MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib plus pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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Nigel Fleeman	Project lead and reviewed clinical effectiveness evidence, including study selection, data extraction, synthesis and interpretation
Rachel Houten	Reviewed cost effectiveness evidence, including study selection, data extraction, synthesis and interpretation; clinical effectiveness review support; development of the economic model
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Data sharing statement:

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

PLAIN ENGLISH SUMMARY

What was the problem?

Renal cell carcinoma is the most common type of kidney cancer. Several drug treatment options are available for NHS patients with advanced or metastatic disease, choice of treatment varies depending on a patient's risk of disease progression. A new drug combination, lenvatinib plus pembrolizumab, may soon become available to treat NHS patients. This review explored whether treatment with lenvatinib plus pembrolizumab offered value for money to the NHS.

What did we do?

We reviewed the effectiveness of treatment with lenvatinib plus pembrolizumab compared with other NHS treatment options. We also estimated the costs and benefits of treatment with lenvatinib plus pembrolizumab compared with current NHS treatments for patients with higher and lower risks of disease progression.

What did we find?

Compared with current NHS treatments, treatment with lenvatinib plus pembrolizumab may increase the time that people with a higher risk of worsening disease were alive. However, for patients with a lower risk of worsening disease, the available evidence is limited and only shows that treatment with lenvatinib plus pembrolizumab may prolong the time that patients have a stable level of disease.

For all patients, compared to all current NHS treatments, treatment with lenvatinib plus pembrolizumab is very expensive.

What does this mean?

Compared with current NHS treatments for untreated aRCC, using published (undiscounted) prices, treatment with lenvatinib plus pembrolizumab may not provide good value for money to the NHS.

ABSTRACT

Background

Renal cell carcinoma (RCC) is the most common type of kidney cancer, comprising approximately 85% of all renal malignancies. Patients with advanced RCC are the focus of this NICE Multiple Technology Appraisal (MTA). A patient's risk of disease progression is based on number of prognostic risk factors; patients are categorised as having intermediate/poor risk or favourable risk of disease progression.

Objectives

The objectives of this MTA were to appraise the clinical and cost effectiveness of lenvatinib plus pembrolizumab versus relevant comparators listed in the final scope issued by NICE.

Methods

The Assessment Group (AG) carried out clinical and economic systematic reviews (SRs) and assessed the clinical and cost effectiveness evidence submitted by Eisai (the manufacturer of lenvatinib) and Merck Sharp & Dohme (MSD) (the manufacturer of pembrolizumab). The AG carried out indirect comparisons. The AG also adapted the economic model submitted by MSD.

Results

The AG SR review identified one relevant randomised controlled trial (CLEAR trial). The CLEAR trial is a good quality, phase III, multi-centre, open-label trial that provided evidence for the efficacy and safety of lenvatinib plus pembrolizumab compared with sunitinib.

AG progression-free survival network meta-analysis (NMA) results for all three risk groups should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons due to within trial proportional hazard (PH) violations or uncertainty regarding the validity of the PH assumption. The AG overall survival NMA results for the intermediate/poor risk subgroup suggested that there was a numerical, but not a statistically significant, improvement in OS for patients treated with lenvatinib plus pembrolizumab compared with patients treated with cabozantinib or nivolumab plus ipilimumab. Due to within trial PH violations or uncertainty regarding the validity of the PH assumption, the AG OS NMA results for the favourable risk subgroup and the all-risk population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons.

AG cost effectiveness results focused on the intermediate/poor risk and favourable risk subgroups. The AG cost effectiveness results, generated using list prices for all drugs, showed that, for all comparisons, treatment with lenvatinib plus pembrolizumab costs more and generated fewer benefits than all other treatments available to NHS patients.

Conclusions

Good quality clinical effectiveness evidence for the comparison of lenvatinib plus pembrolizumab versus sunitinib is available from the CLEAR trial. For most of the AG Bayesian HR NMA comparisons, it is difficult to reach conclusions due to within trial PH violations or uncertainty regarding the validity of the PH assumption. However, the data (clinical effectiveness and cost effectiveness) used to populate the MSD/AG model are relevant to NHS clinical practice and can be used to inform NICE decision making. The AG cost effectiveness results, generated using list prices for all drugs, show that lenvatinib plus pembrolizumab is less cost effective than all other treatment options.

