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

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drafted the report; Ines Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
aRCC	Advanced renal cell carcinoma
BICR	Blinded independent central review
BNF	British National Formulary
CDF	Cancer Drugs Fund
CI	Confidence interval
CIC	Commercial in confidence
CAA	Commercial access arrangement
cPAS	Comparator PAS
CS	Company submission
CSR	Clinical study report
DCO	Data cut-off
DSU	Decision Support Unit
EAG	External Assessment Group
EAMS	Early Access to Medicines Scheme
ECOG PS	Eastern Cooperative Oncology Group performance status (score)
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
FAS	Full Analysis Set
FKSI-19	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 19 items
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IMDC	International Metastatic RCC Database Consortium
IO	Immunotherapy
ITC	Indirect treatment comparison

ITT	Intention-to-treat
IV	Intravenous
MCID	Minimum clinically important difference
MSKCC	Memorial Sloan Kettering Cancer Center
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression free survival
PRO	Patient-reported outcome
PSS	Personal Social Services
QALY	Quality-adjusted life year
Q-TWiST	Quality-adjusted Time Without Symptoms or Toxicity
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RWE	Real-world evidence
SACT	Systemic anti-cancer therapy
SAP	Statistical analysis plan
SLR	Systematic literature review
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
VAS	Visual analogue scale
VEGFR	Vascular endothelial growth factor receptor

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides our critique of the company's adherence to the committee's preferred assumptions from the Terms of Engagement. Section 1.2 provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.4 to 1.7 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Critique of the company's adherence to the committee's preferred assumptions

When avelumab plus axitinib was recommended for untreated advanced renal cell carcinoma (aRCC) within the Cancer Drugs Fund the NICE committee stated that when the guidance was reviewed the updated model should include the preferred assumptions listed below (unless new evidence indicated otherwise) (TA645 paragraph 3.20):

- No stopping rule
- Trial evidence and costs adjusted to reflect subsequent treatments used in NHS practice, including adjusting for life-extending treatments used in the trial not available in the NHS and justifying the methods used to adjust for follow-on treatments
- A range of overall survival extrapolations explored, including the exponential curve
- The modelled overall survival treatment effect over comparators over time, explicitly presented

The company's updated appraisal has adhered to the above points outlined in the managed access agreement.

1.2 Overview of the EAG's key issues

Table 1 Summary of Key issues

ID	Summary of issue	Report sections
1	Effectiveness of avelumab with axitinib versus comparators for people with non-clear-cell aRCC	2.1, 3.2.7.1.2, 3.6
2	Parametric curve used for modelling overall survival in the favourable-risk population	4.2.4.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are changes in the prices used for sunitinib and everolimus; see section 1.8 below.

1.3 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The revised company model base case deterministic results are shown in Table 2. The pairwise ICER for avelumab with axitinib versus sunitinib is [redacted] per QALY. Tivozanib and pazopanib are 'dominated' by sunitinib: that is, they have high costs but by assumption produce the same QALY gain. The pairwise ICER for avelumab with axitinib versus tivozanib is [redacted] per QALY and versus pazopanib is [redacted] per QALY.

Table 2 Base case results of the revised company model, PAS price for avelumab (favourable-risk population).

Treatment	Total		Incremental		ICER
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
Versus sunitinib					
Sunitinib	£93,185	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib					
Tivozanib	£136,173	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib					
Pazopanib	£165,275	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from Table 12 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.

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

No new issues since TA645[1] were identified with respect to the decision problem. We note that treatment choice in adults with untreated aRCC is now determined by considering International Metastatic RCC Database Consortium (IMDC) risk category alongside individual patient characteristics and the company have chosen to focus their submission and economic model base case on the subgroup of patients with favourable-risk aRCC. The company have also presented evidence for the intermediate-/poor-risk subgroup as well as the full intention-to-treat (ITT) population.

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

Issue 1 Effectiveness of avelumab with axitinib versus comparators for people with non-clear-cell aRCC

Report section	2.1, 3.2.7.1.2, 3.6
Description of issue and why the EAG has identified it as important	A key uncertainty from TA645 (paragraph 3.19 of the NICE guidance document) was the lack of data on whether avelumab with axitinib is effective for non-clear-cell disease. The committee agreed that this was one of two uncertainties that could be resolved by collecting further data to monitor whether there is a difference in effectiveness in comparison to those with clear-cell histology (paragraph 3.7 of the NICE guidance document). Data collected from patients treated within the Cancer Drugs Fund shows that median overall survival (OS) in the non-clear cell population (n=[redacted]) is [redacted] than for the clear cell aRCC population (n=[redacted]). However, as the Cancer Drugs Fund does not include data for people with non-clear-cell disease treated with the possible comparator treatments the effectiveness of avelumab with axitinib in comparison to relevant comparators in this group of patients is still unknown.
What alternative approach has the EAG suggested?	No alternative suggested.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion on whether the JAVELIN Renal 101 trial results in people advanced renal cell carcinoma (aRCC) with clear-cell histology are likely to be generalisable to people with aRCC of non-clear-cell histology.

1.6 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 2 Uncertainty over long-term predictions of overall survival

Report section	4.2.4.1
Description of issue and why the EAG has identified it as important	There is a high uncertainty over long-term survival; although many of the parametric survival curves fit the KM data initially, their long-term projections vary significantly beyond 10 years. The company uses a log-normal distribution for avelumab with axitinib for OS, and the generalised gamma for sunitinib (and therefore also pazopanib and tivozanib).They test alternative extrapolations in scenario analysis, which show that the cost-effectiveness results are sensitive to the choice of survival curves.
What alternative approach has the EAG suggested?	Further external evidence is needed to inform the choice of OS curves for the avelumab with axitinib and sunitinib treatment arms.
What is the expected effect on the cost-effectiveness estimates?	In the company revised base case, the ICER is [redacted] per QALY for avelumab with axitinib versus sunitinib. The following ICERs are produced in scenario analyses (see section 6): • OS avelumab with axitinib: o Exponential: [redacted] per QALY o Generalised gamma: [redacted] per QALY • OS sunitinib: o Weibull: [redacted] per QALY o Exponential: [redacted] per QALY Results for pazopanib and tivozanib are presented in Table 21.
What additional evidence or analyses might help to resolve this key issue?	Hazard function plots from the JAVELIN Renal 101 trial OS data to show how hazards changed over time for patients with favourable-risk disease in the avelumab with axitinib and sunitinib arms. Further expert opinion on the plausibility of long term survival extrapolations from the trial data (from 10 years onwards)

1.7 Other key issues: summary of the EAG's view

We have no other key issues.

1.8 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's economic model in section 4, we have implemented a single change to the revised company base case. This involves updating the costs of sunitinib and everolimus using the most recent eMIT prices (see Table 14). Table 3 below presents a comparison of the revised company base case results and the EAG preferred base case, including a PAS discount of [redacted] for avelumab.

Table 3 Company revised base case and EAG preferred base case results (favourable-risk population)

Base case	Treatment	Total cost	Total QALYs	ICER (£/QALY) [a]
Company base case	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
EAG preferred base case	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Source: reproduced using company economic model and EAG base case model.
Ave + axi, avelumab with axitinib; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
[a] Pairwise ICERs for Avelumab with axitinib relative to each comparator. Pazopanib and tivozanib are dominated by sunitinib in all scenarios, as they have a higher cost and by assumption provide the same QALY gain

For further details of the exploratory and sensitivity analyses done by the EAG, see section 6 of this EAG report.

The EAG notes two additional uncertainties related to the cost-effectiveness analysis:

- Relative dose intensity (RDI) has been implemented for the intervention and comparators but not for subsequent treatments; see section 4.2.6.2.3.
- TA645 included oral administration costs but these were not included in the company's submission for the current appraisal. The reason for this change has not been explained. See section 4.2.6.2.4.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Merck on the clinical effectiveness and cost effectiveness of avelumab (Bavencio) in combination with axitinib (Inlyta) for treating adults with untreated advanced renal cell carcinoma (aRCC). It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 2nd December 2024. A response from the company via NICE was received by the EAG on 18th December 2024 and this can be seen in the NICE committee papers for this appraisal.

The key areas of clinical uncertainty identified by the appraisal committee during TA645 and listed in the managed access agreement were:

- the immaturity of the overall survival data and the companies' approach to modelling overall survival over the long term
- the lack of data on whether the treatment is effective for non-clear-cell disease and
- the companies' methods for adjusting both the costs and benefits of subsequent treatments to reflect NHS practice

It was concluded that further data collection within the Cancer Drugs Fund (CDF) could potentially resolve the uncertainty regarding the first two points (immaturity of the survival data and treatment effectiveness for non-clear-cell disease).

For this appraisal the CS addresses the key areas of clinical uncertainty from TA645 by:

- providing data from the final analysis of the JAVELIN Renal 101 trial of avelumab with axitinib versus sunitinib (data cut off 31 August 2023). See section 3.2.1 of this report.
- Presenting real-world evidence on overall survival for patients who received avelumab with axitinib in the UK from the CDF or an Early Access to Medicines Scheme (EAMS). Some of these patients had non-clear-cell disease. See section 3.2.7.1.2 of this report.
- Using data from the McGrane et al. analysis of RWE to adjust the costs of subsequent treatment in a scenario analysis (see section 4.2.6.2.5 of this report). No adjustments for subsequent treatment use are made to the clinical data used to inform the model.

2.2 Background

2.2.1 Background information on advanced renal cell carcinoma (aRCC)

Renal cell carcinoma (RCC) starts in the lining (epithelium) of the tubules of the kidney and is the most common type of kidney cancer, accounting for about 80% of cases.[2] The company report the key facts of the disease appropriately in CS section B.1.3.1. The reported epidemiological data aligns with the latest statistics from Cancer Research UK,[3] one of the company's sources, and the EAG are satisfied that the epidemiological data for aRCC in the CS is relevant to the UK.

Renal cell carcinoma (RCC) has different histological subtypes: clear-cell RCC which is the most common, and non-clear cell RCC which groups together other subtypes. Company data reported for the proportions of people with clear cell RCC and non-clear cell RCC are from a confidential NHS England systemic anti-cancer therapy (SACT) data report[4] produced for this review. However, the proportions of clear cell and non-clear cell aRCC [redacted] to the published McGrane 2024 study of 1319 aRCC patients in the UK of whom 83.1% had a clear cell component.[5]

CS section B.1.3.1.1 describes staging and prognostic risk factors for aRCC. The International Metastatic RCC Database Consortium (IMDC) criteria (also known as Heng Criteria) are commonly used in the UK clinical practice to categorise patients into favourable-, intermediate- and poor-risk subgroups for survival based on the criteria presented in CS Figure 3. A person's disease risk status then helps to decide treatment choice (section 2.2.3).

2.2.2 Background information on avelumab with axitinib

Avelumab in combination with axitinib is indicated for first line treatment of adults with aRCC.[6] In September 2020 avelumab with axitinib was recommended by NICE for use in this population within the Cancer Drugs Fund subject to the conditions set out in its Managed Access Agreement being followed.[1 7] The licensed indication[6] includes:

- all risk groups that now determine the treatment pathway for aRCC patients in the NHS (see treatment pathway in section 2.2.3 below).
- all histological subtypes, i.e. whether clear cell or non-clear cell aRCC, although the company pivotal trial does not evaluate its use in non-clear cell aRCC
- tumours that are programmed cell death ligand-1 (PD-L1) positive and those that are PD-L1 negative.

Avelumab is a type of immunotherapy that blocks the PD-L1 protein. PD-L1 is present on immune cells and it may also be present on cancer cells where it can stop the body's T cells fighting the cancer.[6] However, the recent European Society for Medical Oncology (ESMO) RCC guideline (Powles et al. 2024)[8] states that PD-L1 has been unreliable as a biomarker in renal cancer, and testing people with aRCC to see if their tumour is PD-L1-positive is not routinely available on the NHS. The EAG's clinical expert confirmed this, advising us that they do not take PD-L1 status into account when considering first-line therapy, nor do they test for it.

Axitinib is a tyrosine kinase inhibitor (TKI) that inhibits the vascular endothelial growth factor receptors (VEGFR), VEGFR-1, VEGFR-2 and VEGFR-3, that are implicated in the abnormal growth of blood vessels, tumour growth and disease progression in cancer.[9] Axitinib as a monotherapy is recommended by NICE as a subsequent treatment for aRCC when sunitinib or other cytokine therapy has failed.[10]

For the treatment of adults with aRCC the recommended dose of avelumab in combination with axitinib, according to its marketing authorisation, is 800 mg of avelumab administered intravenously every two weeks and 5 mg of axitinib administered orally twice a day until disease progression or unacceptable toxicity.[6] The dose of axitinib may be increased or reduced, or temporarily discontinued, based on patient safety and tolerability.[6]

2.2.3 The position of avelumab with axitinib in the treatment pathway

There are no treatment guidelines for aRCC specific to the UK. NICE has a kidney cancer guideline (NG10398) in development. However, in practice, our clinical expert advised us that they refer primarily to the NICE recommendations for individual treatments and that the ESMO RCC guideline[8] can be useful with the caveat that funding is not in place in the UK for many of the ESMO treatment pathways.

NICE guidance for individual treatments state that choice of first line treatment for aRCC depends on a person's disease risk status, according to the IMDC criteria for aRCC, and European Cooperative Oncology Group (ECOG) performance status score. Treatment options, according to NICE guidance, for those with favourable-risk disease are: avelumab with axitinib (via the CDF),[1 7] or one of the tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, or tivozanib.[11-13] Treatment options for those with intermediate- or poor-risk disease include the same options as for favourable-risk disease with the additional options of cabozantinib,[14] two further combination immunotherapy/tyrosine kinase inhibitor (IO/TKI) options and a combined immunotherapy option (IO/IO): cabozantinib with nivolumab (TA964),[15] lenvatinib with pembrolizumab (TA858),[16] and nivolumab with ipilimumab

(TA780).[17] The combination IO/TKI and IO/IO therapies were not available at the time of the original avelumab with axitinib appraisal (TA645). Both nivolumab and pembrolizumab are also programmed cell death-1 (PD-1)/PD-L1 checkpoint inhibitor therapies like avelumab.

Therefore, avelumab with axitinib, via the CDF, represents an additional IO/TKI combination treatment option at first line for all aRCC risk groups, and is the only IO/TKI combination treatment recommended for the favourable risk group. This is shown in CS Figure 5 which is replicated in Figure 1 below.

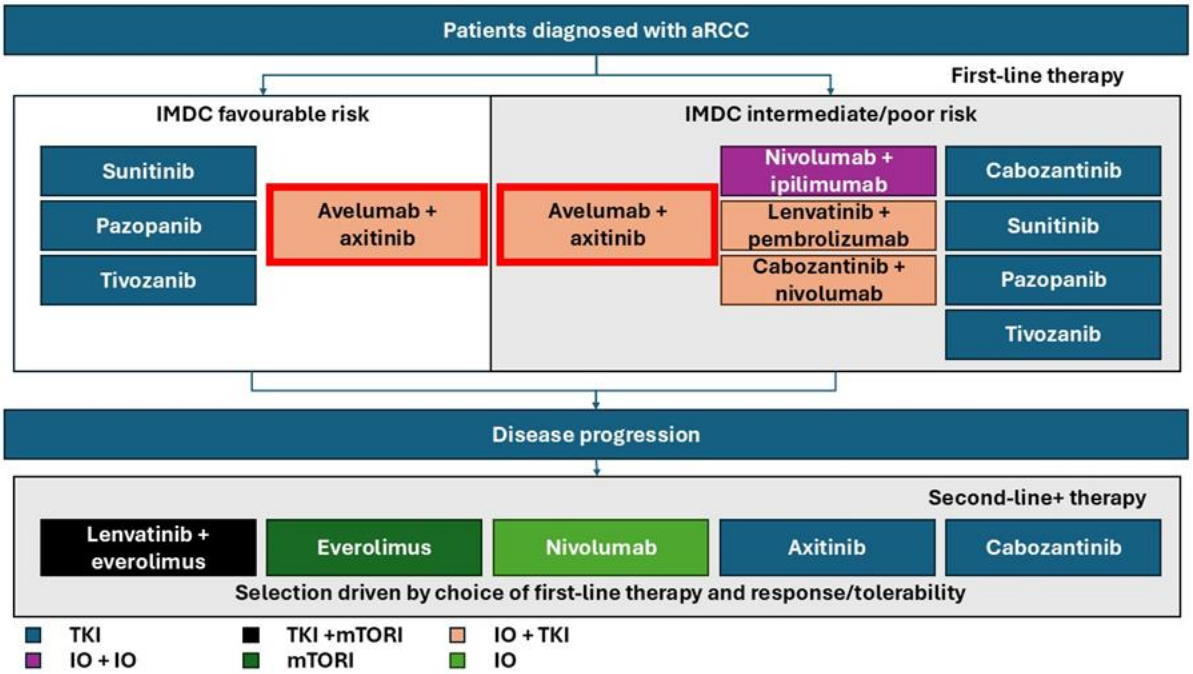

Figure 1 Clinical pathway of care including the anticipated place for avelumab with axitinib

Source: Reproduced from CS Figure 5.
Abbreviations: aRCC, advanced renal cell cancer; CDF, cancer drugs fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; mTORI, mammalian target of rapamycin inhibitor; TKI, tyrosine kinase inhibitor.

Briefly, second line treatment options for aRCC outlined in Figure 1 above include nivolumab (according to TA417, but not after prior immunotherapy),[18] axitinib (according to TA333),[10] cabozantinib (according to TA463),[19] everolimus (according to TA432)[20] or lenvatinib with everolimus (according to TA498).[21] Choice of subsequent treatment options depend on the class of drug received for first line treatment and how the patient tolerated and responded to it. The EAG's clinical expert confirmed this and added that they might also consider trial data for second-line treatments and discussions with colleagues. People who receive an immunotherapy option at first line do not receive another at second line as advised in the

international guidelines.[8 22 23] Our clinical expert added that immunotherapy may not be given in combination with TKI or as dual immunotherapy in the second line setting, even if no immunotherapy was given at first-line, and this is as illustrated in the treatment pathway in Figure 1 above. Furthermore, our clinical expert noted that a patient with complete response to immunotherapy cannot stop treatment and then restart at the point of progression, therefore in order to retain access to a treatment that works a patient with no disease on scans may continue treatment, perhaps unnecessarily, for many years. Nivolumab is the only PD-1/PD-L1 immunotherapy available at second line and beyond. Subsequent treatments are relevant to the economic model and are further discussed in section 4.2.6.2.5.

EAG conclusion on background information

The company have accurately summarised aRCC and the treatment pathway for this. Since avelumab with axitinib entered the CDF in 2020 the treatment pathway for people with aRCC has changed, firstly to take into account a person's prognostic risk status to decide first-line treatment options, and secondly to include three new combination treatments that are available for people with intermediate-/poor- prognostic risk status.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	Adults with untreated aRCC	Adults with untreated aRCC with IMDC favourable-risk disease and intermediate-/poor-risk disease	Aligned with the evolution of the treatment pathway, evidence is additionally presented as subgroups of particular interest: people with favourable-risk disease and people with intermediate-/poor-risk disease.	We agree with the company that treatment choice in adults with untreated aRCC is now determined by considering IMDC risk category alongside individual patient characteristics. The company present their evidence focussing on the favourable-risk subgroup (which is the population in the economic model base case) but also present evidence for the intermediate-/poor-risk subgroup as well as the full ITT population. As noted in TA645[1] the company's key trial, JAVELIN Renal 101 is limited to people with clear cell aRCC.
Intervention	Avelumab with axitinib	Avelumab with axitinib	In line with the NICE final scope.	No additional comment
Comparators	Favourable-risk disease as defined in the IMDC criteria: • Pazopanib • Sunitinib • Tivozanib	Favourable-risk disease as defined in the IMDC criteria: • Pazopanib • Sunitinib • Tivozanib	In line with the NICE final scope.	As was the case in TA645, direct evidence is available from the JAVELIN Renal 101 trial for the comparison with sunitinib. For the comparisons with pazopanib and

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	Intermediate-/poor-risk disease as defined in the IMDC criteria: • Cabozantinib • Nivolumab with ipilimumab • Lenvatinib with pembrolizumab • Cabozantinib with nivolumab • Pazopanib • Sunitinib • Tivozanib	Intermediate-/poor-risk disease as defined in the IMDC criteria: • Cabozantinib • Nivolumab with ipilimumab • Lenvatinib with pembrolizumab • Cabozantinib with nivolumab • Pazopanib • Sunitinib • Tivozanib		tivozanib in the favourable-risk disease subgroup and in the ITT population the company followed the precedent set in previous NICE appraisals and assumed similar efficacy for the TKI monotherapies (i.e. pazopanib and tivozanib assumed to have similar efficacy to sunitinib). For the intermediate-/poor-risk subgroup a network meta-analysis was used to compare avelumab + axitinib to cabozantinib; nivolumab + ipilimumab; lenvatinib + pembrolizumab; cabozantinib + nivolumab; and sunitinib. Pazopanib and tivozanib were assumed to have similar efficacy as sunitinib.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • duration of response • time on treatment/time to next treatment • adverse effects of treatment • health-related quality of life.	As per the final scope, the submission considers the following outcomes: • overall survival • progression-free survival • response rates • duration of response • time on treatment/time to next treatment • adverse effects of treatment	In line with the NICE final scope.	All outcome measures are considered. The network meta-analysis was only conducted for overall survival and progression-free survival (because these were the outcomes informing the economic model).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		• health-related quality of life.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The cost-effectiveness analysis takes into consideration commercial arrangements for the following treatments: • avelumab • pazopanib There are commercial arrangements for the following treatments that could not be taken into consideration since the volume of any Patient Access Scheme (PAS) discounts are unknown: • axitinib • tivozanib • cabozantinib • nivolumab • ipilimumab • pembrolizumab • lenvatinib	The cost-effectiveness analysis is in line with the NICE final scope, except for the specification of PAS discounts which are confidential.	The company's cost-utility analysis adheres to the NICE reference case. The population modelled in the base case is the favourable-risk subgroup, we consider this focus acceptable. The existing simple PAS price discount for avelumab and a published discount for pazopanib are applied in the economic evaluation.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Subgroups	If the evidence allows the following subgroup will be considered: • Favourable-risk advanced metastatic RCC as defined in the IMDC criteria • Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • PD-L1 status	• IMDC favourable-risk subgroup • IMDC intermediate-/poor-risk subgroup • PD-L1 status	In line with the NICE final scope. Evidence is presented for the PD-L1 positive (+) subgroup; however, clinical opinion suggests that PD-L1 status is not relevant to systemic treatment decision-making for aRCC and hence it has not been explored in cost-effectiveness analyses.[1 24]	No additional comment

Source: CS Table 1 with EAG comments added.
aRCC, advanced renal cell carcinoma; CS, company submission; IMDC, international metastatic renal cell cancer database consortium; ITT, intention-to-treat; NICE, National Institute for Health and Care Excellence; PD-L1, programmed cell death-ligand-1; TA, technology appraisal; TKI, tyrosine kinase inhibitor.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company performed two systematic literature reviews (SLRs),

- one to identify randomised controlled trial (RCT) evidence for efficacy, safety and tolerability of all treatments for untreated aRCC which was originally carried out for the company's previous submission to NICE and updated for this submission, and
- a new one to identify real-world evidence (RWE) exploring the benefits of treatment with avelumab in combination with axitinib since its availability in 2019 (see section 3.2.6).

