ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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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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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]

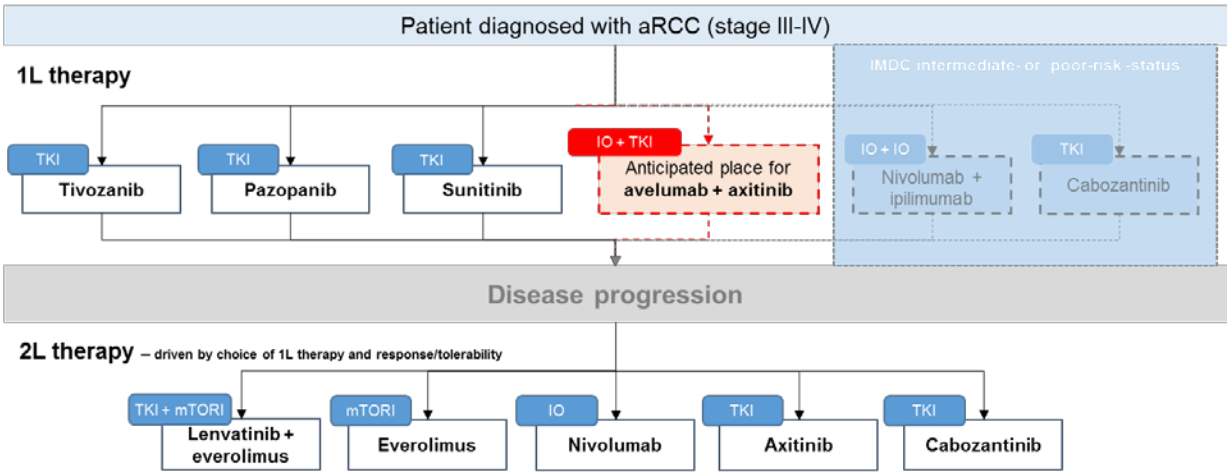
Treatment options

- 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.