Study registration

PROSPERO registration number: CRD4202128587

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Keywords

renal cell carcinoma; systematic review; indirect treatment comparison; lenvatinib; pembrolizumab; economic evaluation; ICER; QALY

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse events
AEOSI	adverse event of special interest
AG	Assessment Group
aRCC	advanced renal cell carcinoma
ASCO	American Society of Clinical Oncology
ASGO-GU	American Society of Clinical Oncology Genitourinary
BIRC	Blinded Independent Review Committee
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost effectiveness analysis
CI	confidence interval
CrI	credible interval;
CS	company submission
CSR	clinical study report
ECCO	European Conference for Clinical Oncology
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D-3L	EuroQol-5 Dimensions-3 levels
ESMO	European Society for Medical Oncology
EU-CTR	European Union Clinical Trials Register
EuroQOL	European Quality of Life
FAS	full analysis set
FDA	US Food and Drug Administration
FE	fixed effects
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms
FP	fractional polynomial
HAS	Haute Autorité de Santé
HR	hazard ratio
HRQoL	health-related quality of life
HTAi	Health Technology Assessment International
IA3	third interim analysis (final data cut-off for PFS)
ICER	incremental cost effectiveness ratios
ICTRP	International Clinical Trials Registry Platform
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
INAHTA	International Health Technology Assessment
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat
K-M	Kaplan-Meier
KPS	Karnofsky performance status
LR*i*G	Liverpool Reviews and Implementation Group
MHRA	Medicines and Healthcare products Regulatory Agency
MKSCC	Memorial Sloan-Kettering Cancer Center
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PBAC	Pharmaceutical Benefits Advisory Committee
PD-1	programmed cell death protein 1

PD-L1	programmed death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PPS	post-progression survival
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life years
QLQ-C30	quality of life questionnaire
RCC	renal cell carcinoma
RCT	randomised controlled trial
SAE	serious adverse event
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
TA	technology appraisal
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TKI	tyrosine kinase inhibitor
TTD	time to treatment discontinuation
VEGFR	vascular endothelial growth factor receptor

SCIENTIFIC SUMMARY

Background

Renal cell carcinoma (RCC) is the most common type of kidney cancer, comprising approximately 85% of all renal malignancies. Patients with advanced RCC (aRCC) have Stage 3 (locally advanced) or Stage 4 (metastatic) disease and are the focus of this NICE Multiple Technology Appraisal (MTA). A patient's risk of disease progression is based on number of prognostic risk factors. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is used in NHS clinical practice to categorise patients into one of two groups, namely favourable risk or intermediate/poor risk.

The focus of this MTA is the clinical and cost effectiveness of lenvatinib plus pembrolizumab. In November 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) approved the use of lenvatinib plus pembrolizumab as a treatment for all patients with untreated aRCC.

Objectives

The comparators listed in the final scope issued by NICE differ depending on risk of disease progression. The objectives of this assessment were to appraise the clinical and cost effectiveness of lenvatinib plus pembrolizumab versus:

1. cabozantinib and nivolumab plus ipilimumab in the intermediate/poor risk subgroup
2. sunitinib, pazopanib and tivozanib in the favourable risk subgroup
3. sunitinib, pazopanib and tivozanib in the all-risk population.

Avelumab plus axitinib and nivolumab plus ipilimumab have been recommended by NICE as treatment options for patients with untreated aRCC in adults. These two treatments are only available via the Cancer Drugs Fund. Only treatment with nivolumab plus ipilimumab is subject to an ongoing CDF review. The AG has, therefore, included it as a comparator and a NICE recommendation is expected to be released on 24 March 2021.

Clinical and economic systematic review methods

The Assessment Group (AG) carried out a systematic review (SR) of clinical effectiveness evidence following the general principles outlined by the Centre for Reviews and Dissemination (CRD). The review was reported using the criteria recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Searches were conducted between 11 October 2021 and 22 November 2021 in accordance with the general principles recommended by the European network for Health Technology Assessment. The protocol is registered with PROSPERO (registration number: CRD42021285879). The AG only reviewed randomised controlled trials (RCTs) and full

economic analyses identified by the searches. However, the AG also considered the evidence provided by the manufacturers of lenvatinib (Eisai Ltd) and pembrolizumab (Merck Sharpe and Dohme [MSD]) provided in submissions to NICE; company submission reference lists were searched for relevant RCTs.