3.1.1 RCT systematic literature review (SLR)

For the RCT SLR, the main healthcare databases, relevant conferences, and the bibliographies of systematic reviews, were last searched on 4 June 2024 (CS section B.2.1 and CS Appendix D.1.1) or 13 May 2024 (CS section B.2.10.1). Screening was carried out using eligibility criteria that align with the NICE scope (CS Appendix D.3 Table 27) and generally the review methods were appropriate. Despite some lack of clarity around reporting, e.g. details in the included PRISMA flow diagram, and that no lists of excluded or included studies were provided with the submission, we consider that the SLR is up to date and not likely to be missing any relevant RCTs. A summary of the EAG's appraisal of the systematic review methods for the RCT SLR is in Appendix 1.

The RCT SLR identified 76 unique studies (503 publications), from the original search and all update searches, that evaluated all relevant treatments for aRCC (CS Appendix D.5 Figure 1). One relevant RCT was identified evaluating avelumab with axitinib compared to sunitinib, JAVELIN Renal 101 (CS section B.2.2 and CS Appendix D.5.1-5.2). The company explain that evidence from a dose-finding phase 1b trial, JAVELIN Renal 100, has been superseded by the final analysis of JAVELIN Renal 101 and real-world evidence (CS section B.2.2) and the EAG agree. We therefore agree that JAVELIN Renal 101 is the only relevant RCT evaluating avelumab with axitinib and we discuss it further in section 3.2 below. This trial provides evidence for both the favourable-risk and intermediate-/poor-risk aRCC subgroups.

The company's SLR additionally identified five relevant RCTs that evaluated comparator treatment options listed in the NICE scope for the intermediate-/poor-risk subgroup and they were included in the company's indirect treatment comparison (ITC) in CS section B.2.10. A list of excluded studies was not provided for the ITC – therefore although we can confirm

that the included studies are relevant, we cannot assess whether all relevant studies were included. We discuss the identification of studies for the ITC in section 3.3.2.

3.1.2 RWE SLR

The RWE SLR sought to identify real-world evidence of the treatment benefits of avelumab with axitinib for UK patients. Therefore, the search dates, from 2019, which was the time of approval of the combination therapy in the UK, to 29 July 2024 are appropriate and retrieve up-to-date evidence. Relevant databases and conferences were searched, and the search terms were broader than for the RCT SLR by not including disease stage. Overall, we consider that the search terms for RWE were comprehensive. The review methods were generally appropriate, and we believe that the RWE SLR would have identified all relevant evidence for avelumab with axitinib in the UK. However, as the RWE SLR did not seek to identify any real-world evidence for comparator treatments it is biased towards avelumab with axitinib.

A summary of the EAG's appraisal of the systematic review methods for the RWE SLR is in Appendix 2. The real-world evidence is discussed further in section 3.2.6.

3.2 Critique of new clinical evidence

The original CS for TA645 included clinical evidence from the company's pivotal phase 3 JAVELIN Renal 101 trial, primarily from interim analysis (IA) 1 (data cut-off 20 June 2018) with a summary of some results from IA2 (data cut-off 28 January 2019). Supportive evidence from a dose-finding Phase 1b trial B9991002 was also included. A detailed critique of the JAVELIN Renal 101 trial was provided in the original EAG report which can be found in the committee papers for TA645.[25] As the Phase 1b trial had no comparator it was not critiqued in the original EAG report and it has not been included in the CS for this managed access review.

The current CS includes the following clinical evidence:

- Updated clinical evidence from the final analysis of JAVELIN Renal 101 (data cut-off 31 August 2023)
- Data from the SACT database for two cohorts of patients: the cancer drugs fund (CDF) cohort (n=[redacted]) and the Early Access to Medicines Scheme (EAMS) cohort (n=[redacted]).
- Real-world evidence published by Nathan et al.[26 27] for 130 patients who received avelumab with axitinib via an EAMS. This publication is considered by the company to have captured evidence from two other studies[28 29] which report patients from single centres who were included in EAMS.

- Real-world evidence published by McGrane et al.[5] from a retrospective review of 1,319 patients from 17 UK centres who initiated treatment for metastatic RCC. Of these, 168 received avelumab with axitinib.
- An indirect treatment comparison in the form of a network meta-analysis for the subgroup of people with intermediate-/poor-risk aRCC. This enables a comparison between avelumab with axitinib and four of the comparators (cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib and nivolumab + cabozantinib) where there is no head-to-head evidence.

In this report we focus on the updated clinical evidence from the final analysis of JAVELIN Renal 101 (sections 3.2.1 to 3.2.5) and the data from the SACT database (sections 3.2.6 to 3.2.7). Because some or all of the patients whose data contributes to the analyses in Nathan et al. and McGrane et al. may also be included in the SACT database we do not consider these sources in detail.

3.2.1 Updated trial evidence

The final analysis for the JAVELIN Renal 101 RCT was planned for after 368 deaths had occurred in the PD-L1 positive population (CS section B.2.3.1). The company amended the primary outcome to apply to the PD-L1 positive subgroup only (discussed and found to be appropriate in the previous appraisal[25]) and this was the primary analysis for overall survival (OS). The data cut-off for the final analysis was 31 August 2023 when 375 deaths had occurred in this population. Median follow-up in the avelumab with axitinib arm is 73.2 months and in the sunitinib arm 73.0 months (CS Table 6). A participant flow diagram is not provided but participant flow is described in CS section B.2.4.3 and summarised in CS Table 11.

3.2.1.1 Trial characteristics

The JAVELIN Renal 101 RCT was described in the original appraisal (see TA645 ERG report section 4.3.1).[25] A summary of the trial methodology is provided in the current CS, Table 6. As stated in CS Table 6 results are presented for favourable and intermediate-/poor-risk subgroups. The favourable-risk subgroup included 190 participants (avelumab with axitinib arm n=94, sunitinib arm n=96) and thus made up 21.4% of the intention-to-treat (ITT) population. The remainder of the trial population, 691 participants, had intermediate-/poor-risk disease (avelumab with axitinib arm n=343, sunitinib arm n=348).

3.2.1.2 Patients' baseline characteristics

The CS reports participant baseline demographic and clinical characteristics for the Full Analysis Set (FAS; i.e. the overall trial population) and also for the IMDC prognostic risk groups in CS Table 8.

In the overall trial population, the EAG for the original appraisal concluded that patients were generally younger and fitter than those seen in NHS clinical practice (as is usual in clinical trials) and that the proportion of patients who had received a prior nephrectomy may be higher in NHS clinical practice but that this would not impact the results of trial. Additionally, the participant characteristics were generally well balanced between the avelumab with axitinib and the sunitinib arms.

Here we focus on the participant characteristics of the 190 participants in the IMDC favourable disease risk group, used in the company base case. The CS assessed differences between the favourable-risk group and the intermediate-/poor-risk group (CS section B.2.3.3), however we will assess any differences between treatment arms within the favourable-risk group and consider the generalisability of the favourable-risk group to NHS clinical practice.

Characteristics are generally well balanced between treatment arms for the favourable-risk subgroup, except that there were more males in the sunitinib arm ([redacted]) compared to the avelumab with axitinib arm ([redacted]). However, the EAG's clinical expert confirmed that sex is not a prognostic factor for aRCC, therefore we do not find it a concern. The proportion of participants with previous nephrectomy is balanced between the avelumab with axitinib and sunitinib arms and is [redacted] in both arms than in the overall trial population: for avelumab with axitinib the favourable subgroup has [redacted] with a previous nephrectomy compared to 79.6% in the overall trial population; and for sunitinib the favourable subgroup has [redacted] with a previous nephrectomy compared to 80.0% in the overall trial population. Our clinical expert noted that there is a high rate of previous nephrectomy in the favourable-risk group in NHS clinical practice and that the proportion is likely to be somewhere between the proportions observed in the favourable-risk subgroup and the overall trial population ([redacted]%). Therefore, in relation to previous nephrectomy, the favourable-risk subgroup may be similar to the population seen in NHS clinical practice than the overall trial population as noted in the previous appraisal. Characteristics are also generally well-balanced between treatment arms for the intermediate-/poor-risk subgroup.

Data for performance status comes from the ECOG performance status score and this characteristic is balanced across all trial groups.

EAG comment on included studies

Comparative evidence for avelumab with axitinib versus sunitinib comes from the same JAVELIN Renal 101 RCT that informed TA645, but the company now focus on the subgroup of 190 favourable-risk patients in this trial. Median follow-up in the trial has increased to 73 months and data are provided from the final trial analysis.

3.2.2 Risk of bias assessment

The EAG's risk of bias assessment, alongside the company's assessment, is in Appendix 3. We agree with the previous EAG's consideration for the original appraisal (TA645) that the JAVELIN Renal 101 trial was generally well designed and well conducted, and we also agree that the open-label nature design would contribute to bias because "*it provides an opportunity for differential use of second-line therapies, for subjective results and investigator-assessed outcomes to be biased*".[25] At the time of the interim analyses used for the original appraisal, blinded independent central review (BICR) was used to minimise bias in the measurement of progression-free survival (PFS) and objective response rate (ORR) outcomes, however after the second interim analysis BICR was not used, and disease progression was assessed by the investigator only (CS Table 7). We suggest that the evidence from JAVELIN Renal 101 presented in this CS and used in the economic model is at moderate risk of bias due to the open-label study design and use of investigator assessment for PFS. This is important because disease progression (PFS) is used in the economic model. We asked the company to plot PFS by BICR and PFS by investigator on the same graph to aid our understanding about the impact that blinding could have had on this outcome (clarification question A1). The company did not consider it appropriate to provide such a plot but did provide the plots side by side (company response to clarification question A1, Figure 1 and Figure 2). The data in the two plots appear broadly comparable.

3.2.3 Outcomes assessment

3.2.3.1 Efficacy outcome(s)

The company summarise and define the JAVELIN Renal 101 trial outcomes in CS Table 7. As noted in the original TA645 appraisal (EAG report section 4.6) the co-primary efficacy outcomes were PFS and OS in patients with PD-L1 positive tumours but clinical advice was that it was reasonable to consider all patients unselected for PD-L1 expression and the NICE committee was satisfied that it could use the results for the total population in its decision making (TA645 guidance paragraph 3.3). Clinical expert advice to us for this managed access review was that in NHS practice PD-L1 status is not considered when selecting first-

line treatment, nor is it tested for. PFS and OS in patients unselected for PD-L1 expression were secondary endpoints.

CS Table 7 includes all the outcomes listed in the NICE scope except time on treatment although this appears in CS Table 6 but referred to as time to treatment discontinuation (TTD). CS Table 7 also lists some outcomes in addition to those listed in the NICE scope: disease control, time to response and PFS on next-line therapy. Of these only disease control and time to response are reported in the CS.

The efficacy outcomes that contribute data to the economic model are OS and PFS with time to treatment discontinuation used to calculate the costs specific to treatment status.

3.2.3.2 Health-related quality of life (HRQoL) outcomes

The generic EuroQol 5-Dimension 5-Level (EQ-5D-5L) index score and visual analogue scale (VAS) score from JAVELIN Renal 101 (CS Tables 6 and 7) are reported in CS section B.2.6.4 for the whole trial population and not for the IMDC risk subgroups, because subgroup analyses were not pre-specified for the HRQoL outcomes. EQ-5D-5L data from favourable disease risk patients was used in the economic model (CS section B.3.4.1); appropriately mapped to 'UK tariff' EQ-5D-3L values using NICE preferred methods (CS section B.3.4.2).

A validated, disease-specific measure, the Functional Assessment of Cancer Therapy – Kidney Symptom Index – 19 items (FKSI-19, also known as the NFKSI-19)[30] was assessed in the trial (CS Tables 6 and 7), and time to deterioration using the FKSI-DRS subscale was assessed up to IA1 (clarification response A2). The CS does not report any minimum clinically important difference (MCID) for the FKSI-19 as used in the JAVELIN Renal 101 trial. A recent systematic review has shown that MCID thresholds for FKSI-19 used in the published literature are heterogeneous,[31] however, as a guide, the recent CheckMate 214 trial of nivolumab + ipilimumab versus sunitinib for aRCC used an MCID of 3 or more points.[32]

The EQ-5D and the FKSI-19 outcomes were measured every 6 weeks at Day 1 of each Cycle which corresponds to the 'off-treatment' period of sunitinib when those participants would have the lowest symptom burden, acknowledged in the CS (CS section B.2.13.1.1) and published literature.[33] Therefore, there could be bias in favour of the sunitinib arm.

3.2.3.3 Safety outcomes

Adverse events and TTD are used in the economic model. Safety results are also reported for avelumab and axitinib as single agents which is appropriate due to the dose adjustments and temporary discontinuations required to manage these treatments, but only for earlier analyses reported in the confidential company clinical safety report 2018[34] (CS section B.2.11.1.2; clarification response A5). TTD is reported specifically in relation to model inputs and not for clinical effectiveness, for the favourable-risk subgroup (CS section B.3.3.3), the intermediate-/poor-risk subgroup (CS Appendix O.4.1) and the ITT population (CS Appendix O.4.2). Adverse events associated with dose modifications and treatment discontinuation are reported in the CS.

Avelumab was investigated for immunogenicity which is appropriate for a monoclonal antibody treatment. Anti-drug antibody results for avelumab are reported in the clinical study report (CSR) (section 5.5) and immune-related adverse events for all study treatments are reported in the CS (CS section B.2.11.4.1).

EAG comment on outcomes assessment

The EAG has no concerns regarding the efficacy and safety outcomes assessment, though we note the potential for bias in favour of the sunitinib arm in the HRQoL outcomes due to the timing of those assessments.

3.2.4 Statistical methods of the included studies

The EAG for the original appraisal concluded that the statistical approach employed by the company was adequate and appropriate, and we have not identified any new issues for the statistical methods around the overall trial population (full analysis set) in the final analysis. Here we focus on the statistical handling of the IMDC risk subgroups.

Analysis populations: CS section B.2.4.1 describes the analysis sets, with the risk subgroup analysis sets for favourable-risk and intermediate-/poor-risk being relevant to the decision problem (CS Table 9). They were pre-specified subgroups for analysis of the OS and PFS outcomes. As subsets of the Final Analysis Set they include all randomised participants (with the appropriate risk status). Adverse events are reported for the Safety Set, which for JAVELIN Renal 101 is all patients who received $\geq$1 dose of study drug, and this is appropriate because it maximises safety data (CS B.2.11; clarification response A4).

Sample size calculations: the sample sizes of the risk subgroups are a smaller size than the overall trial population, and so the results for the risk subgroup populations are not powered to detect statistical difference between the two treatment arms.

Methods to account for multiplicity: analyses of the risk subgroups had no adjustment for multiplicity (CS sections B.2.5 and B.2.13.2.1).

Analysis of outcomes: subgroup analyses were carried out for OS, PFS, objective response (OR) and duration of response as outlined in the statistical analysis plan (SAP) section 6.4, and subject to the same censoring rules as for the overall trial population. In the SAP the intermediate-risk and poor-risk subgroups are listed separately whereas in the CS results are reported for a combined intermediate-/poor-risk subgroup. Results for the risk subgroups are also reported in the CS for time to response. Standard statistical methods, 2-sided unstratified log-rank test, two Cox regression model for heterogeneity, were applied. Sensitivity analyses were not performed for any subgroups. There were no subgroup analyses for the results of the patient-reported outcomes (PROs), EQ-5D-5 and FKSI-19. Hence results of the PROs are reported for the overall trial population in CS section B.2.6.4 but the economic base case is informed by EQ-5D-5L data for the favourable-risk subgroup (CS section B.3.4.1).

Handling of missing data: data was evaluated as observed, and no imputation method for missing values was used unless otherwise specified (CS Table 10 and confirmed in SAP section 5.3). The study protocol does not mention imputation except for the FKSI multi-item scales (section 9.3.2 page 140), however questionnaire completion rates for both EQ-5D and FKSI were high (CSR section 5.6 and Table 14.5.2.1.1.1). PFS was censored if the event was after two or more missing/inadequate post-baseline tumour assessments with sensitivity analysis for regardless of missing assessment or timing of the event (SAP 6.1.1.1); We did not find data on censoring reasons in the IMDC risk groups but in the full analysis set most reasons for censoring were [redacted] across both arms (CSR Table 14.2.5.3.1) and where there were differences, these were not unexpected (e.g. a [redacted] proportion of participants in the avelumab with axitinib arm were ongoing without an event whereas a [redacted] proportion of the sunitinib arm had started a new anti-cancer therapy). In the full analysis set [redacted]% in each arm were lost to follow up for OS (CSR Table 19).

EAG comment on study statistical methods

The statistical methods in the JAVELIN Renal 101 are appropriate. The decision problem focuses on two of the pre-specified subgroups within the trial due to the way in which the treatment pathway has changed since the original appraisal. The favourable- and intermediate-/poor-risk subgroups were not powered to detect statistical significance. The results for the subgroups are handled according to the trial protocol.

3.2.5 Efficacy results of the intervention studies

For the original TA645 appraisal efficacy data were presented for the full analysis set (FAS) population. Since then, subgroups by IMDC prognostic criteria, favourable-risk or intermediate-/poor-risk, have emerged as key subgroups when determining treatment choice in adults with untreated aRCC. The CS therefore presents results separately for these two subgroups and without selecting for PD-L1 expression status (as noted in section 3.2.3.1, the NICE committee for TA645 heard that clinical experts in the NHS do not measure PD-L1 in aRCC and the committee was satisfied that it could use the results for the total population in its decision making). It should be noted that the trial was not powered to detect statistical significance in IMDC subgroups (see section 3.2.4). A summary of PFS and OS results is also presented for the ITT population. We therefore present the results for the two subgroups by IMDC criteria and the ITT population separately below, focussing on the efficacy outcomes that inform the economic model which are OS and PFS and briefly summarising other outcomes. Data on treatment discontinuation is reported in section 3.2.5.7.2 and time to treatment discontinuation is considered in section 4.2.4.3 of this report.

3.2.5.1 JAVELIN RENAL 101 trial results for the favourable-risk subgroup by IMDC criteria

3.2.5.1.1 Overall Survival

CS Table 14 summarises the overall survival results from the final analysis for participants with favourable-risk disease. For participants in the avelumab with axitinib arm of the trial median OS was 14 months longer than in the sunitinib arm (79.4 months, 95% confidence interval [CI] 59.4, not evaluable [NE] versus 65.5 months, 95% CI 53.4, 78.6 respectively, Table 5). Of the 96 deaths that had occurred, 44 (46.8%) were in the avelumab with axitinib trial arm and 52 (54.2%) were in the sunitinib arm. The stratified hazard ratio was 0.73 (95% CI 0.48 to 1.10, p=0.1290) and the unstratified hazard ratio was 0.78 (95% CI 0.52 to 1.17, p=0.2281), values that correspond to a 27% and 22% reduction in the risk of death respectively for the avelumab with axitinib trial participants. CS Figure 6 displays the Kaplan-Meier plot of OS for the favourable-risk disease subgroup and shows that from 30 months onwards the survival curves for the two trial arms separate and remain separated for the remainder of the follow-up period.

3.2.5.1.2 Progression-free survival

BICR for PFS ended after the primary analysis for PFS (IA2, data cut-off 28 January 2019). Thereafter, PFS was assessed by the investigator and consequently PFS reported from the final analysis in the CS is by investigator assessment (CS Table 15 and CS Figure 7). For

favourable-risk disease participants in the avelumab with axitinib arm of the trial median PFS was 20.7 months (95% CI: 16.6, 26.2) in comparison to 13.8 months (95% CI: 11.1, 23.5) in the sunitinib arm (Table 5). The stratified hazard ratio was 0.75 (95% CI 0.53 to 1.07, p=0.1109). The same hazard ratio was obtained from the unstratified analysis with a similar 95% confidence interval (95% CI 0.54 to 1.04, p=0.0873). The hazard ratios correspond to a 25% reduction in the risk of disease progression or death for the avelumab with axitinib trial participants in comparison to those receiving sunitinib. CS Figure 7 displays the Kaplan-Meier plot of PFS for the favourable-risk disease subgroup which shows that the PFS curves for the two trial arms separate early (at the time of first tumour assessment which we believe to have been 6 weeks after randomisation[35]). Although the curves come close together or actually touch a few times thereafter (e.g. at 8 months and again at 24 months as shown in CS Figure 7) they are fully separated for the majority of the follow-up period.