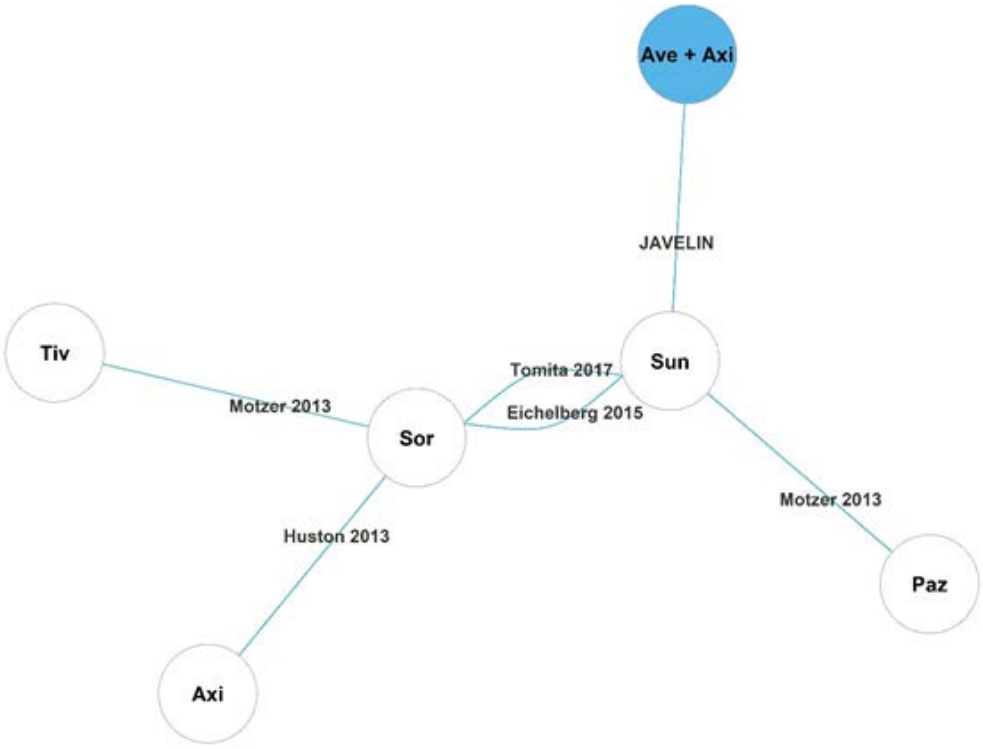


Figure 2 Network diagram for PFS and OS in the all risk status population

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

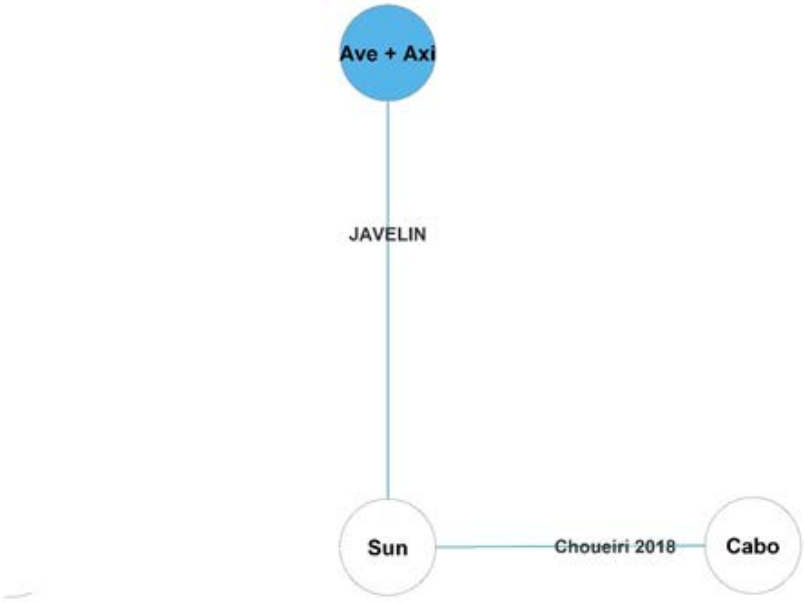


Figure 3 Network diagram for PFS and OS in the IMDC intermediate/poor risk status population

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]).

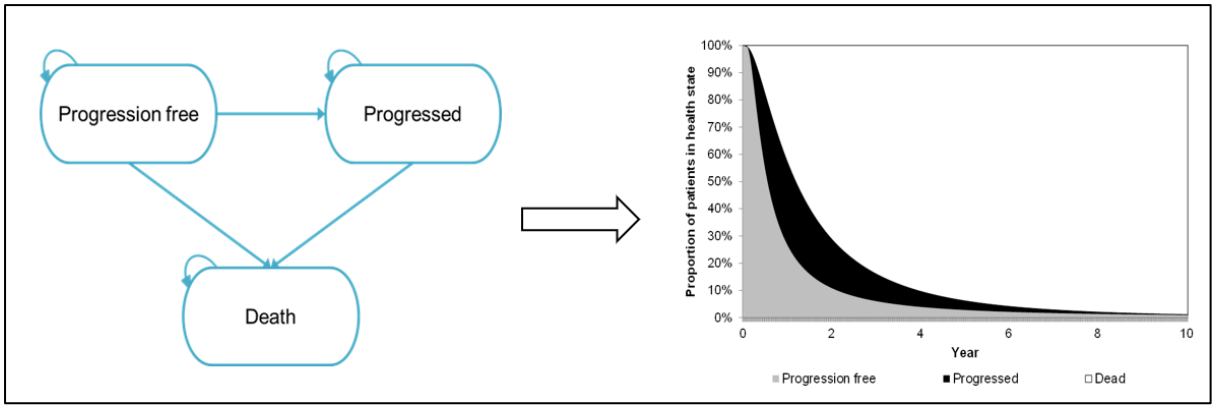


Figure 4 Structure of the company model

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

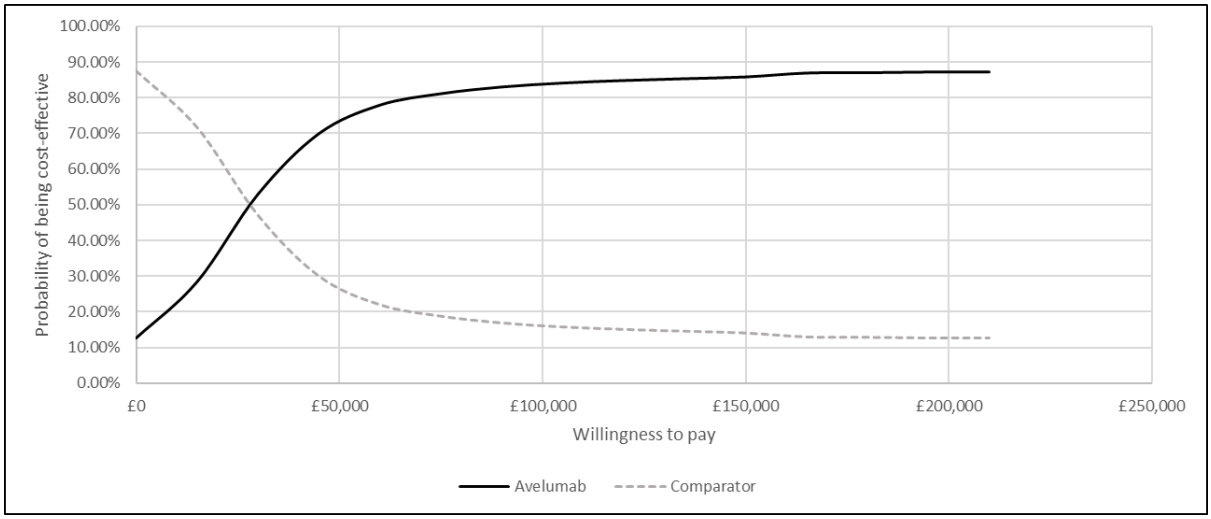


Figure 10 Cost effectiveness acceptability curve of treatment with avelumab+axitinib versus sunitinib

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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£29,542***	
R1. Remove stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£186,529	+£156,987
R2. Remove treatment waning effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,706	-£5,836
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]	£48,714	+£19,171
R4. Use exponential function for OS extrapolation of avelumab+axitinib and sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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]	[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]	£168,525	+£138,983
R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£152,578***	***+£123,036***
R1+R3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£303,784***	***+£274,242***
R1+R2, R4+R6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£1,184,385***	***+£1,154,843***
R1+R3, R4+R6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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]. [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