In line with the final scope issued by NICE, the outcomes considered by the AG were overall survival (OS), progression-free survival (PFS), objective tumour response rate (ORR), adverse events (AEs), health-related quality of life (HRQoL), incremental cost per life year (LY) gained and incremental cost per quality adjusted life year (QALY) gained.

Clinical effectiveness results

Direct clinical effectiveness evidence (CLEAR trial)

The AG SR included one RCT, the CLEAR trial. The CLEAR trial is a good quality, phase III, multi-centre, open-label RCT (with an ongoing extension phase) that provided evidence for the comparison of the efficacy of lenvatinib plus pembrolizumab versus sunitinib.

Results for all outcomes were assessed at the third interim analysis (August 2020, median OS follow-up=26.6 months), the final data cut-off for PFS. The companies also presented OS results from an updated OS analysis (March 2021, median OS follow-up 33 months).

CLEAR trial hazard ratio (HR) results showed statistically significant improvements in PFS and ORR for patients treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib for the intermediate/poor risk subgroup, the favourable risk subgroup and the all-risk population (IA3). The HR results from the updated OS analysis showed a statistically significant improvement for patients treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib for the intermediate/poor risk subgroup and the all-risk population; there were too few events in the favourable risk subgroup for robust OS conclusions to be drawn. Eisai carried out a treatment-switching analysis to test whether adjusting for the effect of subsequent treatments affected OS results. Results, only generated for the all-risk population, continued to show a statistically significant advantage for patients treated with lenvatinib plus pembrolizumab versus sunitinib.

Nearly all the patients in the CLEAR trial lenvatinib plus pembrolizumab and sunitinib arms experienced at least one all-grade adverse event (AE), with more Grade ≥3 AEs reported in the lenvatinib plus pembrolizumab arm than in the sunitinib arm. The proportion of patients who discontinued treatment due to AEs was approximately twice as high for patients in the lenvatinib plus pembrolizumab arm than for patients in the sunitinib arm.

Health-related quality of life (HRQoL) was measured using three tools, including the EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) questionnaire. When compared with treatment with sunitinib, treatment with lenvatinib plus pembrolizumab did not result in any clinically meaningful differences (as measured by pre-defined minimally important differences) in HRQoL using any of the three tools.

Indirect clinical effectiveness evidence

To compare the effectiveness of lenvatinib plus pembrolizumab versus relevant comparators other than sunitinib, the AG carried out Bayesian HR network meta-analyses (NMAs). A decision was taken not to undertake a flexible modelling approach for NMA which relaxes the PH assumption, such as fractional polynomial (FP) NMAs, as interpretation of the estimates provided by these complex modelling techniques can be difficult and results are often not intuitive. While deviance information criterion (DIC) statistics provide an approach to compare the fit of different models, they do not provide information about whether a model is a good fit to the data or whether the estimates generated by the model, including projections of results beyond the follow-up times of trials included in the NMA, are clinically plausible. Furthermore, flexible models which appear similar according to model fit (i.e., according DIC statistics) may generate very different long-term survival estimates.

The AG assessed the feasibility of conducting Bayesian HR NMAs for the three population risk groups (intermediate/poor risk subgroup, favourable risk subgroup and all-risk population), for all outcomes listed in the final scope issued by NICE. However, due to limited data availability, it was not possible to carry out NMAs for all outcomes for all three patient risk groups. Further, as networks were sparse, it was only possible to generate results using fixed effect NMAs.

AG PFS NMA results for the intermediate/poor risk subgroup, the favourable risk subgroup and the all-risk population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons due to within trial proportional hazard (PH) violations or uncertainty regarding the validity of the PH assumption.

AG OS NMA results for the intermediate/poor risk subgroup suggested that there was a numerical, but not a statistically significant, improvement in OS for patients treated with lenvatinib plus pembrolizumab compared with patients treated with cabozantinib or nivolumab plus ipilimumab. Due to within trial PH violations or uncertainty regarding the validity of the PH assumption, the AG OS NMA results for the favourable risk subgroup and the all-risk

population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons.