3.2.5.1.3 Response outcomes

CS table 16 summarises objective response (investigator assessment) which is in favour of avelumab with axitinib. For example, a confirmed best overall response of complete response was observed in 9.6% of the avelumab with axitinib trial arm and 5.2% of the sunitinib arm and an objective response (sum of those with complete response and partial response) was observed in 75.5% and 45.8% in the avelumab with axitinib and sunitinib trial arms respectively. CS section B.2.6.1.4 summarises time to response and duration of response. Time to response was similar in both trial arms and duration of response was numerically in favour of the avelumab with axitinib trial arm by about 3 months.

3.2.5.2 JAVELIN RENAL 101 trial results for the intermediate-/poor-risk subgroup by IMDC criteria

3.2.5.2.1 Overall Survival

Overall survival results from the final analysis for participants with intermediate-/poor-risk disease are summarised in CS Table 17. Median OS was 37.8 months (95% CI 31.2, 42.6) for participants in the avelumab with axitinib arm of the trial and 29.5 months (95% CI 24.8, 36.1) in the sunitinib arm (Table 5). The proportions of deaths that had occurred among participants with intermediate-/poor-risk disease in each trial arm were similar (68.8% of the avelumab with axitinib trial arm and 69.8% of the sunitinib arm). The stratified hazard ratio was 0.90 (95% CI 0.75 to 1.08, p=0.2471) and the unstratified hazard ratio was 0.88 (95% CI 0.74 to 1.06, p=0.1739), values that correspond to a 10% and 12% reduction in the risk of death respectively for the avelumab with axitinib trial participants. CS Figure 8 displays the Kaplan-Meier plot of OS for the intermediate-/poor-risk disease subgroup. The curves

separate at 4 months and remain separate for the rest of the trial period. This is a much earlier separation of the curves than for the favourable-risk population (at 30 months).

3.2.5.2.2 Progression-free survival

As noted above (section 3.2.5.1.2) PFS reported from the final analysis in the CS is by investigator assessment (CS Table 18 and CS Figure 9 for the intermediate-/poor-risk disease subgroup). Participants with intermediate-/poor-risk disease in the avelumab with axitinib arm of the trial had a median PFS of 11.1 months (95% CI: 9.8, 14.6) in comparison to 8.1 months (95% CI: 6.9, 8.4) in the sunitinib arm (Table 5). The stratified hazard ratio was 0.64 (95% CI 0.54 to 0.76, p<0.0001). The same hazard ratio, confidence interval and p-value was obtained from the unstratified analysis. The hazard ratios correspond to a 36% reduction in the risk of disease progression or death for the avelumab with axitinib trial participants in comparison to those receiving sunitinib. CS Figure 9 displays the Kaplan-Meier plot of PFS by investigator assessment for the intermediate-/poor-risk disease subgroup which shows that the curves for the avelumab with axitinib treated patients and the sunitinib treated patients separate early and remain separate over the time period.

3.2.5.2.3 Response outcomes

CS section B.2.6.2.3 reports objective response and CS section B.2.6.2.4 time to response and duration of response. In the intermediate-/poor-risk patients the objective response outcomes from investigator assessment were in favour of the patients who received avelumab with axitinib. Median time to response (confirmed complete or partial response) was was [redacted] months [redacted] median duration of response was longer in the avelumab with axitinib treated patients (19.4 months versus 9.8 months among sunitinib treated intermediate-/poor-risk patients).

3.2.5.3 JAVELIN RENAL 101 trial subsequent treatment in the favourable-risk and intermediate-/poor-risk subgroups by IMDC criteria

In the IMDC favourable-risk subgroup, the proportion of patients in the sunitinib arm receiving a follow-up anticancer treatment was 79.2%, with 64.6% of these receiving a subsequent PD-1 or PD-L1 treatment. In the avelumab with axitinib arm the proportion of favourable-risk patients received a subsequent anticancer treatment was lower (67%) with just 29.8% of these receiving a subsequent PD-1 or PD-L1 treatment. The same pattern was observed among patients with intermediate-risk and poor-risk disease. CS Figure 10 shows subsequent PD-1 or PD-L1 inhibitor treatment in the IMDC risk groups and in the ITT population.

3.2.5.4 JAVELIN RENAL 101 trial results for the ITT trial population

The CS provides a brief summary of overall survival and progression-free survival results in the ITT trial population at the start of CS section B.2.6 which the company has provided for completeness. In current clinical practice, patients are categorised into risk groups for survival using the IMDC prognostic model and the risk group categorisation determines first-line treatment options. Therefore the results presented above, in sections 3.2.5.1 and 3.2.5.2 for the favourable-risk and intermediate-/poor-risk subgroups respectively, are the most relevant to clinical practice. We note that both PFS (by BICR assessment and by investigator assessment) and OS in the ITT population were secondary outcomes, the primary outcomes for the trial were PFS (by BICR assessment) and OS in patients with PD-L1-postive tumours (see section 3.2.5.6.2).

Table 5 summarises the PFS and OS outcomes for the ITT population alongside those of the favourable-risk and intermediate-/poor-risk subgroups. As previously noted, the majority of participants had intermediate-/poor-risk aRCC, only 21.4% had favourable-risk disease. Consequently, the PFS and OS results for the ITT population are most aligned with those of the intermediate-poor-risk subgroup. Median OS was longest (79.4 months and 65.5 months in the avelumab with axitinib and sunitinib arms respectively) and the reduction in the risk of death was greatest in the favourable-risk subgroup (27% from stratified hazard ratio). However, the favourable-risk subgroup PFS and OS confidence intervals are wider than the ITT and intermediate-/poor-risk subgroup confidence intervals which reflects the small size of the favourable-risk subgroup and the greater uncertainty around the central estimates of PFS and OS in this subgroup.

Table 5 Summary of PFS (by investigator assessment) and OS results in the ITT population, favourable-risk and intermediate-/poor-risk subgroups. Final analysis (DCO 31 August 2023)

	ITT population		Favourable-risk subgroup		Intermediate-/poor-risk subgroup	
	Avelumab + axitinib (n=442)	Sunitinib (n=444)	Avelumab + axitinib (n=94)	Sunitinib (n=96)	Avelumab + axitinib (n=343)	Sunitinib (n=348)
PFS						
Median follow up, months (95% CI)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Median PFS, months (95% CI)	13.9 (11.1, 16.6)	8.5 (8.2, 9.7)	20.7 (16.6, 26.2)	13.8 (11.1, 23.5)	11.1 (9.8, 14.6)	8.1 (6.9, 8.4)
HR (95% CI), 1 sided p-value	0.66 (0.565, 0.768) <0.0001		0.75 (0.53, 1.07) 0.1109		0.64 (0.54, 0.76) <0.0001	
OS						
Median follow up, months (95% CI)	73.7 (72.3, 74.6)	73.6 (72.0, 75.5)	Not reported	Not reported	Not reported	Not reported
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	44.8 (39.7, 51.1)	38.9 (31.4, 45.2)	79.4 (59.4, NE)	65.5 (53.4, 78.6)	37.8 (31.2, 42.6)	29.5 (24.8, 36.1)
HR (95% CI), 1 sided p-value	0.88 (0.749, 1.039) 0.0669		0.73 (0.48, 1.10)[a] 0.1290		0.90 (0.75, 1.08)[a] 0.2471	

Source: CS Tables 13, 14, 15, 17 and 18
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NE, not evaluable; OS, overall survival. PFS, progression-free survival
[a] Stratified hazard ratio

3.2.5.5 HRQoL outcomes

3.2.5.5.1 EQ-5D-5L score change from baseline

We agree that the EQ-5D-5L index scores were "*relatively stable over time*" for both treatment arms (CS section B.2.6.4.1). CS Figure 11 shows the sunitinib arm started with a slightly higher baseline score and generally maintained a higher score than the avelumab with axitinib arm; and both arms' scores decreased approaching the end of treatment. The confidence intervals for the scores of the treatment arms frequently overlap indicating uncertainty in any difference between the two arms. Additionally, the assessment schedule potentially favours the sunitinib arm as they were assessed at the point of lowest symptom burden (see section 3.2.3.2 above) so the results may not reliably reflect EQ-5D-5L at other points in the sunitinib treatment schedule.

CS Figure 12 shows that both treatment arms started the trial with almost identical EQ-5D-5L VAS scores and made small score increases for the duration of the trial. However, the mean scores for change from baseline, -5.0 for avelumab with axitinib and -4.3 for sunitinib, are not described as clinically meaningful, and there is little difference between the two treatment arms as the line plots frequently cross and the confidence intervals of the treatment groups consistently overlap up to the end of treatment.

3.2.5.5.2 FKSI-19 score change from baseline

CS Figure 13 shows that both treatment arms started the trial with almost identical FKSI-19 total scores, and that up to Cycle 21 there were small differences between the treatment groups but the plot lines frequently cross and the confidence intervals frequently overlap showing no significant differences between groups. After Cycle 21, up to Cycle 32 just before the end of the trial, the sunitinib group shows a slightly greater increase in score (i.e. better HRQoL) than the avelumab with axitinib group and the degree of overlap in the confidence intervals for the two groups reduces. The sunitinib group was assessed at the point of lowest symptom burden in a treatment cycle (week 6 being the off-treatment period) but this was the case throughout the trial, not just after Cycle 21, so the reason for this apparent slight increase in sunitinib HRQoL is unclear. However, sunitinib's apparent better performance in FKSI-19 results is not clinically meaningful, as the MCID should be about a 3-point difference (see section 3.2.3.2 above).

The results for the prespecified PROs do not show any clear or meaningful difference between treatments and may be biased in favour of sunitinib due to the assessment scheduling.

3.2.5.5.3 Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST)

Results for the post-hoc Q-TWiST analysis are reported in CS Appendix M.2 and are supportive of a 3.20-month gain in quality-adjusted time without symptoms or toxicity for avelumab with axitinib compared to sunitinib. The CS states this is a 10.9% relative improvement, thus achieving an established 10% MCID.[36] The company have not explained the reason for this post-hoc analysis.

3.2.5.6 Subgroup analyses

Subgroups specified in the NICE scope and company decision problem are the IMDC favourable-risk subgroup, the IMDC intermediate-/poor-risk subgroup and PD-L1 status (CS Table 1). Subgroup analyses in JAVELIN Renal 101 were pre-specified for the OS, PFS, OR and duration of response outcomes.

Subgroup analyses were not planned for the EQ-5D-5L, FKSI-19 and FKSI-DRS outcomes according to the study SAP, however, the Nolla et al. 2023 publication[33] refers to PRO results according to risk subgroups albeit for an earlier data cut-off. The authors note that the poor risk disease category had significantly better FKSI-19, FKSI-DRS, and EQ-5D VAS scores for avelumab with axitinib treated patients compared to those treated with sunitinib, however the effect sizes were considered too small to be conclusive, [33] and the poor-risk subgroup alone is not a subgroup of interest in the NICE scope. We do not believe that any (post-hoc) subgroup analyses of PROs for the final analysis would add anything meaningful mainly due to assessment scheduling.

3.2.5.6.1 IMDC risk status

The IMDC risk subgroups were among the prespecified trial subgroups in JAVELIN Renal 101 for further analysis of OS, PFS and OR outcomes. These results for the IMDC risk subgroups have been discussed in sections 3.2.5.1 and 3.2.5.2 above and the time to treatment discontinuation results by subgroup inform the economic model (section 4.2.4.3).

3.2.5.6.2 PD-L1 status

PD-L1 status was originally a pre-specified subgroup in the JAVELIN Renal 101 trial and a data-driven protocol amendment made the PD-L1 positive subgroup the subject of the co-primary outcomes, discussed in the previous appraisal's EAG report section 4.5.[25] Results for the subgroup of patients with PD-L1 positive tumours, subdivided by IMDC favourable- and intermediate-/poor-risk status, are reported in CS Table 20 and are described by the company as "*generally similar*" to the ITT population in both IMDC risk groups (CS section B.2.7).

Overall survival. In the favourable-risk subgroup, participants with PD-L1 positive tumours had a [redacted]% reduction in risk of death for avelumab with axitinib compared to sunitinib (stratified analysis, CS Table 14) which was [redacted] than the 27% risk reduction reported for the favourable-risk subgroup overall (CS Table 20). Median OS was [redacted] in the PD-L1 positive subgroup of favourable-risk participants for both the avelumab with axitinib and sunitinib arms: in the avelumab with axitinib arm the PD-L1 positive subgroup median OS was [redacted] (95% CI [redacted]) months, compared to 79.4 months (95% CI 59.4 – not estimable) in the favourable-risk subgroup overall in the sunitinib arm the PD-L1 positive subgroup median OS was [redacted] months (95% CI [redacted]) compared to 65.5 months (95% CI 53.4 – 78.6) in the favourable-risk subgroup overall (CS Tables 14 and 20 respectively). Results for the PD-L1 positive patients in the intermediate-/poor-risk subgroup were very similar to the results for the intermediate-/poor-risk as a whole (CS Tables 17 and 20).

Progression free survival. In the favourable-risk subgroup for participants with PD-L1 positive tumours there was a [redacted] reduction of risk of progression or death for avelumab with axitinib compared to sunitinib ([redacted]%, CS Table 20) in comparison to the total subgroup of participants with favourable-risk disease (25% risk reduction, (CS Table 15). In both trial arms, median PFS was slightly shorter in the PD-L1 positive subgroup than in the overall subgroup of favourable-risk participants: in the avelumab with axitinib arm [redacted] months (95% CI [redacted]) compared to 20.7 months (95% CI 16.6- 26.2) for all favourable-risk participants; in the sunitinib arm [redacted] months (95% CI [redacted]) compared to 13.8 months (95% CI 11.1 to 23.5) for all favourable-risk participants (CS Tables 15 and 20). In the intermediate-/poor-risk subgroup avelumab with axitinib treatment in comparison to sunitinib treatment led to a [redacted] reduction of risk of progression or death for participants with PD-L1 positive tumours than for the intermediate-/poor-risk subgroup as a whole: [redacted]% risk reduction (CS Table 20) compared to a 36% risk reduction (CS Table 18). Median PFS for the PD-L1 positive subgroup was similar to the intermediate-/poor-risk subgroup as a whole (CS Tables 18 and 20).

Objective response. In the favourable-risk subgroup patients with PD-L1 positive status do marginally better than the favourable-risk subgroup as a whole receiving avelumab with axitinib, but results are mostly similar (CS Tables 16 and 20). A similar pattern was observed in the intermediate-/poor-risk subgroup patients (CS Tables 19 and 20).

3.2.5.6.3 Other JAVELIN Renal 101 pre-specified subgroup analyses

Further pre-specified subgroup analyses were undertaken within the JAVELIN Renal 101 trial as described in the CS and EAG report for the previous appraisal of this topic (TA645[1]

[37]). Results for these subgroups are not reported in the CS but they are available for the outcome of overall survival in the CSR[38] The result for most of the subgroups is consistent with the overall survival for the full trial population (i.e. all participants regardless of disease risk category) being numerically in favour of avelumab with axitinib but with confidence intervals that cross 1.0. Confidence intervals do not cross 1.0 for the Heng (IMDC) poor risk subgroup, the Caucasian/White race subgroup and the male gender subgroup, (CSR Figure 14.2.3.1.5[38]). With the exception of the PD-L1 subgroup, the study was not powered to detect treatment effects in subgroups and the results should be interpreted cautiously.

3.2.5.7 Safety outcomes

The company report safety outcomes from the final analysis of JAVELIN Renal 101, and for completeness, they additionally provide a confidential summary of clinical safety report of pooled safety results from an earlier interim analysis of JAVELIN Renal 101, JAVELIN Renal 100, and two other clinical studies of monotherapy avelumab and axitinib.[34] We focus on the evidence from the final analysis of JAVELIN Renal 101 because it has a comparator arm and is the most up-to-date.

Results are reported for the safety set which is for the overall trial population, not according to IMDC risk subgroup, as this provides the most comprehensive information. An overarching summary for the on-treatment period is provided in CS Table 31.

The extent of exposure to each study drug is reported in section 4.6 of the CSR: avelumab was [redacted] weeks, axitinib was [redacted] weeks, and sunitinib was [redacted] weeks.[38] The extent of exposure to avelumab and axitinib is [redacted] as the extent of exposure to sunitinib. Similar to the EAG opinion in the previous appraisal (TA645 EAG report 4.9.1[25]), this reflects the improved PFS for patients receiving avelumab with axitinib versus sunitinib and the increase in follow-up time since TA645 when the difference in extent of exposure was described as marginally longer for avelumab with axitinib.

3.2.5.7.1 Adverse events

Treatment-emergent adverse events: The most common treatment-emergent adverse events (TEAEs) are summarised in CS Table 32. In the avelumab with axitinib arm the most common TEAEs were diarrhoea [redacted], hypertension ([redacted]), fatigue ([redacted] and nausea ([redacted] These were the most common TEAEs in the sunitinib arm too, though experienced by a smaller proportion of participants than in the avelumab with axitinib arm, at [redacted] respectively. The most common Grade $\geq$3 TEAE was hypertension for both study arms: [redacted] for avelumab with axitinib and [redacted] for sunitinib. This is consistent with earlier analyses.

Treatment-related TEAEs: The most common treatment-related TEAEs are reported in CS Table 33 and similarly show that diarrhoea and hypertension are the most common for both arms, with higher frequency in the avelumab with axitinib arm. The comparison made in CS section B.2.11.1.2 between avelumab with axitinib as a combination therapy and each agent as a monotherapy is between the JAVELIN Renal 101 final analysis and the two clinical trials of avelumab and axitinib as monotherapies that were included in the aforementioned company confidential summary of clinical safety report.[34] It shows that diarrhoea, hypertension, hypothyroidism and increased alanine aminotransferase were all reported at higher frequencies for the avelumab with axitinib combination than for either single agent alone, though these are all known adverse events for these treatments.

Serious TEAEs: More patients reported serious TEAEs in the avelumab with axitinib arm ([redacted]%) than in the sunitinib arm ([redacted]%) (CS Table 35). The most common serious TEAEs differed between treatment arms: in the avelumab with axitinib arm they were diarrhoea ([redacted]), acute myocardial infarction ([redacted]), disease progression ([redacted]) and acute kidney injury ([redacted]), whereas in the sunitinib arm they were abdominal pain ([redacted]), anaemia ([redacted]) and acute kidney injury ([redacted]) (CS Table 35). There were no serious treatment-related TEAEs reported for ≥2% of patients in either treatment arm (CS section B.2.11.2.2).

Deaths: During the trial, [redacted]) of patients in the avelumab with axitinib arm and [redacted]) of patients in the sunitinib arm died. The most common cause of death was disease progression for both arms, [redacted]) in the avelumab with axitinib arm and [redacted]) in the sunitinib arm (CS section B.2.11.2.1). Similarly, the most common TEAE leading to death was disease progression: [redacted]) in the avelumab with axitinib arm and [redacted]) in the sunitinib arm (CS Appendix Table 38).

Adverse events of special interest: The EAG for the previous appraisal noted areas of uncertainty around potential cardiovascular adverse events associated with VEGF TKIs (here, axitinib and sunitinib) and risk of myocarditis associated with avelumab and other checkpoint inhibitors, and immune-related adverse events associated with the mechanism of action of avelumab.[25] These, and infusion-related adverse events relating only to avelumab due to method of administration, are of special interest and are reported in CS section B.2.11.4.

Cardiac disorders were reported for [redacted]% of patients in the avelumab with axitinib arm compared to [redacted]% of patients in the sunitinib arm, of which [redacted]% and [redacted]% of events respectively were Grade ≥3 (CS section B.2.11.4.3). Additionally, cardiac-related adverse events were reported for decreased ejection fraction, increased troponin T, and increased

myocardial necrosis marker: these events were [redacted] in the avelumab with axitinib arm (CS section B.2.11.4.3). As mentioned above, acute myocardial infarction was the second most common serious TEAE in the avelumab with axitinib arm ([redacted]), [redacted] Grade ≥3, compared to [redacted] in the sunitinib arm. Cardiac-related adverse events are not reported as leading to dose interruption, dose reduction or discontinuation of any study drug (CS section B.2.11.3). There were [redacted] deaths due to cardiac disorders in the avelumab with axitinib arm compared to [redacted] in the sunitinib arm (CS Appendix Table 38).

Immune-related adverse events were reported for 50.7% of patients in the avelumab with axitinib arm compared to 4.8% of patients in the sunitinib arm reflecting avelumab's mechanism of action; 14.7% and 0.2% respectively were Grade ≥3 events (CS section B.2.11.4.1). Thyroid disorders were the most common immune-related adverse events ([redacted]%) in the avelumab with axitinib arm (CS section B.2.11.4.1). No immune-related adverse events were reported as leading to death (CS Appendix Table 38) or to changes in treatment (CS section B.2.11.3).

CS section B.2.11.4.2 and CS Table 31 report that infusion-related reactions were experienced by [redacted]% of participants. CS Table 32 reports TEAEs which included 57 (13.1%) infusion-related reactions of all grades of which [redacted]% were Grade ≥3 infusion-related reactions. It is not clear to us why the proportion of patients with infusion-related reactions differs between CS Table 31 and CS Table 32. Treatment-related infusion-related reactions at any grade in ≥10% of participants were reported in 12.9% of patients, and Grade ≥3 infusion-related reactions in ≥5 participants were reported for 1.6% of patients (CS Table 33).

Final summary: The safety results from the final analysis show no new concerns and they are consistent with previous analyses. The additional evidence from greater extent of exposure may provide more certainty around cardiovascular and immune-related adverse events which do not appear to affect dose changes or treatment discontinuation. Cardiac events have led to death, but the numbers of events are low and the proportions are low and similar in both arms.

3.2.5.7.2 Treatment discontinuation

The proportions of patients with permanent discontinuations due to adverse events are similar for both study arms: discontinuing either avelumab or axitinib (34.3%) compared to sunitinib (17.5%), and discontinuing both avelumab and axitinib (13.1%) compared to sunitinib (17.5%) (CS section B.2.11.3.1).

Time to treatment discontinuation is used in the economic model (CS Table 6; CS section B.3.3.3) and was derived from the JAVELIN Renal 101 trial data. The CS does not report time to treatment discontinuation in the clinical effectiveness or safety results sections of the CS.

