluamb+axitinib can be cost-effective if the trial data is used to model overall survival and the committee acknowledge that most patients are not treated with immune-oncology combinations until progression **Comments received from clinician:** - Current modelling is highly flawed if it is only based on assumptions of equivalent overall survival between TKIs and axitinib - avelumab **Comments received from patient organisations:** - As the overall survival data from JAVELIN Renal 101 matures and ongoing data collection from the Early Access to Medicine Scheme (EAMS) continues, we are confident that this will be sufficient to show an overall survival benefit
Technical team judgement after engagement	No change. Ongoing data collection in the Javelin 101 trial would address a key uncertainty in this appraisal.

4. Other issues for information

Tables 1 to 3 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: avelumab+axitinib versus sunitinib, pazopanib and tivozanib (all risk status population) (using company base case, that is, using discounted prices for avelumab and axitinib and list prices for comparators)

Alteration	Technical team rationale	Approximate changes from base case		
		Sunitinib	Pazopanib	Tivozanib
Company base case	–	**<30,000**	**<30,000**	**<30,000**
1. Set OS for sunitinib, pazopanib and tivozanib to be the same as the OS for avelumab+axitinib	Issue 1, 3	+£120,000	+£140,000	+£27,000
2. Remove stopping rule	Issue 6	+£160,000	+£160,000	+£80,000
3. Remove treatment waning effect	Issue 6	-£5,000	-£6,000	-£1,000
4. Use exponential function for OS extrapolation of avelumab+axitinib and sunitinib	Issue 5	+£7,000	+£9,000	+£1,000
5. Set avelumab+axitinib PFS and OS to be the same as avelumab+axitinib PFS and OS in the comparison with sunitinib and pazopanib	Issue 4	-	-	-£1,000

Table 2: Technical team preferred assumptions and impact on the cost-effectiveness estimate: avelumab+axitinib versus cabozantinib (IMDC intermediate/poor risk status population) (using company base case, that is, using discounted prices for avelumab and axitinib and list prices for comparators)

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	***Dominant***	
1. Avelumab+axitinib OS assumed to be the same and PFS worse than cabozantinib.	Issue 2	*Dominated*	
2. Remove stopping rule	Issue 6	>£200,000	-
3. Remove treatment waning effect	Issue 6	<£30,000	-

Table 3: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Javelin Renal 101 trial was an open label trial due to the different routes of administration of the randomized interventions. Participants and investigators were not blinded to treatment allocation. Regarding endpoint assessment, blinded independent central review was used for tumor assessment (RECIST version 1.1).	Lack of participant and investigator blinding is a potential source of bias. Blinded independent central review was used to minimize bias on endpoint adjudication. The risk of bias remains on patient-reported outcomes including EQ-5D-5L.	Unknown

Table 4: Other issues for information

Issue	Comments
Equivalence of sunitinib and pazopanib	The company has assumed that the effectiveness of pazopanib is equivalent to the effectiveness of sunitinib in line with previous NICE technology appraisals (TA512, TA581).

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