3.2.6 Real-world evidence on avelumab with sunitinib

In this section our principal focus is on data from the SACT database because, as noted above (section 3.2) and confirmed in clarification response A6, some or all of the patients whose data contributes to the analyses in Nathan et al.[26 39 40] and McGrane et al. [5] may also be included in the SACT cohort. McGrane et al.[5] is considered in section 3.2.8 because data from this source provides information for real-world outcomes from TKIs as first-line therapy for aRCC as well as real-world outcomes following IO+TKI combination treatment.

3.2.6.1 Overview of the SACT dataset

The National Disease Registration Service (NDRS) collected SACT data for [redacted] unique patients who received avelumab with axitinib within the CDF and an additional [redacted] patients who received avelumab with axitinib within the EAMS. Of these patients, [redacted]% of the CDF cohort and [redacted]% of the EAMS cohort were identified has having completed treatment. The median treatment duration was [redacted] months (95% CI [redacted]) for all patients in the CDF cohort and [redacted] months (95% CI [redacted]) for all patients in the EAMS cohort. The median follow-up times for the CDF and EAMS cohorts (measured from initiation of treatment to last treatment data in the SACT dataset plus the length of prescription) were [redacted]months and [redacted] months respectively.

3.2.6.2 Characteristics of patients in the SACT dataset

The baseline demographics and clinical characteristics of patients in the SACT dataset are provided side-by side for the CDF and EAMS cohorts in CS Table 22. In the CDF cohort the proportion of patients with favourable-risk aRCC was [redacted] than in the JAVELIN Renal 101 trial and [redacted] than the estimate by Esterberg et al.[41] cited by the company in section CS B.1.3.2 on epidemiology of kidney cancer ([redacted]% in the CDF cohort versus 21% in the FAS for the overall JAVELIN Renal 101 trial and 16% estimated by Esterberg et al.[41]. Data on IMDC risk group status was not recorded in the EAMS cohort. In comparison to the JAVELIN Renal 101 RCT, the median age of the patients in the SACT dataset is [redacted] (median [redacted] years in the CDF cohort which makes up 89% of the SACT dataset and [redacted] in the EAMS cohort in comparison to 62 years and 61 years in the avelumab with axitinib and sunitinib FAS trial arms respectively) and a [redacted] proportion had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 at treatment initiation than was observed for

the JAVELIN Renal 101 trial arms at baseline ([redacted]% in the CDF cohort and [redacted]% in the EAMS cohort in comparison to [redacted]% and [redacted]% in the avelumab with axitinib and sunitinib FAS trial arms respectively). The ECOG PS status of the patients in the SACT dataset suggest that they would likely have a poorer prognosis than participants in the JAVELIN Renal 101 trial. Our clinical expert confirmed that fitter patients (i.e. ECOG PS of 0) tolerate treatment side-effects better so therefore have a lower dose reduction or treatment cessation rate and consequently achieve better response rates. They also noted that patients with ECOG PS of 0 are not clinically affected by their metastatic disease, suggesting that either their disease is being treated more promptly or is having less physiological effect than in those patients who have a PS greater than 0.

It was an inclusion criterion for the JAVELIN Renal 101 trial that participants had aRCC with a clear cell component whereas this restriction on histological subtype did not apply to the SACT dataset. Therefore [redacted]% of the CDF cohort had RCC with a clear cell component and the remaining patients either had unclassified RCC ([redacted]%) or RCC of another histological subtype, [redacted] papillary RCC ([redacted]%) or chromophobe RCC ([redacted]%) with a further four histological subtypes recorded in CS Table 22. The histological subtype was not recorded for [redacted] ([redacted]%) of the CDF cohort and [redacted] for the EAMS cohort.

3.2.7 Results from the SACT dataset

3.2.7.1 Overall survival in the SACT dataset

Overall survival results for the SACT dataset are presented in CS section B.2.8.2.2 and summarised below in Table 6.

Table 6 Summary of overall survival results in the CDF and EAMS cohorts in comparison to the JAVELIN Renal 101 avelumab with axitinib trial arm.

	CDF cohort (n=[redacted])	EAMS cohort (n=[redacted])	JAVELIN Renal 101 Avelumab + axitinib (n=442)
Median follow-up time	[redacted] months [redacted]	[redacted] months [redacted]	73.7 months (95% CI 72.3, 74.6)
Maximum follow-up period for survival	[redacted] months	[redacted] months	Not reported
Number of deaths [a]	[redacted] [b]	[redacted] [b]	[redacted]

	CDF cohort (n=[redacted])	EAMS cohort (n=[redacted])	JAVELIN Renal 101 Avelumab + axitinib (n=442)
Median OS (95% CI)	[redacted] months (95% CI [redacted])	[redacted] months (95% CI [redacted])	44.8 months (39.7, 51.1)
Clear-cell histology subgroup, Median OS	[redacted] months (95% CI [redacted]) [n=[redacted]]	RCC histology not recorded	
Non clear-cell histology subgroup, Median OS	[redacted] months (95% CI [redacted]) [[redacted]][c]		Non clear-cell aRCC excluded from trial.
Favourable-risk subgroup OS (95% CI)	[redacted]	IMDC risk group status not recorded	79.4 months (59.4, NE) [n=94]
Intermediate-risk subgroup OS (95% CI)	[redacted]		37.8 months (31.2, 42.6) [n=343]
Poor-risk subgroup OS (95% CI)	[redacted]		

Source: EAG Table compiled from data presented in CS section B.2.8.2.2, CS Table 13, CS Table 14, CS Table 17 and the source reference for the SACT data.[4]
aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; CI, confidence interval; EAMS, Early Access to Medicines Scheme; IMDC, International Metastatic RCC Database Consortium; NE, not evaluable; OS, overall survival; RCC, renal cell carcinoma
[a] For the total population (i.e. all risk groups combined). In the CDF and EAMS cohorts this was at the end of follow-up period (2nd July 2024) for the JAVELIN Renal 101 trial this was at final analysis.
[b] Percentage calculated by EAG
[c] n calculated by EAG

3.2.7.1.1 People with clear cell aRCC

As the JAVELIN Renal 101 trial only included participants with clear cell aRCC the analogous real-world evidence is the clear-cell histology subgroup in the CDF cohort (n=[redacted]). This subgroup had a median overall survival of [redacted] months (95% CI [redacted]) which is [redacted] than the 44.8 months (95% CI 39.7, 51.1) median survival observed in the avelumab with axitinib arm of the JAVELIN Renal 101 trial. We do not know the IMDC risk group profile for the clear-cell histology subgroup in the CDF cohort but we know that across all the patients in CDF cohort the proportion with favourable-risk aRCC was [redacted] than in the JAVELIN Renal 101 trial as noted above (section 3.2.6.2). Histology subgroups were not reported for the EAMS cohort but median survival was [redacted] than in the avelumab with

axitinib arm of the JAVELIN Renal 101 trial ([redacted] months versus 44.8 months). OS was longer in the EAMS cohort over time and the NHS England SACT report states that the difference was statistically significant at 18, 24 and 36 months (CS Table 23). The company do not comment on possible reasons for this, but we note from CS Table 22 that the EAMS cohort was [redacted] and a [redacted] proportion had ECOG PS 0 at treatment initiation.

3.2.7.1.2 People with non-clear cell aRCC

As stated in section 2.1 one of the key areas of clinical uncertainty identified by the appraisal committee during TA645 and listed in the managed access agreement was the lack of data on whether the treatment is effective for non-clear-cell disease. Patients with non-clear cell disease made up approximately [redacted]% of the SACT dataset. The median OS among these patients was [redacted] months (95% CI: [redacted]). This [redacted] OS was statistically significantly different to that of the patients with clear-cell disease (Figure 2).

Figure 2 Kaplan-Meier survival plot by RCC histology in the CDF cohort (N=1,294)

Source: Reproduction of Figure 9 from the NHS England report[4]
CDF, Cancer Drugs Fund; RCC, renal cell carcinoma

3.2.7.1.3 Subgroups by IMDC risk category

When considering overall survival for subgroups by IMDC risk category, median overall survival was [redacted] for the favourable-risk category subgroup in the CDF cohort. Overall survival for both the intermediate-risk and poor-risk category subgroups from the CDF cohort were [redacted] than in the combined intermediate-/poor-risk category subgroup for the avelumab with axitinib arm of the JAVELIN Renal 101 trial. The source reference for the CDF data[4] presents Kaplan-Meier plots by IMDC factor and we reproduce this below in Figure 3. The SACT dataset does not provide evidence for overall survival for patients who receive sunitinib so this source does not provide an estimate for the treatment difference between avelumab with axitinib and sunitinib in real world NHS practice.

Figure 3 Kaplan-Meier survival plot by IMDC factor for the CDF cohort (n=1,294)

Source: Reproduction of Figure 8 from the NHS England report[4]
IMDC, International Metastatic RCC Database Consortium

3.2.7.2 Treatment duration

The company presents results on treatment duration for the CDF and EAMS cohorts in CS section B.2.8.2.3 and the results are summarised in Table 7. There were statistically

significant differences in treatment duration [redacted] and [redacted] and treatment duration was longer in the EAMS cohort than in the CDF cohort with the differences at 24 and 36 months being statistically significant (CS Table 24).

Table 7 Treatment duration in the CDF and EAMS cohorts

	CDF cohort (n=[redacted])	EAMS cohort (n=[redacted])
Completed treatment by 29 February 2024	[redacted]	[redacted]
Median follow-up time[a]	[redacted]	[redacted]
Median treatment duration	[redacted]	[redacted]
Clear-cell histology subgroup, median treatment duration	[redacted]	RCC histology not recorded
Non clear-cell histology subgroup, median treatment duration	[redacted]	
Favourable-risk subgroup median treatment duration (95% CI)	[redacted]	IMDC risk group status not recorded
Intermediate-risk subgroup median treatment duration (95% CI)	[redacted]	
Poor-risk subgroup median treatment duration(95% CI)	[redacted]	

Source: Compiled by EAG from data presented in CS section B.2.8.2.3.
CDF, Cancer Drugs Fund; CI, confidence interval; EAMS, Early Access to Medicines Scheme; IMDC, International Metastatic RCC Database Consortium; RCC, renal cell carcinoma.
[a] Median observed time from initiation of treatment to last treatment date in the SACT dataset plus the length of prescription.

3.2.8 Real-world evidence on TKIs as first-line therapy

The SACT dataset provides evidence on the real-world effectiveness of avelumab with axitinib as a first-line therapy for aRCC but it does not provide any data for patients who receive sunitinib or other TKI therapies first-line. We therefore looked to the analyses by two of the other real-world evidence sources identified by the company, Nathan et al. 2024[26 27] and McGrane et al. 2024,[5]. Nathan et. al 2024[26 27] only reports on aRCC patients who received avelumab with axitinib via the EAMS at 10 UK sites. McGrane et al. 2024[5] retrospectively reviewed patients from 17 UK NHS trusts who started systemic anti-cancer therapy for first-line metastatic RCC between 01 January 2018 and 30 June 2021, including an analysis of data from patients in the IMDC favourable-risk group. We focus on the favourable-risk patients here because the company's focus in the CS is the favourable-risk subgroup.

McGrane et al. 2024[5] included 1,286 patients in their analysis (a total of 1,319 met the inclusion criteria but the 33 patients who received treatments described as Misc/Other were

omitted from the analysis). Patient demographics and clinical characteristics at baseline for the whole cohort, 294 of whom had favourable-risk disease, are shown in CS Table 29. First-line treatments were grouped by drug class. In the IO+TKI group there were 66 patients with favourable-risk disease and 95.5% received avelumab with axitinib. Patients with favourable-risk disease in the TKI group (n=206) received sunitinib (50.5%), pazopanib (31.6%) or tivozanib (15%) with only 2.9% receiving cabozantinib. As shown earlier in Figure 1 patients with favourable-risk disease are not eligible to receive cabozantinib as a first-line therapy. We report outcomes from McGrane et al. 2024[5] in Table 8. For both progression-free survival and overall survival McGrane et al.[5] report that a log-rank test suggested a statistically significant difference between the IO+TKI and TKI groups with IO+TKI therapy delaying the time to death or progression (hazard ratio (HR) =0.60, 95% CI 0.39, 0.91) and delaying the time to death (HR=0.42, 95% CI 0.18, 0.99) versus TKI therapy. Despite the limitations of this real-world study which is based on retrospective data collection, it does provide data from UK NHS centres showing an overall survival benefit for favourable-risk patients receiving IO/TKI (predominantly avelumab with axitinib) in comparison to favourable-risk patients who received a TKI (predominantly either sunitinib, pazopanib or tivozanib). However, these difference in outcome may have been due to factors other than the first-line treatment received because the patients receiving different treatment types may have differed in one or more characteristics that could affect outcomes.

Table 8 Summary of PFS and OS results in real-world favourable-risk patients

	McGrane real-world evidence[5] Favourable-risk patients	
	IO+TKI (n=66), avelumab+axitinib (95.5%)	**TKI (n=206), sunitinib (50.5%), pazopanib (31.6%), tivozanib (15%) or cabozantinib (2.9%)[a]**
PFS		
Median PFS, months (95% CI)	25 months (95% CI not reported)	14.6 months (95% CI 34.4 months, NE)
HR (95% CI)	0.60 (95% CI 0.39, 0.91)	
OS		
Median OS, months (95% CI)	Not reached	41.1 months (95% CI 34.4 months, NE)
HR (95% CI)	0.42 (95% CI 0.18 to 0.99)	

Source: CS section B.2.8.4 and McGrane et al.[5]
CI, confidence interval; HR, hazard ratio; IO, immunotherapy; NE, not evaluable; OS, overall survival. PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
[a] As per Figure 1 favourable-risk patients are not eligible to receive cabozantinib as a first-line treatment.

3.2.9 Pairwise meta-analysis of intervention studies

Pairwise meta-analysis was not conducted because the JAVELIN Renal 101 trial is the only trial included in the CS that directly evaluates avelumab with axitinib with a relevant comparative treatment option.

3.3 Critique of studies included in the indirect comparison

3.3.1 Rationale for ITC

There are no head-to-head trials comparing avelumab with axitinib to treatment options other than sunitinib, and as noted in Table 4 treatment choice in adults with untreated aRCC is now determined by considering IMDC risk category alongside individual patient characteristics. The range of comparator treatments available differs according to the population being considered: ITT population, favourable-risk subgroup or intermediate-/poor-risk subgroup.

For the ITT population and favourable-risk subgroup the relevant comparators for decision-making are the single-agent TKIs (sunitinib, pazopanib and tivozanib). In previous NICE appraisals it has been considered reasonable to assume that sunitinib and pazopanib have broadly equivalent efficacy and that tivozanib may have a similar effect to sunitinib or pazopanib.[1 12-14 16 17 42] Therefore, the relative effects from the JAVELIN Renal 101 trial, where the comparator is sunitinib, are taken to represent the effects that would be obtained if pazopanib and tivozanib were the comparators. Consequently, an ITC is not necessary for the ITT or favourable-risk populations.

For the subgroup of people with intermediate-/poor-risk aRCC the comparators include the three single-agent TKIs listed above and four additional options: cabozantinib, nivolumab + ipilimumab, pembrolizumab + lenvatinib and nivolumab + cabozantinib. There is no head-to-head evidence comparing avelumab with axitinib with these four additional comparators so the company have conducted an ITC in the form of a network meta-analysis (NMA) to enable a comparison for the intermediate-/poor-risk subgroup.

As already noted, the company's focus in their submission is the favourable-risk subgroup; consequently we have taken a light-touch approach to our critique of the company's NMA for the intermediate-/poor-risk subgroup.

3.3.2 Identification, selection and feasibility assessment of studies for NMA

The company identified evidence from the most recent update of their clinical SLR (originally conducted in 2018 to inform TA645) which is described in CS Appendix D and critiqued by us in section 3.1.1. Five studies were identified that included data for the intermediate-/poor-risk subgroup for two or more treatments relevant to this appraisal. One of these is the JAVELIN Renal 101 trial. All the studies are listed in CS Table 30. The company were able to construct a network connecting the five trials though sunitinib which was a common comparator between them. The company's network diagram is provided in CS Figure 15. The company focussed on the PFS and OS outcomes as these were the key clinical outcomes used to inform the economic model and these outcomes were available for each trial. As the company point out in CS B.2.10.6 the evidence comes from a subgroup of patients in each trial and it is therefore likely to be more uncertain, particularly as the RCTs were not powered for subgroup analyses.

The company also assessed the Kaplan-Meier estimates for OS and PFS from each study to see if the proportional hazards assumption held. These assessments are provided in CS Appendix N. The company concluded that for the purpose of estimating relative effects to use in the economic model the proportional hazards assumption was reasonable. We note that in the NICE appraisal for lenvatinib with pembrolizumab (TA858)[16] the committee concluded that the proportional hazards approach could be used for decision-making even though they agreed with the EAG that the proportional hazards assumption was violated for PFS in the intermediate-/poor-risk subgroup. The committee agreed that results should be interpreted cautiously and they took the uncertainty into consideration.

3.3.3 Clinical heterogeneity assessment

The company do not discuss treatment effect modifiers that could influence the relative treatment effects. As part of clarification question A9 we asked the company to provide further information on the baseline characteristics for the participants from the studies that were included for the intermediate-/poor-risk subgroup. The company provided this (Table 3 in the company response to clarification questions) but it is only possible to compare median age, gender, prior nephrectomy and disease-risk status across four of the five trials because for other characteristics there are missing data for one or more for the trials and no baseline characteristics were available for the CLEAR trial. The company raise the heterogeneity of

the studies in CS section B.2.10.6 where they discuss the limitations and uncertainties in the ITC and indicate that there is some uncertainty about the heterogeneity of the studies because data were not available for all studies to enable comparisons of characteristics, particularly for the intermediate-/poor-risk subgroup. However, the company also state that the design and patient baseline characteristics of the studies are generally similar. We agree that this is likely to be the case.

3.3.4 Similarity of treatment effects and consistency in the network

None of the connections in the network included data from more than one study and there were no loops in the network. Therefore, similarity of treatment effects and consistency could not be investigated.

3.3.5 Risk of bias assessment for studies included in the NMA

The company did not provide risk of bias assessments in the CS for the five trials included in the NMA. We requested these (Clarification question A9) and in the response the company provided their assessments, but these had not all been done using the same tool because of the time period over which the company had conducted their original SLR and then updated this. For three trials (CABOSUN, CheckMate 214 and JAVELIN renal 101) the NICE checklist was used, for the remaining two trials (CLEAR and CheckMate 9ER) the response to clarification question A9 Table 5 states that the assessment has used the Cochrane ROB 2.0 checklist. However, when used correctly, the ROB 2.0 checklist should provide risk of bias judgements of 'low', 'high' or 'some concerns' for the five domains assessed whereas the company has reported judgements as Y or N (presumably signifying 'Yes' or 'No') and has not provided the underlying answers from the signalling questions. The company's assessment is therefore flawed and of very limited use. We note that risk of bias assessments for the trials have also been previously reported during other NICE appraisals as shown in Appendix 4. These assessments have shown that none of the trials would be considered at an overall low risk of bias because all are open label trials and a variety of other risks of bias have been raised (Appendix 4).

EAG comment on the studies included in the NMA

The studies included in the company's NMAs are those that have been included in previous NICE appraisals in this topic area. None of the studies were blinded and therefore they are at risk of performance and detection bias. Even though overall survival is an objective outcome, this might still be affected if the choice of second-line therapies differed between study arms outcome due to the lack of blinding. The extent to which the PFS outcome may be affected by the lack of blinding is less certain.

Independent central review (ICR) PFS or BICR PFS was available for all studies which may have helped to minimise bias but we know that for the JAVELIN Renal 101 trial data presented in the CS, only investigator assessments of PFS are available beyond the second interim analysis.

3.4 Critique of the NMA

The company report the methodology used for the NMA in CS B.2.10.4 and in the ITC report update document supplied in the clarification response.[43]

3.4.1 Data inputs to the NMA

The OS and PFS data inputs to the NMA were not provided in the CS but were provided in response to clarification question A9, Table 2. The company does not indicate what time-points the data comes from in the different trials. CS Table 30 indicates that ICR or BICR data were available for all studies and which data cut the evidence comes from for the CheckMate 9ER, CheckMate 214 and CLEAR studies.

3.4.2 Statistical methods for the NMA

The CS states that their proportional hazard NMA methods followed the guidance provided in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2-4.[44-46] The treatment effect model used was that described in NICE DSU TSD 2[45] and the models were implemented using the *gemtc* package in R software. Markov chain Monte Carlo (MCMC) methods were used to estimate relative treatment effects and 95% credible intervals using a minimum of 50,000 samples after convergence was achieved. The company state that autocorrelation plots were used to assess autocorrelation and that, if needed, a thinning interval was applied. The company does not report if thinning was actually necessary.

3.4.2.1 Choice between random effects and fixed-effect model

Fixed- and random-effects models were fitted to the data and goodness of fit was then compared using the deviance information criteria (DIC) and/or the total residual deviance and model choice was also guided by clinical plausibility of the estimated relative treatment effects.

3.4.3 Summary of EAG critique of the NMA

The company have provided very brief details of their NMA in the CS but this may be because it enables a comparison for the intermediate-/poor-risk subgroup of patients which is not the focus of the CS. From the information provided in the CS it seems that appropriate NMA methods have been chosen and implemented.

3.5 Results from the NMA

3.5.1 Overall survival in the intermediate-/poor-risk population

The CS presents results from the fixed-effects model only (results for the random effects model are presented in the ITC report provided with the clarification response). CS section B.2.10.6 states that the point estimates for the fixed- and random-effects models were similar but the credible intervals were substantially wider for the random-effects model. DIC was also similar between models. The company conclude that the relatively low number of studies (both in the network and with only a single study informing each treatment comparison), is the likely cause of the wide credible intervals for the random-effects model. The EAG concurs.

Figure 4 reproduces the forest plot for overall survival from the CS for the results from the fixed effect model in which avelumab with axitinib is the reference treatment. The credible intervals for the comparators all reach or cross the line for hazard ratio = 1 indicating that the results are not statistically significant. The point estimates suggest that in comparison to sunitinib, avelumab with axitinib and the other four comparator treatments lead to a reduction in the hazard of death but the reduction is greater for the other four comparator treatments. However, given the uncertainties associated with the NMA and because the results come from the fixed effect model which does not account for any heterogeneity between trials our view is that the results are very uncertain.

Figure 4 OS forest plot for intermediate-/poor-risk population comparing avelumab with axitinib to all other treatments – fixed-effects model

Source: Reproduction of CS Figure 16
CrI, credible interval; HR, hazard ratio

3.5.2 Progression-free survival in the intermediate-/poor-risk population

Similarly to the overall survival results, the CS only presents progression-free survival results from the fixed-effects model (results for the random effects model are presented in the ITC report provided with the clarification response). DIC was again similar between fixed and random effects models.

Figure 5 reproduces the forest plot from the CS showing avelumab with axitinib as the reference treatment. For two comparators, sunitinib and pembrolizumab + lenvatinib, the credible intervals do not cross the line for hazard ratio = 1 indicating that there is a statistically significant difference in the results. In comparison to sunitinib, avelumab with axitinib is associated with a lower hazard of progression or death whereas in comparison to pembrolizumab + lenvatinib, avelumab with axitinib is associated with a higher hazard of progression or death. For the other comparators where the 95% credible interval crosses the hazard ratio = 1 line, compared to nivolumab + ipilimumab, the point estimate for avelumab with axitinib suggests a lower hazard of progression or death. For the remaining 3 comparators (cabozantinib, nivolumab + cabozantinib and pembrolizumab + lenvatinib) there is a numerical increase in the hazard of progression or death for avelumab + axitinib treatment. Again, we view that these fixed effect results fail to take into account heterogeneity and are thus very uncertain.

Figure 5 PFS forest plot for intermediate-/poor-risk population comparing avelumab with axitinib to all other treatments – fixed-effects model

Source: Source: Reproduction of CS Figure 17
CrI, credible interval; HR, hazard ratio

3.6 Conclusions on the clinical effectiveness evidence

The appraisal committee during TA645 concluded that further data collection within the CDF could resolve the uncertainty by allowing for more mature survival data to be collected and providing evidence for the effectiveness of avelumab with axitinib in non-clear-cell aRCC.

The updated comparative evidence in the CS is from the final analysis of JAVELIN Renal 101 (data cut-off 31 August 2023) with median follow-up in the avelumab with axitinib arm of 73.2 months and 73.0 months in the sunitinib arm. As noted during TA645, the JAVELIN Renal 101 trial only enrolled patients with clear-cell aRCC. In our opinion the evidence from JAVELIN Renal 101 is at moderate risk of bias due to the open-label study design and use of investigator assessment for PFS. PFS and OS are both used in the economic model. All outcomes from JAVELIN Renal 101 were updated from the final analysis for this appraisal.

Since avelumab with axitinib entered the CDF in 2020, the treatment pathway for people with aRCC has evolved and decisions about first-line treatment now consider a person's prognostic risk status. The company have focussed their submission for this appraisal on the IMDC favourable-risk group (which is the population in the economic model base case) but also present evidence for the intermediate-/poor-risk subgroup as well as the full ITT population.

Has the uncertainty arising from the immature survival data presented for TA645 been resolved?

Overall survival data from the company pivotal trial, JAVELIN Renal 101, is now mature and median survival time was reached for the ITT population and for both the favourable-risk and intermediate-/poor-risk subgroups. Therefore, we have more certainty in the OS results than in the previous appraisal. In the ITT population, although OS was numerically in favour of avelumab with axitinib in comparison to sunitinib, the difference between groups was not statistically significant (see section 3.2.5.4 above). PFS in the ITT population was statistically significantly in favour of avelumab with axitinib.

The pre-specified IMDC risk subgroups in the JAVELIN Renal 101 trial provide direct comparative evidence for the IMDC risk subgroups in the NICE scope, albeit the favourable-risk subgroup is small at 21.4% (n=190) of the ITT population. OS and PFS outcomes from the favourable-risk subgroup both inform the base case economic model, these were numerically better for avelumab with axitinib compared to sunitinib (section 3.2.5.1 above). OS and PFS were also in favour of avelumab with axitinib in comparison to sunitinib in the

intermediate-/poor-risk subgroup (section 3.2.5.2 above). The trial was not powered to detect statistical significance in IMDC subgroups.

RWE for OS that is directly generalisable to NHS practice is derived from the CDF (n=[redacted] patients) and EAMS (n=[redacted]) cohorts presented in the NDRS SACT report. Patients had aRCC of a variety of histological subtypes (i.e. not limited to clear-cell aRCC) and IMDC status at treatment initiation but information on disease risk status and RCC histological type was not recorded for the EAMS cohort. The CDF cohort had a [redacted] median OS than the JAVELIN Renal 101 trial ITT population, and the EAMS cohort had a [redacted] median OS than the JAVELIN Renal 101 ITT population.

For the subgroup of patients with IMDC favourable-risk disease (n=[redacted] and with aRCC of any histological type in the CDF cohort, median OS was [redacted] so therefore RWE is less certain for this subgroup. For the subgroup with clear-cell histology and any IMDC risk category (n=[redacted]) median OS was [redacted] than in the JAVELIN Renal 101 ITT population.

The RWE from the SACT report is not comparative, however, further UK RWE from McGrane et al. 2024,[47] compares drug treatments by class. In the group of 294 favourable-risk patients, 66 received combination therapy of IO + TKI and avelumab with axitinib treatment accounted for 95.5% of this group. The remaining 206 favourable-risk patients had received a TKI with 97.1% of these receiving either sunitinib, pazopanib, or tivozanib (the remaining 2.9% received cabozantinib). The patients who received a TKI had a shorter median PFS and OS than reported for the favourable-risk patients in this real-world study who received a combination therapy with IO + TKI. However, great caution is needed in interpreting these data because the patients who received a TKI only and those who received combination therapy with IO + TKI were not randomised or matched in anyway and therefore the differences observed in outcome may have been due to factors other than the first-line treatment received.

Has the uncertainty around clinical effectiveness in the non-clear cell aRCC population been resolved?

Evidence for the non-clear cell aRCC population is provided from the CDF via the NDRS SACT Report provided with the CS. It shows that median OS in the non-clear cell population (n=[redacted]) is [redacted] than for the clear cell aRCC population (n=[redacted]) (section 3.2.7.1.2 above). However, as there is no comparator group in the SACT data we cannot observe any differences between treatments. Similarly, the Nathan et al. UK RWE study included analysis of participants with non-clear cell aRCC, but there was no

comparator treatment. The McGrane study (which reported comparative treatment data by drug class) included participants with both clear and non-clear cell aRCC but did not report results for these participants by aRCC histology subgroups. As noted above in section 3.1.2 the RWE SLR did not seek to identify comparative RWE evidence, and the JAVELIN Renal 101 trial excluded people with non-clear cell aRCC. Therefore, we can observe a greater disease burden in people with a non-clear cell disease component, but uncertainty remains around the comparative effectiveness of avelumab with axitinib in people with non-clear cell aRCC.

4 COST EFFECTIVENESS

This section presents a summary and critique of the cost effectiveness evidence included in the company's submission. Section 5 reports results from the company's economic analyses and the EAG's validation of the model. Additional analyses conducted by the EAG are presented in section 6.

The results in sections 4 to 6 all relate to the favourable-risk subgroup, which is the focus of the company's submission. We report results for the intermediate/poor-risk subgroup and the ITT population in Appendix 5.

4.1 EAG comment on company's review of cost-effectiveness evidence

The company summarise the results of their systematic review of cost-effectiveness evidence in CS section B.3.1, which updates their review for TA645. The methods and results of the original and updated economic reviews are described in a report provided with the CS references.[48] A single search was used to identify cost-effectiveness studies and sources of evidence for utilities and for resource use and costs. The searches for TA645 were conducted in September 2017 and March 2019, and the new update search in June 2024. The EAG considers that the search methods are appropriate.

The searches for TA645 did not find any cost-effectiveness studies for avelumab with axitinib. The company state that the updated search identified five studies that presented cost-effectiveness results for avelumab with axitinib, all relating to the aRCC population (CS section B.3.1). Tables 7 and 8 of the economic systematic review report (2024)[48] summarise methods and results for seven studies including avelumab with axitinib and sunitinib and/or nivolumab + ipilimumab: [1 49-54] The company do not discuss these papers, but we do not consider that they add relevant additional information.

See sections 4.2.5 and 4.2.6.1, respectively, for discussion of the reviews of sources of evidence for quality of life ('utility') and for resource use and costs.

4.2 Critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 9 summarises the EAG view's on whether the company's economic analysis complies with methodological criteria specified in the NICE reference case checklist.[55] We consider that the company's approach is reasonable.

Table 9 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes, for patients (carer outcomes are not included)
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes, cost-utility analysis. The company report pairwise ICERs, not fully incremental results. This is reasonable as two of the comparators are dominated (see section 5.1)
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, the time horizon is lifetime in the base case
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, EQ-5D-5L data collected from patients in the clinical trial (4.2.5.2)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, utilities are mapped UK population values using the Hernández-Alava et al. (2017) function.[56]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of	Yes. The severity modifier is not applicable for the

Element of health technology assessment	Reference case	EAG comment on company's submission
	individuals receiving the health benefit	favourable-risk population (see section 4.3)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: Produced by the EAG based on information from the company's submission and model
EQ-5D, European Quality of Life Working Group Health Status Measure 5 Dimensions; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life year.

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model structure is described in CS section B.3.2.2. It is a partitioned survival structure model, programmed in Microsoft Excel with a time horizon of 40 years and a cycle length of one week. The model structure comprises three health states: progression-free, progressed disease, and death. The company divide the progression-free health state into on- and off- treatment periods to reflect costs and health outcomes as patients may discontinue treatment prior to documented disease progression. The structure is illustrated in CS Figure 18 (reproduced in Figure 6 below).

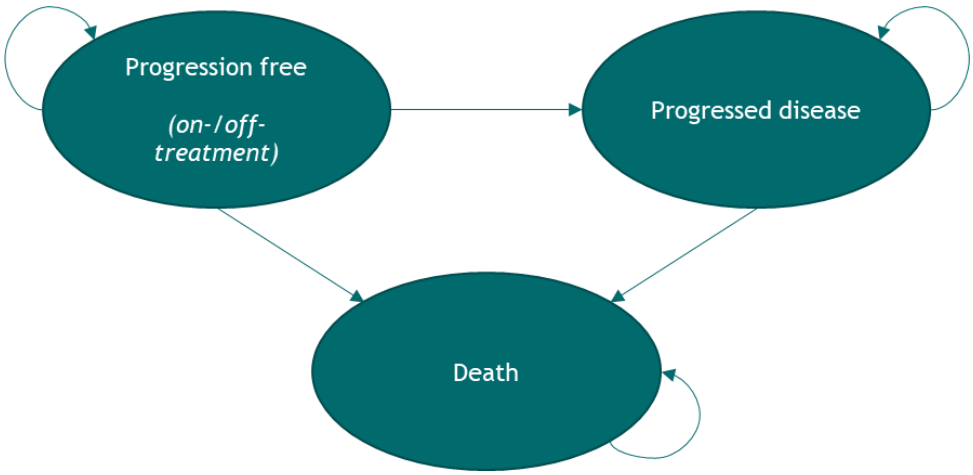

Figure 6 Company's economic model structure

Source: Reproduced from CS Figure 18.

Patients enter the model in the progression-free health state and can transition to the progressed disease or death health states. Patients in the progressed disease health state are only able to remain in the progressed disease state or transition to the death state. The proportion of patients in the progression-free state is estimated directly from the modelled PFS curves, whilst the proportion of patients in the death state is calculated from the inverse probability of the OS curve at that time. The proportion of patients in neither the progression-free nor death health states make up the progressed disease health state. The company assume that initial treatment ceases upon disease progression.

EAG comment on model structure

The model structure is appropriate. It is the same as that used in the original company submission and accepted by the NICE committee for TA645.

4.2.3 Decision problem for the model

4.2.3.1 Population

The base case population for the company's economic analysis is the subgroup of patients with favourable-risk disease (CS section B.3.2.1). The main economic sections of the CS (3.2 to 3.9) focus on the model inputs and results for this population. The company also report results for the intermediate/poor-risk subgroup (CS B.3.10) and for the ITT population (Appendix O).

The base case favourable-risk population is narrower than the population of all adults with untreated aRCC included in TA645 and in the NICE scope for the current managed access review. The company give two reasons for this change: 1) that there is a greater unmet need for the favourable-risk subgroup, as additional treatment options are now available for people with intermediate/poor-risk disease; and 2) that the JAVELIN Renal 101 study "*showed avelumab + axitinib to be clinically effective vs. sunitinib*" (CS B.3.2.1 page 105). The latter statement is true for the ITT population, as there was a significant effect on PFS, but we note that the trial was not powered for statistical significance in the IMDC subgroups, and numerical improvements in PFS and OS in these subgroups were not statistically significant (Table 5). Nevertheless, based on the assumption that pazopanib and tivozanib have similar efficacy to sunitinib (3.3.1), indirect evidence is not required to model cost-effectiveness in the favourable-risk subgroup. In contrast, indirect evidence is required to model the effect of other comparators in the intermediate-/poor-risk subgroup.

The modelled cohort for the base case reflect the characteristics of the favourable-risk subgroup in the JAVELIN Renal 101 trial: [redacted]% female with a mean age of [redacted] years (CS Table 40).

4.2.3.2 Interventions and comparators

The modelled intervention is avelumab at a fixed dose of 800mg administered by intravenous infusion once every two weeks with oral axitinib at 8mg twice daily. The comparators match those specified in the NICE scope. For the base case favourable-risk population, the comparators are sunitinib, tivozanib and pazopanib. The company cite SACT data which indicates that sunitinib is the most prescribed TKI monotherapy for people with favourable-risk untreated aRCC in UK practice, followed by pazopanib and then tivozanib (see CS section B.3.2.3). We discuss dosing assumptions for the comparators and subsequent treatments for the base case analysis in section 4.2.6.2 below.

For the intermediate/poor-risk subgroup analysis, the model includes NICE scope includes four additional comparators: cabozantinib monotherapy, nivolumab + ipilimumab, lenvatinib + pembrolizumab and cabozantinib + nivolumab. Information about dosing for comparators in the intermediate/poor-risk subgroup is provided in CS Appendix section O.1.

EAG conclusion on the decision problem for economic analysis

The EAG considers that the company's focus on the favourable-risk population in their base case for economic modelling is reasonable. Given that different comparators are indicated for the favourable-risk and intermediate/poor-risk subgroups, and that they have very different prognoses, it would not be appropriate to model these subgroups together in the ITT population. We agree with the company's rationale for selecting the favourable-risk subgroup for their base case, based on unmet need in this population and reduced uncertainty over clinical effectiveness relative to the intermediate/poor-risk subgroup.

4.2.4 Treatment effectiveness and extrapolation

The economic model uses parametric curves fitted to data for OS, PFS and TTD from the JAVELIN Renal 101 trial for avelumab, axitinib and sunitinib. The company assume that estimates for tivozanib and pazopanib are equivalent to sunitinib. We discuss results for the favourable-risk population in this section. The company report survival curves for the intermediate/poor-risk subgroup and the ITT population in CS Appendix O.

Although treatment waning was originally applied in TA645, this was removed following technical engagement. Therefore, in line with this decision, the company have not

implemented treatment waning in this appraisal. Similarly, a two-year stopping rule that was initially applied for avelumab with axitinib in TA645 has also been removed from the current appraisal. Patients cease first-line treatment prior to or at disease progression only.

4.2.4.1 Overall survival

KM estimates of OS for patients with favourable-risk disease from the JAVELIN Renal 101 trial are provided in CS Figure 6. CS section B.3.3.2 reports how parametric survival models were fitted to these data to produce extrapolations for use in the economic model. Six standard parametric survival distributions were used, including the exponential, as requested by NICE in the Managed Access Agreement. The fitted curves for avelumab with axitinib and sunitinib are shown in CS Figures 20 and 21, respectively. Goodness-of-fit statistics (AIC and BIC) and landmark survival estimates (at 1, 2, 5 and 10 years) are reported in CS Tables 41 and 42 for avelumab with axitinib, and in CS Tables 43 and 44 for sunitinib. The cost-effectiveness model includes an adjustment of the fitted extrapolations to ensure that the mortality risk for the modelled population cannot be lower than that expected for members of the general population of the same age and sex.

The hazard plots for the outcomes of OS were provided in Figure 3 of the company's clarification response. The company state that the evidence does not clearly support the proportional hazards assumption, and therefore that they chose to fit parametric curves to each treatment arm independently. Figure 7 and Figure 8 below show the fitted extrapolations for avelumab with axitinib and sunitinib, respectively. Table 10 reports overall survival estimates for patients with favourable-risk disease based on extrapolated results from the JAVELIN Renal 101 trial, including adjustment for general population mortality.

Table 10 OS adjusted for general population mortality (favourable-risk population)

Parametric function	Estimated survival				
	5 years	10 years	20 years	30 years	40 years
Avelumab with axitnib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parametric function	Estimated survival				
	5 years	10 years	20 years	30 years	40 years
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's model

Figure 7 Avelumab with axitinib OS extrapolations (favourable-risk population)

Source: Produced by the EAG from the company's economic model

Figure 8 Sunitinib OS extrapolations (favourable-risk population)

Source: Produced by the EAG from the company's economic model

The company used visual inspection, statistical goodness-of-fit and expert opinion on the plausibility of the long-term survival estimates from three clinicians to choose the parametric distribution for their base case and alternatives for scenario analysis (CS Table 78).

- For avelumab with axitinib, the company chose the log-normal distribution for the base case and generalised gamma and log-logistic distributions for scenario analysis.
- For sunitinib (and by assumption, for tivozanib and pazopanib) the company chose the generalised gamma for their base case, with log-logistic and Weibull distributions as scenarios.

The EAG notes that according to AIC/BIC scores the log-logistic, Weibull and log-normal OS distributions have a very similar fit for the avelumab + axitinib arm. And for sunitinib, the Weibull, log-logistic and log-normal have a similar statistical fit.

For comparison, the RCC Pathways Pilot model (Lee et al. 2023)[15 57], the exponential distribution was selected for sunitinib for the favourable-risk population, with the Weibull curve explored as a scenario. The exponential gives a very poor fit to the KM with the updated final analysis of JAVELIN Renal 101 data, but the Weibull still provides a good fit.

For the EAG's preferred analysis, we retain the company's base case OS extrapolations, and we report scenarios with the generalised gamma for avelumab + axitinib, and with the Weibull for sunitinib. In addition, we report results using the exponential distribution, as this was requested by the committee in TA645. The exponential provides a comparison against an assumption of a constant hazard, but it does not provide a good fit to the updated trial data in either arm.

4.2.4.2 Progression free survival

The KM estimates of PFS for avelumab with axitinib and sunitinib from the JAVELIN Renal 101 study are presented in CS Figure 7. The parametric curves, including the exponential, fitted to each arm are provided in CS Figure 22 and CS Figure 23. The hazard plots for the outcomes of PFS are given in clarification response Figure 4. As with OS, the company assume that proportional hazards do not hold and fit models independently for each arm. The company selected the log-normal curve for avelumab with axitinib, and the generalised gamma model for sunitinib (and therefore also tivozanib and pazopanib). We note that the model includes an adjustment to prevent PFS exceeding OS.

Table 11 PFS adjusted for general population mortality (favourable-risk population)

Model	Estimated survival (years)				
	5	10	20	30	40
Avelumab + axitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's model

The EAG notes that the best fitting curves according to AIC/BIC scores are the log-normal model for avelumab with axitinib and the log-normal and exponential models for sunitinib. However, as the PFS data is now very mature all of the survival distributions have a similarly good fit to the KM data and provide similar long-term extrapolations and cost-effectiveness results. We report selected PFS scenarios in section 6 of this report (see Table 20).

4.2.4.3 Time to treatment discontinuation

The parametric curves were fitted to avelumab and axitinib individually, as patients may discontinue the drugs independently and TTD data is available by medication from the JAVELIN Renal 101 trial. The KM estimates for avelumab, axitinib, and sunitinib are provided in CS Figure 24, and the log-cumulative hazard plots are presented in clarification response Figure 5. CS Figures 25, 26 and 27 show the parametric survival model fits for avelumab, axitinib, and sunitinib, respectively (including the exponential model). As with OS and PFS, the company argue that the proportional hazards assumption does not hold and fits parametric curves independently for each treatment. The company selects the generalised gamma model for avelumab, axitinib, and sunitinib (and therefore tivozanib and pazopanib). We note that the model includes an assumption that patients discontinue avelumab + axitinib on disease progression.

The EAG notes that the best fitting curves according to AIC/BIC scores are the Gompertz and exponential models for both avelumab and axitinib (independently) and the exponential model for sunitinib. As with PFS, TTD data is very mature and all of the parametric

distributions provide a similar and very good fit to the KM data. We report selected scenarios for the TTD in EAG analysis (see Table 20).

Table 12 TTD (favourable-risk population)

Model	Estimated survival (years)				
	5	10	20	30	40
Avelumab					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from the company's economic model

EAG comment on treatment effectiveness and extrapolation

The EAG agrees with the company's methods and selection of base case extrapolations for OS, PFS, and TTD. We note that there is still high uncertainty over long-term survival, as there are several alternative parametric survival distributions with a good fit to the KM data that give very different projections of survival at 10 years and beyond. Thus, cost-effectiveness estimates are sensitive to the choice of OS extrapolation.

4.2.5 Health related quality of life

The company describe their approach to estimating health-related quality of life (utility) for the cost-effectiveness analysis in CS section B.3.4.

Base case utilities for the progression-free and progressed disease health states are estimated from EQ-5D-5L data for patients with IMDC favourable-risk disease in the

JAVELIN Renal 101 trial. Results are also reported for a scenario with an alternative specification of the utility analysis, and for scenarios with utilities from previous NICE appraisals. Age-adjustment of utilities is applied (see section 4.2.5.3 below). Specific disutilities for adverse events are not used, as it is assumed that the effects of such events are already reflected in the trial data.

The approach to utility estimation is consistent with that accepted in TA645, although the utility values differ due to changes in the target population (favourable-risk only rather than ITT), the availability of longer trial follow-up and a change in the NICE-preferred method for valuing EQ-5D-5L data.[55] See the subsections below for further discussion.

4.2.5.1 Systematic literature review for utilities

The updated review of utility studies identified 17 UK studies, of which 8 were NICE TAs.[48] The company do not discuss these results, but instead compare the utility estimates from the updated analysis of JAVELIN Renal 101 trial data with estimates from previous NICE appraisals (CS section B.3.4.3 and Table 59), as in the submission for the original appraisal TA645. The previous appraisals all relate to an ITT population, rather than the favourable-risk subgroup considered in the current appraisal, see discussion in section 4.2.5.4 below.

4.2.5.2 Utility estimates from trial data

The methods used to analyse the EQ-5D-5L data from the JAVELIN Renal 101 trial are described in CS sections B.3.4.1 and B.3.4.2, with further information in the company's response to clarification question B7.

EQ-5D-5L data were collected at the beginning of each 6-week treatment cycle, and after treatment discontinuation at day 30, 60 and 90 and then every 3 months.[58] The questionnaire data was mapped to EQ-5D-3L 'UK tariff' utility values using the Hernández-Alava et al. (2017) function, as recommended by NICE.[55 56] The company report that as the number of missing utility observations is low ([redacted]), imputation is not necessary (clarification response B7). We note that it is not clear from the description in the clarification response whether this cited proportion of missing data accounts for all observations that would have been due in follow-up for non-censored participants, or whether it only applies to submitted EQ-5D-5L questionnaires.

Utility values were estimated using pooled data for both treatment arms in the favourable-risk subgroup and analysed with a linear mixed-effects regression to account for repeated measurement. The base case utility model included progression status as the only fixed effect covariate (Model 1). A scenario with treatment status (on/off treatment) as an

additional covariate (Model 2) is reported, but not used in the base case as the treatment status coefficient was not statistically significant.

We noted a discrepancy in the reporting of the Model 2 'On treatment' status coefficient as a positive value ([redacted]) in CS Table 57, and the way that it is applied in the company's model as a decrement (due to an adjustment in cells X160-X162 on the Parameters sheet). The company clarified in their factual accuracy check that there was an error in CS Table 57 and that the on-treatment coefficient should have a negative value ([redacted]), as in their economic model. The on-treatment utilities reported in CS Table 58 are also incorrect, see Table 13 below for the correct values.

The company do not report any other tests of alternative model specifications (clarification response B7), but we note that the simple base case utility model is consistent with that accepted in the TA645, and in NICE appraisals of the comparators (TA178, TA215 and TA512).[12 13 59] The company submission for TA645 reported that the coefficient for the treatment arm was not significant and that clinical expert opinion supported the assumption of equal health state utilities for avelumab with axitinib and sunitinib.

Results for the favourable-risk subgroup are reported in CS Tables 57 and 58. Equivalent results for the intermediate/poor risk subgroup and the ITT population are reported in CS Appendix O.5.1, Tables 86 and 87.

4.2.5.3 General population utilities and age adjustment

The model includes an adjustment to reflect declining quality of life with age in the general population based, on the Ara and Brazier (2010) formula (see CS section B.3.4.5).[60] This adjustment is correctly applied and in accordance with NICE guidance.[55] We confirm that the modelled utility in the progression-free health state remains lower than expected utility for people of the same age and gender in the general population, based on both the Ara and Brazier formula and more recent estimates of general population utility in England reported by McNamara et al. (2023).[61]

4.2.5.4 Summary of utility estimates

Table 13 shows the utility estimates for the progression free (PF) and progressed disease (PD) health states from the company's updated analysis of JAVELIN Renal 101 data (favourable-risk and ITT populations), together with values from the previous analysis of JAVELIN Renal 101 data for TA645, and from NICE appraisals for the comparators sunitinib, pazopanib and tivozanib (TA178, TA215, TA512) and the sunitinib arm in TA581. [12 13 59 62 63]

The utilities from previous appraisals are all derived from ITT trial populations with untreated aRCC, including people with poor, intermediate and favourable-risk disease. As might be expected, utilities for the favourable-risk subgroup in the updated JAVELIN Renal 101 analysis are higher than the equivalent analysis in the ITT population and ITT estimates from previous appraisals. We also note that the loss of utility associated with disease progression in the updated JAVELIN Renal 101 trial analysis is somewhat lower for the favourable-risk subgroup than for the ITT population: [redacted] versus [redacted] in Model 1. The progression disutility is also much higher in the TA645 analysis of the JAVELIN Renal 101 trial data (0.070), which may be related to the shorter duration of follow up.

Table 13 Comparison of utility values from the trial and other NICE appraisals

Population	Analysis	Treatment arm	Treatment status	Health state utilities		
				PF	PD	Decrement
Updated analysis of JAVELIN Renal 101 utility data						
Favourable risk (CS Table 58)	Model 1	Pooled [a]	-	[redacted]	[redacted]	[redacted]
	Model 2	Pooled [a]	On [c] Off	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
ITT population (CS Table 87)	Model 1	Pooled [a]	-	[redacted]	[redacted]	[redacted]
	Model 2	Pooled [a]	On [c] Off	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
Utilities from TA645 and previous NICE appraisals for comparators						
ITT population	TA645	Pooled [a]		0.753	0.683	0.070
	TA178	Sunitinib [b]	-	0.780	0.700	0.080
	TA215	Pazopanib	-	0.700	0.590	0.110
	TA512	Tivozanib	-	0.726	0.649	0.077
	TA581	Sunitinib	-	0.719	0.699	0.020

Source: Adapted by the EAG from CS Tables 58, 59, Appendix Table 87 and from the model
aRCC, advanced renal cell carcinoma; CS, company submission; ITT, intention-to-treat; PF, progression free; PD, progressed disease; TA, technology appraisal.
[a] Pooled data for both treatment arms: avelumab with axitinib and sunitinib.
[b] Values from TA178 Assessment Group model for first-line treatments, same as in TA169.
[C] Values differ from those in CS Table 58 because the 'on treatment' coefficient in the Model 2 regression is applied as a negative value, as in the company's submitted model.

EAG comment on utilities

The methods used to estimate health state utilities in the JAVELIN Renal 101 trial are consistent with NICE's preferred methods,[55] and with the approach used in the original analysis of the trial data for TA645.[1] The base case utility values for the favourable-risk subgroup in the current appraisal are higher than those in TA645, which were estimated for the ITT trial population and with shorter follow-up. To investigate the impact of this change, we report an additional EAG scenario analysis with the TA645 utilities. For comparison, we also report an

exploratory scenario analysis with utilities from updated trial data for the ITT population (as reported in CS Table 87). The approach to utility analysis is also consistent with approaches in NICE appraisals for comparators, but values from comparator appraisals are also related to ITT populations and are of less relevance than those from TA645. We therefore do not report scenario results with utilities from other appraisals.

4.2.6 Resources and costs

4.2.6.1 Systematic literature review for costs and resource use

Results from the systematic review of evidence for cost and resource use are reported in section 4 of the updated economic systematic review report (2024).[48] The review included 18 studies, of which 10 were NICE appraisals.[1 11-17 59 63]

In the following sections, we compare the company's resource use and cost assumptions with those in the original appraisal TA645 and with reference assumptions from the PenTAG RCC Pathways pilot assessment report (Lee et al. 2023).[15 57]

4.2.6.2 Drug costs

4.2.6.2.1 Unit costs

Unit costs for intervention and comparator drugs are reported in CS Table 61 and unit costs for other drugs used in subsequent treatment are reported in CS Table 70 (also listed in Tables 45 and 46 in CS Appendix K). Costs for premedication with an antihistamine and paracetamol are added to the intervention costs (CS Table 62).

The company used list prices sourced from the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT), cited access date 13/04/23. We checked updates of the BNF and eMIT (access date 13/01/25). [64 65] The latest edition of eMIT (July 2023 to June 2024) reports lower weighted average prices for sunitinib and everolimus, which we use in EAG analyses (see section 6).

The company apply an existing simple PAS price discount of [redacted]% for avelumab and a published discount of 12.5% for pazopanib (NICE TA215).[12] Price discounts are also available for axitinib, tivozanib and for other drugs used in subsequent treatment, but these are confidential. We provide cost-effectiveness results including all available NHS price discounts in a confidential addendum to this report. The company use scenario analysis to illustrate the impact of potential price reductions for axitinib (CS Table 78),

[redacted]. We do not report these scenarios as this is not usual practice.

Table 14 summarises unit costs for all drugs in the company's model, updated prices used in the EAG base case and sources for drug costs in the confidential EAR Addendum.

4.2.6.2.2 Dosing assumptions

We summarise dosing assumptions and total drug acquisition and administration costs used in the company's base case model in Table 15. Dosing assumptions are reported in CS section B.3.2.3 for the intervention and comparators, and in CS Table 71 for subsequent treatments. Other information is obtained by the EAG from the company's model.

Adjustment for wastage is not necessary for avelumab, as it is available in 200 mg vials for infusion, with a recommended dose of 800 mg every 2 weeks. For simplicity, the company assume a fixed infusion dose of 240 mg for nivolumab in subsequent treatment (3 mg/kg, with an assumed mean body weight of 80 kg). Other drugs are administered orally, with an assumption of no wastage.

4.2.6.2.3 Relative dose intensity

The company apply relative dose intensity (RDI) adjustments to costs of the intervention and comparator drugs, see CS Table 63. RDIs for avelumab, axitinib and sunitinib are derived from JAVELIN Renal 101 trial data (ITT population, final analysis); and estimates for tivozanib and pazopanib are derived from trial data, as used in the NICE appraisals TA512 and TA215 respectively.[12 13 66]

The model includes some RDI estimates for subsequent treatments (Costs!U44-U55), but these do not inform the company's cost-effectiveness results. We note that the RCC Pilot Pathway reports RDI estimates from trial and real-world evidence (Table 87 in Lee et al. 2023)[57]. The real-world figures are redacted but we list the RDI values for subsequent treatments from clinical trials in Table 15. A scenario using these RDIs is performed in section 6.

4.2.6.2.4 Drug administration costs

The model includes a cost of £217 for administration of drugs by intravenous infusion (NHS National Cost Collection 2022/23, SB12Z Outpatient).[67] No cost is applied for administration of oral medications, which differs from the approach in TA645 which included a one-off cost for initiation of exclusively oral medication (HRG code SB11Z), and ongoing pharmacist costs for continuing use (TA645 company submission Table B.3.46). The RCC Pathway Pilot

Assessment Report follows this approach, with a cost of £197.25 for initiation of oral therapy and £11 per new pack of medication required (Table 88, Lee et al. 2023).[1 57] It is likely that the company's exclusion of costs for delivery of oral drugs is conservative because the one-off cost for initiation of oral therapy is incurred for the comparators but not for the intervention (as the cost for initiation of axitinib is already covered in the administration cost for avelumab).

Table 14 Unit costs for drugs used in the base case model (favourable-risk population)

Drug	Form	Unit	Pack size	Company base case		EAG analysis - if different		cPAS Addendum
				Cost	Source	Cost	Source	Source
Intervention								
Avelumab	Infusion vial	200 mg	1	[redacted]	CS, PAS price			CS, PAS price
Axitinib	Tablet (oral)	5 mg	56	£3,517	BNF 2024			Confidential PAS price
Comparator								
Sunitinib	Capsule (oral)	50 mg	28	£348.78	eMIT 2023	£89.07	eMIT Jul 23-June 24	eMIT July 23-June 24
Tivozanib	Capsule (oral)	1.34 mg	21	£2,052	BNF 2024			Confidential PAS price
Pazopanib	Tablet (oral)	400 mg	30	£980.88	Public PAS price [a]			Public PAS price [a]
Subsequent treatments								
Cabozantinib	Tablet (oral)	40 mg	30	£5,143	BNF 2024			Confidential PAS price
		60 mg	30	£5,143	BNF 2024			
Everolimus	Tablet (oral)	5 mg	30	£429.75	eMIT 2023	£252.29	eMIT Jul 23-June 24	eMIT July 23-June 24
		10 mg	30	£488.32	eMIT 2023	£283.71	eMIT Jul 23-June 24	
Lenvatinib	Capsule (oral)	4 mg	30	£1,437	BNF 2024			Confidential PAS price
		10 mg	30	£1,437	BNF 2024			
Nivolumab	Infusion vial	240mg	1	£2,633	BNF 2024			Confidential PAS price

Source: Produced by the EAG using information from CS Appendix K, BNF 2024 and eMIT (accessed 13 Jan 2025)[64 65] and NICE Pricing tracker form (received 14 Jan 2025)

BNF, British National Formulary; CAA, commercial access arrangement; CS, company submission; eMIT, drugs and pharmaceutical electronic market information tool; PAS patient access scheme.

[a] Unit cost for pazopanib includes publicly available simple price discount of 12.5% (NICE TA215) applied to the list price £1,121 (BNF 2024)

Table 15 Dosing assumptions used in the base case model (favourable-risk population)

Regimen	Drug	Route	Dose	Frequency	Admin cost [a]	Relative dose intensity		Time on treatment (days) [d]
						Company base case [b]	Subsequent treatment [c]	
Intervention								
Ave + axi	Avelumab	IV	800 mg	Every 2 weeks	£217.22	91.7%		TTD
	Axitinib	Oral	5 mg	Twice daily		83.7%		TTD
Comparators								
Sunitinib	Sunitinib	Oral	50 mg	Once daily 4/6 weeks		81.9%		TTD
Tivozanib	Tivozanib	Oral	1.34 mg	Once daily 3/4 weeks		94.0%	94.0%	TTD
Pazopanib	Pazopanib	Oral	800 mg	Once daily		86.0%	86.0%	TTD
Subsequent treatments								
Cabozantinib	Cabozantinib	Oral	60 mg	Once daily		100%	93.3%	231.7
Everolimus	Everolimus	Oral	10 mg	Once daily		100%	84.0%	167.3
Axitinib	Axitinib	Oral	5 mg	Once daily		100%	99.0%	220.5
Sunitinib	Sunitinib	Oral	50 mg	Once daily 4/6 weeks		100%	81.9%	172.9
Nivolumab	Nivolumab	IV	240 mg	Every 2 weeks	£217.22	100%	97.5%	294.0
Len + Eve	Lenvatinib	Oral	18 mg	Once daily		100%	70.4%	243.5
	Everolimus	Oral	5 mg	Once daily		100%	89.3%	243.5
Pazopanib	Pazopanib	Oral	800 mg	Once daily		100%	86.0%	348.6

Source: Produced by the EAG using information from CS sections B.3.2.3 and B.3.5.1 and from the company's model.
Admin, administration; Ave + axi, avelumab with axitinib; IV intravenous infusion; Len + Eve, lenvatinib with everolimus; RDI, relative dose intensity; TTD, time to treatment discontinuation.
[a] NHS National Cost Collection 2022/23 (SB12Z Outpatient). No costs are applied for oral medications.
[b] RDIs for intervention and comparators from CS Table 63. RDI not applied in costings for subsequent treatments in the company's model.
[c] RDIs based on trial data from Table 87 RCC Pilot Pathways Assessment Report (2023).[57]
[d] TTD distribution for intervention and comparators based on JAVELIN Renal 101 TTD favourable-risk data, assuming TTD for tivozanib and pazopanib is the same as for sunitinib (see 4.2.4.3).

Table 16 Subsequent treatment assumptions for the favourable-risk subgroup

Subsequent treatments	**Company base case** (JR101, rescaled to remove nivolumab after Ave + axi)		**No rescaling for nivolumab**		**TA645**[1]		**100% nivolumab or cabozantinib**		**UK ROC study (McGrane 2024)**[5]	
	Ave + axi	Sunitinib	Ave + axi	Sunitinib	Ave + axi	Sunitinib	Ave + axi	Sunitinib	Ave + axi	Sunitinib
Cabozantinib	59.45%	30.56%	42.91%	30.56%	25.40%	15.80%	100.00%	-	70.61%	59.29%
Everolimus	24.10%	12.01%	17.40%	12.01%	4.90%	1.70%	-	-	-	-
Axitinib	22.50%	13.10%	16.24%	13.10%	9.10%	9.60%	-	-	-	13.27%
Sunitinib	20.89%	15.28%	15.08%	15.28%	9.10%	13.00%	-	-	-	1.77%
Nivolumab	-	86.23%	42.91%	86.23%	8.50%	60.50%	-	100.00%	-	67.26%
Len + eve	19.28%	14.19%	13.92%	14.19%	6.70%	9.00%	-	-	45.39%	6.19%
Pazopanib	8.03%	10.92%	5.80%	10.92%	4.20%	6.80%	-	-	10.09%	5.31%
Total cost	[redacted]	£75,057	[redacted]	£75,057	[redacted]	£49,693	[redacted]	£59,855	[redacted]	£69,699

Source: Produced by the EAG using information from CS Table 69, CS Appendix Table 95 and the company's model
Ave + axi, avelumab with axitinib; Eve, everolimus; JR101, JAVELIN Renal 101, Len, lenvatinib; UK ROC study, UK renal oncology collaborative study.

4.2.6.2.5 Subsequent treatment use

We summarise the company's base case and scenario assumptions regarding the use of subsequent treatments in the favourable-risk subgroup in Table 16 below (based on CS Table 69 and Appendix P Table 95). The base case analysis uses the distribution of subsequent treatments observed for patients with favourable risk in the JAVELIN Renal 101 trial, with an adjustment to exclude nivolumab as a subsequent treatment after avelumab with axitinib as this is not usual practice (company response to clarification question B8).

We agree that the adjustment for nivolumab is appropriately applied in the model, with rescaling of other subsequent treatments. A clinical expert advising the EAG stated that rechallenge with axitinib and sunitinib after use of these agents at first line is not seen in clinical practice. We tested the effect of adjusting the company's base case to exclude subsequent use axitinib or sunitinib after first-line use, this led to an increase in subsequent treatment costs in both arms, and a small decrease in the ICER.

The company report three scenarios for subsequent treatment use in the favourable-risk subgroup, see summary in Table 16. We note the scenario based on subsequent treatment use for favourable-risk patients in the UK real world cohort reported by McGrane et al. (2024)[5] and suggest that this may be more representative of UK practice than the JAVELIN Renal 101 trial, although the number of patients in the favourable-risk subgroup treated with an immunotherapy/TKI combination at first line was low (n=66).

4.2.6.3 Adverse event incidence and costs

The model includes costs for treatment-related adverse events of grade ≥3 experienced by more than 5% of patients, see CS Table 56. In the initial version of the model, the same unit cost was used for all adverse events, based on an average of all non-elective short stay codes from the NHS National Cost Collection 2021. This is explained in the company response to clarification question B9, and adverse event specific costs were added to an updated version of the model submitted with the clarification response. We agree that this is appropriate and has minimal impact on the cost-effectiveness results.

4.2.6.4 Health state resource use

Assumptions regarding the use of additional health services (CS Table 65) are consistent with those in TA645 (ERG report Table 31).[1] Prior to progression, it is assumed that patients have a monthly GP visit and blood test and a three-monthly CT scan, in addition to services required for delivery of therapy or treatment of adverse events. After progression, it is assumed that patients have one GP visit and 1.5 community nurse visits per month, and

daily pain medication. These assumptions are also broadly consistent with the approach in the RCC Pathways Pilot analysis (Table 84, Lee et al. 2023).[57]

Unit costs for health services are reported in CS Table 66. We note that the cited cost for a CT scan is high (£193 compared with £135 from the 2023/24 National Cost Collection, code RC27Z), but this only has a small impact on the ICER.

4.2.6.5 End of life costs

The model includes a cost of £7,483 for end of life health and social care, based on estimates by Round et al. (2015), uprated for inflation.[68 69] This source was used in TA645. A higher estimate of £8,714 is used in the RCC Pathways Pilot model (Lee et al. 2023)[57] but only has a small impact on the ICER.

EAG conclusions on resource use and costs

The company's overall approach to estimating resource use and costs is mostly reasonable and consistent with the TA645, although we noted some discrepancies that we address in EAG additional analysis (see section 6). These include updated prices for sunitinib and everolimus based on the most recent version of eMIT in the EAG base case (Table 14), and additional scenario analyses for RDI adjustments for subsequent treatments (Table 15);

4.3 QALY weighting for severity

Severity is described in CS section B.3.6. The company used the QALY shortfall calculator from Schneider et al.[70] to calculate the expected QALYs for the general population, using the baseline characteristics from the economic model (see CS Table 40: age [redacted], [redacted] female). This results in an expected total QALYs for the general population of 12.29 and an estimated total QALYs for people living the disease managed with current treatment of 4.25. The absolute and proportional QALY shortfalls were 8.04 and 65.41%, respectively. Therefore, no severity modifier was applied for the favourable-risk population in this appraisal. The EAG agrees with the company's conclusion.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reports their base case pairwise cost-effectiveness analysis results for avelumab with axitinib versus sunitinib, tivozanib and pazopanib for the favourable-risk population in CS Table 75.

The company's base case analysis is conducted with a confidential PAS price discount for avelumab and a published discount on the list price for pazopanib (NICE TA215).[12]. Confidential price discounts are also available in the NHS for axitinib, tivozanib and for other drugs used in subsequent treatment. Cost-effectiveness results including all confidential price discounts are presented in a separate addendum to this report. See Table 14 and the discussion in section 4.2.6.2.1 for further information about the unit costs and price discounts applied in the company's base case, and in the confidential EAR Addendum.

In their response to the clarification questions, the company updated their model, which changed their original base case results for the favourable-risk population. The revised model received as part of the clarification response (and referred to here as 'the revised company model') includes the following changes:

- Adverse event specific costs are applied rather than a single value for all adverse events, with costs updated to the 22/23 National Cost Collection.
- Blood test, CT scan, simple intravenous infusion (IV) and complex IV costs have been updated from 21/22 to 22/23 National Cost Collection values.
- All poor risk subsequent therapies are considered (only affects the intermediate-/poor-risk population results – see Appendix 5)

A summary of the above changes is presented in Table 11 of the clarification response document. We have reproduced the cost-effectiveness results from the revised company model for the favourable-risk population in Table 17. The pairwise ICER for avelumab with axitinib versus sunitinib is [redacted] per QALY, versus tivozanib is [redacted] per QALY and versus pazopanib is [redacted] per QALY. We note that these changes had a minor impact on the model results (the change was < £1,000 per QALY for each of the comparisons).

We note that the company only report pairwise ICERs, not fully incremental results as specified in the NICE Reference Case.[55] In practice this is not important, because tivozanib and pazopanib are dominated by sunitinib in all analyses based on their relative costs, due

to the assumption that the three TKI comparators have equal effects (equal QALYs). We report fully incremental results for the EAG analyses in section 6.

Table 17 Base case results of the revised company model (favourable-risk population).

Treatment	Total		Incremental		ICER [a] (£/QALY)
	Cost (£)	QALYs	Cost (£)	QALYs	
Versus sunitinib					
Sunitinib	£93,185	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib					
Tivozanib	£136,173	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib					
Pazopanib	£165,275	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from Table 12 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company reports deterministic sensitivity analysis results in the form of tornado diagrams, showing the top 10 most influential parameters for the favourable-risk population. The comparisons versus sunitinib, tivozanib and pazopanib are shown in CS Figures 37-39. The range of variation for the input parameters was based on the available variance estimates or, when not available, the standard error was assumed to be 10% of the mean values. The company reports the impact on incremental net monetary benefit (NMB) at a willingness-to-pay (WTP) threshold of £30,000 per QALY in these diagrams. The deterministic sensitivity analysis shows that the model results are robust to reasonable variation of the parameter inputs. Across all comparators, the most influential parameters are the RDI for axitinib, the days on treatment for nivolumab and the RDI of pazopanib.

5.2.2 Scenario analysis

The scenario analyses conducted in the original company model for the favourable-risk population and their respective results are presented in CS Table 78. The EAG was able to

replicate the results from all the scenarios. The scenarios with the greatest impact on the model results are the changes in the price of axitinib, the use of alternative parametric curves for OS, alternative discount rates for costs and QALYs, shorter time horizons, change in the sources of utilities and subsequent therapies' distribution and excluding RDIs.

5.2.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis results from 5,000 iterations of a Monte-Carlo simulation, using the original company model for the favourable-risk population are given in CS Table 77 (also presented in Table 18 below). The pairwise ICER per QALY gained is reported as [redacted] per QALY for avelumab with axitinib versus sunitinib, [redacted] per QALY versus tivozanib and [redacted] per QALY for pazopanib. The normal distribution was used for all the input parameters in the probabilistic sensitivity analysis, which is not consistent with usual practice because cost parameters are skewed and cannot be negative, and probabilities should be constrained to values between 0 and 1. See section 5.3.4 below for further detail and EAG corrections to the company's PSA results.

Uncertainty in the ICER calculation is demonstrated by the cost-effectiveness scatter plots for avelumab with axitinib versus comparators (CS Figures 34-36). At a WTP threshold of £30,000 per QALY, the probabilities of avelumab with axitinib to be cost-effective are 0% versus sunitinib, around 20% versus tivozanib and around 70% versus pazopanib (CS Figures 31-33).

Table 18 Probabilistic results company's base case (favourable-risk population)

Treatment	Total		Incremental		ICER [a]
	Cost (£)	QALYs	Cost (£)	QALYs	(£/QALY)
Versus sunitinib					
Sunitinib	£93,021	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib					
Tivozanib	£137,918	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib					
Pazopanib	£168,095	[redacted]			[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 77 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib

5.2.4 Subgroup analysis

The company report results for the intermediate/poor-risk subgroup in CS section B.3.10, with model inputs and results for the ITT population presented in CS Appendix O. The EAG discussion of the model inputs, assumptions and results for the two alternative populations is presented in Appendix 5.

5.3 Model validation and face validity check

5.3.1 Company model validation

The company's approach to validate their model is described in CS section B.3.12. Quality control checks included reviewing for potential coding errors, inconsistencies and plausibility of inputs by an independent economist who was not involved in the model development process. Some examples of the validity checks that were applied in every sheet or overall by the use of a checklist are: extreme value testing, logical relationship testing and consistency checks.

In addition, the company report clinical expert from three medical oncology specialists based in England and Wales, who currently treat patients with aRCC in NHS practice. They were asked about treatment pathway for aRCC and plausibility of survival estimates.

5.3.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations, and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources.
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses.
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- Checking individual equations within the model ('white box' checks)
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

5.3.3 Company corrections to the model

The company's corrections to their original model are described in section 5.1 above. The EAG was able to replicate the results of the revised company model after applying the changes described in clarification responses B9, B10 and B11 to the original version of the model.

5.3.4 EAG corrections to the company model

Other than the issues raised by the EAG in the clarification questions stage, the only technical errors that we identified in the company's economic model relate to the probabilistic sensitivity analysis.

The company used normal distributions for the percentage relative dose intensity (RDI) parameters, and for all cost and resource use parameters that were included in the PSA. This is not appropriate as the sampled values are not restricted to feasible ranges (0%-100% for the RDIs and ≥0 for resource use and costs). We therefore edited the model to use gamma distributions for PSA sampling of cost and resource use parameters and beta distributions for the RDI percentages.

The company used a fixed standard error of 5% of the mean for resource use, cost and RDI parameters in the PSA, so uncertainty over these parameters is not based on empirical evidence. Other parameters in the PSA are based on empirical variance-covariance estimates, as outlined below.

- **PFS and OS**: Uncertainty over the fitted survival curves is modelled using multivariate normal distributions with empirical variance-covariance matrices ('PSMs' sheet).
- **TTD**: The duration of treatment for sunitinib is sampled for the PSA in the same way as PFS and OS. However, probabilistic sampling of TTD for avelumab and axitinib is not propagated to the cost-effectiveness results: TTD parameters for avelumab and axitinib (ToT!H33-M35 and ToT!V33-AA35 respectively) are linked to the deterministic values on the PSMs sheet (column T) rather than to the probabilistic values (column Y).
- **Utilities**: Probabilistic values for the trial-based health state utilities are sampled using a multivariate normal distribution for the regression coefficients, with an empirical variance-covariance matrix. But these sampled values do not feed through to the cost-effectiveness results: the live values used in the model (in Utilities!K43-O45) link to the deterministic values (e.g. for the base case, Utilities!G29-G30 for the base case, rather than Utilities!G29-G30).

We made the following corrections to the PSA: gamma distributions for resource use and cost parameters; beta distributions for RDIs; and inclusion of probabilistic values for health state utilities and TTD for avelumab and axitinib.

Revised probabilistic results for the company's base case analysis are reported in Table 19. These results are based on 5,000 iterations, which is sufficient to show stable results: Figure 9 illustrates convergence for the comparison with sunitinib. The cost-effectiveness scatterplot in Figure 10 illustrates the extent of uncertainty for this comparison.

Table 19 EAG-corrected PSA company's base case (favourable-risk population)

Treatment	Total			Incremental			ICER [a]
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	(£/QALY)
Versus sunitinib							
Sunitinib	£93,316	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib							
Tivozanib	£138,208	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib							
Pazopanib	£168,332	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 77 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib

Figure 9 PSA convergence: company base case (avelumab + axitinib versus sunitinib)

Source: Produced by the EAG from an edited version of the company's model
INMB, Incremental Net Monetary Benefit at threshold of £30,000 per QALY gained

Figure 10 Cost-effectiveness plane (avelumab + axitinib versus sunitinib)

Source: Produced by the EAG from an edited version of the company's model
PSA, probabilistic sensitivity analysis; WTP willingness to pay (cost-effectiveness threshold)

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A full summary of EAG observations on key aspects of the company's economic model is presented in Appendix 6. Table 20 lists the additional analyses conducted by the EAG on the company's base case model. Results of these scenario analyses are reported in Table 21.

Table 20 Summary of EAG's exploratory analyses

Analysis	Company base case assumption	EAG scenario	Section in EAG report
OS avelumab with axitinib	Log-normal	• Exponential • Generalised gamma	4.2.4.1
OS sunitinib	Generalised gamma	• Weibull • Exponential	4.2.4.1
PFS avelumab with axitinib	Log-normal	• Log-logistic • Exponential • Generalised gamma	4.2.4.20
PFS sunitinib	Generalised gamma	• Log-logistic • Exponential	4.2.4.20
TTD avelumab	Generalised gamma	• Gompertz • Exponential	4.2.4.3
TTD axitinib	Generalised gamma	• Gompertz • Exponential	4.2.4.3
TTD sunitinib	Generalised gamma	• Log-logistic • Exponential	4.2.4.3
Utilities	Trial EQ-5D-5L data mapped to UK EQ-5D-3L values with the NICE recommended method (Model 1)	• Model 1 – ITT population • TA645 – ITT population	4.2.5.2
Drug acquisition costs	List prices from BNF and eMIT, with PAS price discounts for avelumab and pazopanib.	Updated eMIT prices for sunitinib and everolimus (Table 14)	4.2.6.2.1
Relative dose intensity	RDI adjustment to costs for avelumab, axitinib and sunitinib (JAVELIN Renal 101), tivozanib (TA512) and pazopanib (TA215). No RDI used for subsequent treatments.	• Exclude RDI for intervention and comparator • Include RDI for subsequent treatments (Table 15)	4.2.6.2.3

Analysis	Company base case assumption	EAG scenario	Section in EAG report
Subsequent treatment mix	JAVELIN Renal 101 trial data.	• TA645 • 100% nivolumab or cabozantinib • UK ROC study	4.2.6.2.5

Source: Produced by the EAG
RDI, relative dose intensity.

Table 21 Results of EAG scenarios on company base case (favourable-risk population, deterministic analysis)

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
Company base case	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS avelumab with axitinib: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS avelumab with axitinib: generalised gamma	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: Weibull	Sunitinib	£92,762	[redacted]	[redacted]
	Pazopanib	£164,842	[redacted]	[redacted]
	Tivozanib	£135,744	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: exponential	Sunitinib	£94,576	[redacted]	[redacted]
	Pazopanib	£166,665	[redacted]	[redacted]
	Tivozanib	£137,565	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: log-logistic	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: generalised gamma	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: log-logistic	Sunitinib	£92,342	[redacted]	[redacted]
	Pazopanib	£175,281	[redacted]	[redacted]
	Tivozanib	£141,977	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: exponential	Sunitinib	£93,241	[redacted]	[redacted]
	Pazopanib	£163,826	[redacted]	[redacted]
	Tivozanib	£135,317	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: Gompertz	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: Gompertz	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: exponential	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
TTD sunitinib: log-logistic	Sunitinib	£93,334	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD sunitinib: exponential	Sunitinib	£93,163	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: Model 1 – ITT population	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: TA645 – ITT population	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	[redacted]
Drug acquisition costs: updated eMIT prices for sunitinib and everolimus	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Exclude RDI for intervention and comparator	Sunitinib	£94,137	[redacted]	[redacted]
	Pazopanib	£177,713	[redacted]	[redacted]
	Tivozanib	£139,192	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Include RDI for subsequent treatment	Sunitinib	£89,012	[redacted]	[redacted]
	Pazopanib	£161,102	[redacted]	[redacted]
	Tivozanib	£132,000	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: TA645	Sunitinib	£69,013	[redacted]	[redacted]
	Pazopanib	£141,104	[redacted]	[redacted]
	Tivozanib	£112,022	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
	Sunitinib	£78,697	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
Subsequent treatment mix: 100% nivolumab or cabozantinib	Pazopanib	£150,788	[redacted]	[redacted]
	Tivozanib	£121,686	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: UK ROC study	Sunitinib	£88,078	[redacted]	[redacted]
	Pazopanib	£160,169	[redacted]	[redacted]
	Tivozanib	£131,067	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Source: Produced by the EAG from the company's model
Ave + axi, avelumab with axitinib; RDI, relative dose intensity; UK ROC study, UK renal oncology collaborative study.
[a] Pairwise ICERs for avelumab with axitinib relative to each comparator. We note that pazopanib and tivozanib are dominated by sunitinib in this analysis, as they have a higher cost and by assumption provide the same QALY gain.

6.2 EAG's preferred assumptions

We have identified a sole key aspect of the company base case with which we disagree. Our preferred model assumption is to use the updated eMIT prices for sunitinib and everolimus as presented in Table 14. The EAG preferred base case results, compared with the company base case results, are provided in Table 22 below. When implementing the EAG assumption, the ICER increases by [redacted] per QALY for avelumab with axitinib versus sunitinib. Probabilistic results for the EAG preferred analysis are shown in Table 23.

Table 22 Comparison of company base case and EAG base case results (favourable-risk population, deterministic analysis)

Base case	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
Company base case	Sunitinib	£93,185	[redacted]	[redacted]
	Pazopanib	£165,275	[redacted]	[redacted]
	Tivozanib	£136,173	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
EAG preferred base case	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	

Source: reproduced using company economic model and EAG base case model.
Ave + axi, avelumab with axitinib; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

[a] Pairwise ICERs for avelumab with axitinib relative to each comparator. We note that pazopanib and tivozanib are dominated by sunitinib in this analysis, as they have a higher cost and by assumption provide the same QALY gain.

Table 23 EAG preferred analysis (favourable-risk population, probabilistic analysis)

Treatment	Total			Incremental			ICER [a]
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	(£/QALY)
Versus sunitinib							
Sunitinib	£89,737	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus tivozanib							
Tivozanib	£137,688	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Versus pazopanib							
Pazopanib	£167,817	[redacted]	[redacted]				[redacted]
Ave + axi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: Reproduced from CS Table 77 of the clarification response document.
Ave + axi, avelumab with axitinib; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality adjusted life year.
[a] Pairwise ICERs for avelumab with axitinib relative to comparator. We do not report fully incremental ICERs because tivozanib and pazopanib are dominated by sunitinib

6.3 Scenario analysis on the EAG's preferred assumptions

We repeated the same scenarios performed on the company base case on the EAG preferred base case. Results are provided in Table 24 below.

Table 24 Results of scenario analyses with the EAG's preferred assumptions (favourable-risk population, deterministic analysis)

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
EAG's preferred base case	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS avelumab with axitinib: exponential	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	[redacted]
OS avelumab with axitinib: generalised gamma	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: Weibull	Sunitinib	£89,072	[redacted]	[redacted]
	Pazopanib	£164,361	[redacted]	[redacted]
	Tivozanib	135,263	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
OS sunitinib: exponential	Sunitinib	£90,886	[redacted]	[redacted]
	Pazopanib	£166,184	[redacted]	[redacted]
	Tivozanib	£137,084	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: log-logistic	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: exponential	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS avelumab with axitinib: generalised gamma	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: log-logistic	Sunitinib	£88,657	[redacted]	[redacted]
	Pazopanib	£174,804	[redacted]	[redacted]
	Tivozanib	£141,500	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
PFS sunitinib: exponential	Sunitinib	£89,560	[redacted]	[redacted]
	Pazopanib	£163,345	[redacted]	[redacted]
	Tivozanib	£134,836	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: Gompertz	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD avelumab: exponential	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: Gompertz	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD axitinib: exponential	Sunitinib	£89,495	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD sunitinib: log-logistic	Sunitinib	£89,533	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
TTD sunitinib: exponential	Sunitinib	£89,489	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: Model 2 – favourable-risk population	Sunitinib	£89,495	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: Model 1 – ITT population	Sunitinib	£89,494	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Utilities: TA645 – ITT population	Sunitinib	£89,494	[redacted]	[redacted]
	Pazopanib	£164,794	[redacted]	[redacted]
	Tivozanib	£135,692	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Exclude RDI for intervention and comparator	Sunitinib	£89,738	[redacted]	[redacted]
	Pazopanib	£177,232	[redacted]	[redacted]
	Tivozanib	£138,711	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
RDI: Include RDI for subsequent treatment	Sunitinib	£85,391	[redacted]	[redacted]
	Pazopanib	£160,691	[redacted]	[redacted]
	Tivozanib	£131,589	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: TA645	Sunitinib	£65,530	[redacted]	[redacted]
	Pazopanib	£140,830	[redacted]	[redacted]
	Tivozanib	£111,728	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: 100% nivolumab or cabozantinib	Sunitinib	£75,488	[redacted]	[redacted]
	Pazopanib	£150,788	[redacted]	[redacted]
	Tivozanib	£121,686	[redacted]	[redacted]
	Ave + axi	[redacted]	[redacted]	
Subsequent treatment mix: UK ROC study	Sunitinib	£84,766	[redacted]	[redacted]
	Pazopanib	£160,066	[redacted]	[redacted]
	Tivozanib	£130,964	[redacted]	[redacted]

Scenario	Treatment	Total cost	Total QALYs	ICER (£/QALY)[a]
	Ave + axi	[redacted]	[redacted]	

Source: Produced by the EAG from the company's model
Ave + axi, avelumab with axitinib; RDI, relative dose intensity; UK ROC study, UK renal oncology collaborative study.
[a] Pairwise ICERs for Avelumab with axitinib relative to each comparator. Pazopanib and tivozanib are dominated by sunitinib in all scenarios, as they have a higher cost and by assumption provide the same QALY gain.

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of avelumab with axitinib compared to sunitinib, pazopanib, and tivozanib for patients with aRCC. The main focus of the company submission, and therefore this report, is on the favourable-risk population. Information on the intermediate/poor-risk and ITT populations can be found in Appendix 5. For all analyses, pazopanib and tivozanib are assumed to be clinically equivalent to sunitinib, which reflects conclusions in TA645 regarding pazopanib although TA512 had concluded that tivozanib was 'at best' similar to sunitinib or pazopanib. At current prices tivozanib and pazopanib are dominated by sunitinib.

The EAG considers the structure of the model to be reasonable, appropriate, and consistent with previous cost-effectiveness models for aRCC. The company made some minor changes to the model in response to clarification questions. The company's revised base case shows a deterministic ICER of [redacted] per QALY for avelumab with axitinib versus sunitinib, including a PAS discount for avelumab of [redacted]. The mean probabilistic ICER for this base case is [redacted] per QALY, considerably higher than the deterministic equivalent due to higher estimated life years gained in the sunitinib arm. The company noted that "some probabilistic draws of the generalised gamma model for the sunitinib arm (used to model OS) result in unrealistic extrapolations" (CS B.3.9.1). The EAG considers that there were errors in the company's PSA and made some corrections (see 5.3.4). The EAG-corrected mean probabilistic ICER for the company's base case comparison with sunitinib is [redacted] per QALY, a little higher than the company's estimate due to the use of gamma (rather than normal) distributions for resource use and cost parameters in the PSA.

The EAG noted that prices for sunitinib and everolimus used in the company's model are out of date, and we used the updated eMIT prices in the EAG preferred base case (Table 14). Incorporating this change, the deterministic EAG preferred ICER increases to [redacted] per QALY for avelumab with axitinib versus sunitinib, or [redacted] per QALY in the probabilistic analysis. The scenarios with the most influential impact on the model results are the choice

of OS curve for both the intervention and comparator, excluding relative dose intensity, and changing the source of utilities.

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8 APPENDICES

Appendix 1 EAG appraisal of systematic review methods for RCT evidence

Table 25 EAG appraisal of systematic review methods for RCT evidence

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	A PICOS for the broad SLR to support all Health Technology Assessment (HTA) applications is in CS Appendix D Table 26 and a PICOS appropriately matched to the NICE scope is in CS Appendix D Table 27.
Were appropriate sources of literature searched?	Yes	Core healthcare databases (MEDLINE and MEDLINE In-Process, Embase, Cochrane CDSR and CENTRAL, DARE and the HTA Database), four main urology and cancer conferences, and the bibliographies of relevant systematic reviews were searched (CS Appendix D.2).
What time period did the searches span and was this appropriate?	Yes	Searches for the original SLR were conducted from database inception, and the latest update searches were carried out on 4 June 2024. There were no gaps in coverage between all update searches (CS Appendix D.2). The conferences were searched from 2016 to 2024 (CS Appendix D.2.1).
Were appropriate search terms used and combined correctly?	Yes	Subject headings and free text terms were used for kidney cancer and advanced disease stage, for all the interventions in the NICE scope, and for RCT study design (CS Appendix D.1.1).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Eligibility criteria specified according to the PICOS are reported in CS Appendix D Table 26. A separate PICOS that matches the NICE final scope is reported in CS Appendix D Table 27.
Were study selection criteria applied by two or more reviewers independently?	Yes	All screening was performed by two independent reviewers and any uncertainty was checked by a third reviewer (CS Appendix D.3).
Was data extraction performed by two or more reviewers independently?	Yes	The number of reviewers is not reported, but more than two reviewers is implied because the CS states that a senior reviewer checked the extracted data against the original source article (CS Appendix D.4).
Was a risk of bias assessment or a quality assessment of the included studies	Yes	The JAVELIN Renal 101 trial was assessed using the NICE RCT checklist in the STA manual (CS Appendix D.5.2). Risk of bias assessment tools differed between SLR updates, the RCTs included in

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
undertaken? If so, which tool was used?		the ITC were assessed using the NICE checklist and the Cochrane RoB 2.0 checklist (clarification question A9).
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Critical appraisal was conducted in parallel to the data extraction – all extracted data including quality checks were verified and checked by another independent reviewer (clarification question A10).
Is sufficient detail on the individual studies presented?	Mostly	All relevant study documents (CSR, protocol, SAP) and publications were provided for the pivotal JAVELIN Renal 101 trial. It is unclear whether the PRISMA flow diagram for the RCT SLR (CS Appendix D Figure 1) screening information is aligned with the PICOS in Table 26 or the PICOS that is aligned with the NICE scope in Table 27, and it is unclear how the middle column relates to each update search results. RCTs included in the ITC, were not summarised in sufficient detail in the main CS, however this was addressed by some tabulation of baseline characteristics in response to clarification question A9.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Mostly	An ITC was conducted for the intermediate-/poor-risk populations for overall survival and progression free survival. Details of the methods in the CS were limited, e.g. there was no critical appraisal of the included RCTs and no assessment of heterogeneity, but this was later provided in clarification question A.9. The ITC is discussed in sections 3.3 and 3.4

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CSR, clinical study report; DARE, Database of Abstracts of Reviews of Effects; ITC, indirect treatment comparison; NMA, network meta-analysis; PICOS, population intervention comparator outcomes study design framework; PRISMA, Preferred Reporting Items for Systematic Reviews; RCT, randomised controlled trial; RoB, risk of bias; SAP, statistical analysis plan; SLR, systematic literature review.

Appendix 2 EAG appraisal of systematic review methods for RWE evidence

Table 26 EAG appraisal of systematic review methods for RWE evidence

Systematic review components and processes	EAR response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	Comparators were not searched for nor eligible for inclusion. The review question is set up to identify supportive evidence for avelumab plus axitinib, not further comparative evidence. CS Appendix D.6.
Were appropriate sources of literature searched?	Yes	Core healthcare databases of MEDLINE, MEDLINE In-Process, Embase and Cochrane for CDSR and CENTRAL, and the bibliographies of relevant systematic reviews were searched. A broader range of conferences, than for the RCT SLR, was also searched. CS Appendix D.6.3.1.
What time period did the searches span and was this appropriate?	Yes	Databases and conferences were searched from 2019 to 29 July 2024. The start date is appropriate to the first approval date for the avelumab with axitinib combination (FDA, May 2019; EMA, May 2019; available via EAMS August 2019; EC, October 2019). The searches are only three months old. CS Appendix D.6.3.1.
Were appropriate search terms used and combined correctly?	Yes	The search included the relevant disease terms but did not search on disease stage, so the search is broader than for the RCT SLR. The RWE terms were comprehensive (CS Appendix D.6.3.2).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes. Partially.	Eligibility criteria are reported in CS Appendix D Table 34. The criteria are relevant to the company's purpose for the SLR, but it is only partially relevant to the decision problem because it is focusing on the intervention only and does not seek to identify real-world evidence for the comparator treatments.
Were study selection criteria applied by two or more reviewers independently?	Yes	Two reviewers worked independently to review all abstracts and full-text articles identified by the search strategy, and a third reviewer arbitrated any discrepancies (CS Appendix D.6.3.4).

Systematic review components and processes	EAR response (Yes, No, Unclear)	EAG comments
Was data extraction performed by two or more reviewers independently?	Yes	A second reviewer verified the extracted data against the original source paper (CS Appendix D.6.3.4). Therefore, data extraction was not performed independently, but the process is sufficient.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	Included studies (UK only) were appraised using the ROBINS-I tool (CS Appendix D.6.4.3 and Table 36). Summary results and overall risk of bias judgements were made, but no justifications or details are reported for any of the judgements.
Was a risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	Critical appraisal was conducted in parallel to the data extraction – all extracted data including quality checks were verified and checked by another independent reviewer (clarification question A10).
Is sufficient detail on the individual studies presented?	Yes	The relevant study reports and publications were provided with the submission. An RWE SLR report was provided with the clarification response.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not carried out	The evidence that was identified was not suitable for statistical synthesis. A narrative summary was provided in CS section B.2.8.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; EAMS, Early Access to Medicines Scheme; EC, European Commission; EMA, European Medicines Agency; FDA, Food and Drug Administration (USA); ITC, indirect treatment comparison; NMA, network meta-analysis; PICOS, population intervention comparator outcomes study design framework; RCT, randomised controlled trial; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions; RWE, real-world evidence; SLR, systematic literature review.

Appendix 3 Risk of bias assessment for JAVELIN Renal 101

Table 27 Risk of bias assessment for JAVELIN Renal 101

Question	Company assessment	EAG comment
Was the randomisation method adequate?	Yes. Patients were centrally assigned to randomised in a 1:1 ratio to avelumab with axitinib or sunitinib treatment, via an interactive response technology system. Randomisation was stratified by ECOG performance status and region. However, subgroups were not stratified by baseline characteristics and there were minor differences between the subgroups, although baseline characteristics were generally balanced between the treatment arms with the risk subgroups.	Agree. **Low risk of bias.**
Was the allocation adequately concealed?	Due to the different routes of administration, concealment of treatment allocation was not possible. For PFS, BICR was used to minimise bias (see below).	The company comments refer to blinding. The method of allocation using an interactive response technology system usually indicates that the allocation was concealed. **Low risk of bias.**
Were the groups similar at the outset of the study in terms of prognostic factors?	In patients irrespective of PD-L1 expression as well as in patients with PD-L1 positive tumours, similar distributions of ECOG performance status, MSKCC and IMDC (Heng) prognostic criteria at baseline were observed in both treatment arms. Baseline characteristics were balanced between the treatment arms within the risk subgroups, with the exception of the sunitinib arm containing a greater proportion of male patients ([redacted]%) vs the avelumab with axitinib arm ([redacted]%) in the favourable-risk group.	Agree. **Low risk of bias** for the overall trial population (ITT analysis). Clinical expert advice to the EAG was that sex is not a prognostic factor for aRCC so the proportion of male and female participants is not a concern.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Although JAVELIN Renal 101 was an open-label study, BICR was used to minimise bias that could be introduced into the assessment by the investigator, based on the knowledge of treatment assignment at randomisation. To mitigate the potential for bias in determining disease progression, expedited BICR	As an open-label study the investigators and participants were not blind to treatment allocation. BICR assessment for disease progression was not performed after the second interim analysis.

Question	Company assessment	EAG comment
	review was performed for investigator-assessed disease progression. All radiographic images were collected and objectively verified by an independent third-party core imaging laboratory. All patients' files and radiologic images must be available for source verification and peer review.	Therefore, the results reported in the final analysis for this submission include investigator-assessed disease progression and so may be at risk of bias. It is not possible for the EAG to verify consistency of BICR PFS assessments with the investigator PFS assessments by viewing the results on the same plot as the company do not believe it is appropriate to do so (clarification response A1) Other subjective outcomes are also at risk of bias. **Moderate risk of bias.**
Were there any unexpected imbalances in drop-outs between groups?	No. Patients discontinued avelumab (94.6%), axitinib (93.9%), and sunitinib (97.7%) in comparable proportions.	Agree. (See CS Table 11). **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All primary and secondary endpoints described in the protocol are reported in the clinical study report.	Agree with company assessment of the protocol and the CSR. The CS states that time to deterioration in FKSI-DRS was assessed (CS Table 6 and 7) however clarification response A2 confirms that time to deterioration in FKSI-DRS was only assessed and presented at the first interim analysis and data was not available for the final analysis. FKSI-DRS scores by visit are reported in the final

Question	Company assessment	EAG comment
		analysis CSR. **Low risk of bias**.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed using the full analysis set, defined as all randomised patients. Unless otherwise specified, all data were evaluated as observed, and no imputation method for missing values was used.	Agree. Additionally, the favourable- and intermediate-/poor-risk subgroup analyses, relevant to this appraisal, included all randomised patients within the per protocol pre-specified subgroups. **Low risk of bias.**
Was there good quality assurance for this trial?	Yes. The trial was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki Council and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, applicable ISO 14155 guidelines, medical device guidelines, and other applicable laws and regulations, including privacy laws. A quality assurance audit was conducted	Does not affect risk of bias. No EAG comment.

Source: Reproduced from CS Table 12, with added EAG comments.
Abbreviations: BICR, blinded independent central review; CIOMS, Council for International Organization of Medical Sciences; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms (subscale of FKSI-19); GCP, good clinical practice; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMDC, International Metastatic RCC Database Consortium; ISO, International Organization for Standardization; ITT, intention-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death ligand 1; PFS, progression free survival.

Appendix 4 Trials included in the company NMA

Table 28 Trials included in the company NMA, their use in previous NICE appraisals and identified risk of bias.

Trial name (trial author and year)	Comparison	In NMAs for previous NICE appraisals	Domain level risk of bias concerns[a] reported in or inferred from previous appraisals
CABOSUN (Choueiri 2018)	Cabozantinib vs Sunitinib	TA645 TA858 TA964	High risk of selection bias due to dynamic allocation of treatment[57] High risk of performance and detection bias due to lack of blinding[25 71] partly mitigated by use of BICR assessments for PFS and ORR outcomes.[71] Risk of bias due to missing outcome data reported as unclear[57] with methods used to account for missing data judged either adequate[25] or inadequate[57].
CheckMate 214 (Motzer 2018)	Nivolumab + ipilimumab vs Sunitinib	TA858 TA964	High risk of performance bias due to lack of blinding for subjective outcomes[57 71] Unclear risk of attrition bias[57].
JAVELIN Renal 101 (Motzer 2019)	Avelumab + axitinib vs Sunitinib	TA645 TA964	High risk of performance[57] and detection bias due to lack of blinding[25] Some concerns about inadequate methods to account for missing data[57].
CLEAR (Motzer 2021)	Lenvatinib + pembrolizumab vs Sunitinib	TA858 TA964	High risk of performance bias due to lack of blinding[71] Unclear[57] risk of attrition bias due to very high differential attrition with unclear methods to account for missing data. Unclear reporting bias due to some trial registry outcomes not being reported in published papers.[57]
CheckMate 9ER (Choueiri 2021)	Nivolumab + cabozantinib vs Sunitinib	TA964	High risk of performance and detection bias due to lack of blinding[57] Unclear[57] risk of attrition bias due to very high differential attrition with unclear methods to account for missing data.

Source: EAG table compiled from information in the EAG reports from previous NICE appraisals
BICR, blinded independent central review; ORR, objective response rate; PFS, progression free survival.
[a] Only concerns of high or unclear risks of bias are reported here. Reports of low concerns of bias are not included in this table.

Appendix 5 EAG critique of economic analyses for intermediate-/poor-risk and ITT populations

CS Appendix O contains the model inputs and assumptions specific to the intermediate-/poor-risk and ITT subgroups. It also presents the model results for the ITT population while CS section B.3.10 shows the model results for the intermediate-/poor-risk subgroup. In their response to the clarification questions, the company updated their model. The revised model received as part of the clarification response (and referred here as 'the revised company model') includes changes to:

- Adverse event specific costs are applied rather than a single value for all adverse events, with costs updated to the 22/23 National Cost Collection.
- Blood test, CT scan, simple IV and complex IV costs have been updated from 21/22 to 22/23 National Cost Collection values.
- All poor risk subsequent therapies are considered (only affects the intermediate-/poor-risk population results)

The company's deterministic pairwise results for the intermediate-/poor-risk subgroup and the ITT population are shown in Table 29 and Table 30 below. Avelumab plus axitinib is dominated or presents ICERs above £60,000 per QALY against all the comparators in both populations.

Table 29 Revised company results for the intermediate-/poor-risk subgroup – PAS price for avelumab

Technologies	Total			Incremental		ICER (£/QALY)	INMB (£30,000 / QALY)
	Costs	LYG	QALYs	Costs	QALYs		
Versus sunitinib							
Sunitinib	£72,283	5.05	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus tivozanib							
Tivozanib	£99,613	5.05	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus pazopanib							
Pazopanib	£117,935	5.05	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus cabozantinib							
Cabozantinib	£128,584	6.49	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus nivolumab plus ipilimumab							
Nivolumab plus ipilimumab	£117,515	7.67	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus lenvatinib with pembrolizumab							
Lenvatinib with pembrolizumab	£196,392	7.09	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus cabozantinib with nivolumab							
Cabozantinib with nivolumab	£151,668	8.17	[redacted]				
Avelumab + axitinib	[redacted]	5.81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from Table 13 of the clarification response document.
ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LYG, life-years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life-years

Table 30 Revised company results for the ITT population – PAS price for avelumab

Technologies	Total			Incremental		ICER (£/QALY)	INMB (£30,000 / QALY)
	Costs	LYG	QALYs	Costs	QALYs		
Versus sunitinib							
Sunitinib	[redacted]	5.59	[redacted]				
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus tivozanib							
Tivozanib	[redacted]	5.59	[redacted]				
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Versus pazopanib							
Pazopanib	[redacted]	5.59	[redacted]				
Avelumab + axitinib	[redacted]	6.70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from Table 14 of the clarification response document.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life-years; NMB, net monetary benefit.

EAG best case scenario analysis for intermediate/poor-risk and ITT populations

The EAG has changed the model inputs and assumptions for these two subgroups in order to obtain the most optimistic results for avelumab with axitinib. See Table 31 for the results and Table 31 below for the model inputs and assumptions of the best-case scenarios. Please note that this is just an exploratory exercise to show how the model behaves for these populations and some of the inputs and assumptions might lack face validity and not be plausible. Also, we note that these results use the PAS price discount for avelumab and the agreed discount for pazopanib, but no confidential price discounts are applied for axitinib or for any comparator or subsequent.

We conclude that, even in the best-case scenario explored by the EAG, avelumab plus axitinib is not cost-effective at a WTP threshold of £30,000 per QALY, except in the following situations:

- **Poor-/intermediate-risk population**: avelumab with axitinib is dominant versus pembrolizumab + lenvatinib and cabozantinib + nivolumab. However, we note that some of the assumptions behind these results are not clinically valid. For example, the HRs for OS are assumed to be the same as for sunitinib, in which avelumab with axitinib has a greater survival than the comparators. If a lower or equal survival is assumed for avelumab with axitinib and these two comparators, the ICERs are higher than £30,000 per QALY.

- **ITT population**: avelumab with axitinib has ICERs lower than pairwise £30,000 per QALY versus tivozanib and pazopanib. This is driven by the change in the RDIs as shown in Table 31, which might not be clinically valid. The RDIs for avelumab with axitinib are much lower than in the base case (around 60%) and also much lower than the RDIs for tivozanib and pazopanib (around 90%). This assumption seems counter-intuitive, and it is not supported by the available evidence. By changing this, the ICER for avelumab with axitinib versus tivozanib and pazopanib is above £30,000 per QALY.

Based on the above findings, we have not conducted a detailed critique of the model inputs and assumptions for the intermediate-/poor-risk and ITT subgroups.

Table 31 EAG exploratory best-case scenario results

Comparator	Pairwise ICERs (£/QALY)	
	Intermediate-/poor-risk	ITT population
Sunitinib	[redacted]	[redacted]
Tivozanib	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]
Cabozantinib	[redacted]	-
Nivolumab + ipilimumab	[redacted]	-
Pembrolizumab + Lenvatinib	[redacted]	-
Cabozantinib + nivolumab	[redacted]	-

Source: Produced by the EAG from the company's model
CS, company submission; HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; RDI, relative dose intensity; ToT, time on treatment.

Table 32 EAG exploratory best-case scenarios parameters and assumptions

Model feature		Intermediate-/poor-risk	ITT population
Comparator treatments and dosing details		CS Appendix O Table 49	CS Appendix O Table 49
Baseline characteristics		CS Appendix O Table 50	CS Appendix O Table 51
OS curves	Avelumab + axitinib	Log-normal	Log-normal
	Sunitinib/ tivozanib/ pazopanib	Weibull	Weibull
OS HRs	Cabozantinib	0.88	-
	Nivolumab + ipilimumab	0.88	-
	Pembrolizumab + Lenvatinib	0.88	-
	Cabozantinib + nivolumab	0.88	-
PFS curves	Avelumab + axitinib	Gompertz	Gompertz
	Sunitinib/ tivozanib/ pazopanib	Exponential	Exponential
PFS HRs	Cabozantinib	0.64	-
	Nivolumab + ipilimumab	[redacted]	-
	Pembrolizumab + Lenvatinib	[redacted]	-
	Cabozantinib + nivolumab	[redacted]	-
ToT curves	Avelumab	Exponential	Exponential
	Axitinib	Exponential	Exponential
	Sunitinib/tivozanib/pazopanib	Log-logistic	Log-logistic
	Cabozantinib	Log-logistic	-
HRQoL	Progression-free	0.80 (TA417)	0.80 (TA417)
	Progressed disease	0.76 (TA417)	0.76 (TA417)

Model feature		Intermediate-/poor-risk	ITT population
RDIs	Avelumab	94%	62.9%
	Axitinib	94%	62.9%
	Sunitinib	94%	94%
	Tivozanib	94%	94%
	Pazopanib	94%	94%
	Cabozantinib	94%	-
	Nivolumab	94%	-
	Ipilimumab	94%	-
	Pembrolizumab	62.9%	-
	Lenvatinib	62.9%	-
Subsequent therapies		CS Appendix O Table 91	CS Appendix O Table 93

Source: Produced by the EAG
CS, company submission; HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; RDI, relative dose intensity; ToT, time on treatment.

Appendix 6 Summary of EAG conclusions on the company's model

Table 33 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG additional analysis
Key model features			
Model structure	Partitioned survival model	We agree	No change
Population	Untreated aRCC favourable-risk subgroup in base case. Results for poor / intermediate risk (CS B.3.10) and ITT population (Appendix O).	We agree. Results are less favourable for poor-intermediate risk and ITT groups. We check that this conclusion applies with all confidential drug price discounts.	EAG to report base case results for the poor-intermediate risk and ITT groups in the EAR confidential price addendum
Comparators	Sunitinib, pazopanib and tivozanib	We agree	No change
Perspective	NHS and PSS	We agree	No change
Time horizon	40 years	We agree	No change
Discounting	3.5% for costs and outcomes	We agree	No change
Model inputs			
Baseline characteristics	Based on favourable-risk subgroup in JAVELIN Renal 101 trial (mean age [redacted] years, [redacted] female)	We agree	No change
Clinical effectiveness			
OS avelumab with axitinib	Log-normal	AIC/BIC best fit: log-logistic. The EAG considers the choice of parametric curve for OS to be a key issue. See Key Issue 2.	No change to base case EAG scenarios: • Log-logistic, exponential, and generalised gamma
OS sunitinib	Generalised gamma	AIC/BIC best fit: Weibull. Pathways model: base case exponential, scenario Weibull.	No change to base case EAG scenarios:

Parameter	Company base case	EAG comment	EAG additional analysis
		The EAG considers the choice of parametric curve for OS to be a key issue. See Key Issue 2.	• Weibull and exponential
PFS avelumab with axitinib	Log-normal	AIC/BIC best fit: log-normal.	No change to base case EAG scenarios: • Log-logistic, exponential, and generalised gamma
PFS sunitinib	Generalised gamma	AIC/BIC best fit: log-normal and exponential. Pathways model: base case log-logistic, scenario Weibull.	No change to base case EAG scenarios: • Log-logistic and exponential
TTD avelumab	Generalised gamma	AIC/BIC best fit: Gompertz and exponential.	No change to base case EAG scenarios: • Gompertz and exponential
TTD axitinib	Generalised gamma	AIC/BIC best fit: Gompertz and exponential.	No change to base case EAG scenarios: • Gompertz and exponential
TTD sunitinib	Generalised gamma	AIC/BIC best fit: exponential. Pathways model: base case log-logistic, scenario generalised gamma.	No change to base case EAG scenarios: • Log-logistic and exponential

Parameter	Company base case	EAG comment	EAG additional analysis
Adverse event incidence	CS Table 56, based on treatment related grade ≥ 3 from the JAVELIN Renal 101 trial	We agree	No change
Utilities			
Health state utilities	Trial EQ-5D-5L data mapped to UK EQ-5D-3L values with the NICE recommended method.	We agree with the company's base case health state utilities (Model 1), and the scenario with treatment status (Model 2). Age-adjustment of utilities is appropriate.	No change to base case EAG scenarios (see Table 13): • Model 2 - favourable risk • Model 1 - ITT population • TA645 - ITT population
Adverse event disutilities	Not included, as disutility from AEs is reflected in trial EQ-5D data.	We agree. Accepted in TA645	No change
Severity modifier	Not applicable.	We agree	No change
Resource use and costs			
Drug acquisition costs	List prices from BNF and eMIT, with PAS price discounts for avelumab and pazopanib. Scenarios for potential price reductions for axitinib.	eMIT 2023-24 has lower prices for sunitinib and everolimus. Results with other all available discounts in confidential EAR addendum. We do not report alternative price scenarios for axitinib, as this is not usual practice.	EAG base case: Update eMIT prices for sunitinib and everolimus (Table 14) EAG addendum: include all available price discounts from the NICE Pricing Tracker form
Relative dose intensity	RDI adjustment to costs for avelumab, axitinib and sunitinib (JAVELIN Renal 101), tivozanib (TA512) and pazopanib (TA215). No RDI used for subsequent treatments.	We agree with the approach for the intervention and comparators, but note that RDI estimates for subsequent treatments in clinical trials are available (Table 15)	No change

Parameter	Company base case	EAG comment	EAG additional analysis
Administration costs	Delivery costs for IV drugs only: avelumab and nivolumab. No costs for administration of oral therapies.	TA645 included costs for oral drugs as well as IV. Costs for initiation and ongoing delivery of oral medications are available from RCC Pathway pilot model	No change
Subsequent treatment mix	JAVELIN Renal 101 trial data. Scenarios based on TA645[1]; assumption of 100% nivolumab or cabozantinib, and RWE from the UK ROC study (McGrane 2024)[5]	We agree with the base case and scenarios reported by the company. We McGrane et al. scenario may be more reflective of UK practice than the JAVELIN Renal 101 trial, although the sample size is limited (n=66 with favourable-risk disease treated IO/TKI combination at first line was low	No change to EAG base case EAG scenarios: • TA645 • 100% nivolumab or cabozantinib • UK ROC study
Other health state costs	Various (CS Tables 65 and 66)	We agree	No change
Adverse event costs	Updated in response to clarification question B.9	We agree	No change
End of life costs	Estimate from Round et al. (2015), uprated for inflation.[68 69]	We agree	No change

Source: produced by the EAG from information in the CS and model, and from various other sources
NHS, National Health Service; PAS, Patient Access Scheme; PD, progressed disease; PF, progression-free; PSS, personal social services; RDI, relative dose intensity.