AG ORR NMA results for the intermediate/poor risk subgroup, suggested that treatment with lenvatinib plus pembrolizumab led to a statistically significant improvement in ORR versus nivolumab plus ipilimumab, but not to a statistically significant improvement in ORR for the comparison of lenvatinib plus pembrolizumab versus cabozantinib. It was not possible to generate results for the IMDC/MSKCC favourable risk subgroup due to data limitations. AG ORR NMA results for the all-risk population, suggest that treatment with lenvatinib plus pembrolizumab led to a statistically significantly improvement in ORR versus sunitinib and versus pazopanib.

AG Grade ≥3 AE NMA results for the intermediate/poor risk subgroup, suggested that treatment with lenvatinib plus pembrolizumab led to statistically significantly more Grade ≥3 AEs versus cabozantinib. It was not possible to generate results for the IMDC/MSKCC favourable risk subgroup. AG Grade ≥3 AE NMA results for the all-risk population suggested that treatment with lenvatinib led to statistically significantly more Grade ≥3 AEs versus sunitinib and versus pazopanib.

Economic systematic review results

The AG SR identified one relevant cost effectiveness study. This study compared the cost effectiveness of lenvatinib plus pembrolizumab versus sunitinib (and versus other treatments). However, the study was undertaken from the perspective of the US health care system, only generated results for the all-risk population and included comparators that are not recommended by NICE as treatment options for patients with aRCC. Therefore, the extent to which results were generalisable to the NHS was unclear.

Cost effectiveness analysis methods

The Eisai and MSD company submissions to NICE included partitioned survival models built in Microsoft Excel. The AG considered that results from both models could be used to inform decision making but that, in some instances, the companies could have made more appropriate assumptions and parameter choices. The AG did not develop a de novo economic model; instead, the AG modified the model provided by MSD (referred to as the MSD/AG model). Neither of the companies produced cost effectiveness results for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab (intermediate/poor risk subgroup), despite both models having the functionality for this comparison. Furthermore, Eisai did not generate any cost effectiveness results for the favourable risk subgroup.

The MSD/AG model was populated with OS, PFS and TTD data from the CLEAR trial (lenvatinib plus pembrolizumab versus sunitinib for favourable risk subgroup and the all-risk population). AG PFS and OS NMA results were used to estimate effectiveness for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab for the intermediate/poor risk population. NICE ACs have concluded that sunitinib and pazopanib are of equivalent effectiveness and that, at best, tivozanib may have a similar effect to sunitinib or pazopanib. These conclusions were based on all-risk population data; the AG has assumed that this assumption holds for the favourable risk population.

The most important changes made by the AG to the MSD model were different choices for estimating PFS, OS and time to treatment discontinuation (TTD) for the intervention and comparator treatments, and modelling two lines, rather than one line, of subsequent treatment.

Cost effectiveness analysis results

AG cost effectiveness results presented in this report were estimated using list prices. AG cost effectiveness results generated using confidential discounted prices are presented in a confidential appendix.

For the intermediate/poor risk subgroup, AG base case cost effectiveness results suggested that treatment with lenvatinib plus pembrolizumab generated more QALYs than cabozantinib and more QALYs than nivolumab plus ipilimumab, but at a greater overall cost than either of these two treatments. Using list prices, the incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab exceed £100,000.

For the favourable risk subgroup, AG base case cost effectiveness results suggested that treatment with sunitinib generated more QALYs than lenvatinib plus pembrolizumab at a lower overall cost, i.e., treatment with lenvatinib plus pembrolizumab was dominated by treatment with sunitinib (and, using the assumption of equivalent effectiveness, by pazopanib and tivozanib).

The AG carried out extensive one-way sensitivity analyses, scenario analyses and PSA. Results from these analyses demonstrate that AG base case cost effectiveness results are robust.

Clinical and cost effectiveness conclusions

Good quality clinical effectiveness evidence for the comparison of lenvatinib plus pembrolizumab versus sunitinib was available from the CLEAR trial. For most of the AG Bayesian HR NMA comparisons, it was difficult to reach conclusions due to within trial PH

violations or uncertainty regarding the validity of the PH assumption. However, the data (clinical effectiveness and cost effectiveness) used to populate the MSD/AG model are relevant to NHS clinical practice and can be used to inform NICE decision making. The all-risk population comprises patients with intermediate/poor risk and patients with favourable risk disease. The AG cost effectiveness analyses have focused on the two subgroups. For all comparisons, the ICERs per QALY gained estimated by the AG were over £100,000.

1 BACKGROUND

1.1 Description of the health problem

Renal cell carcinoma (RCC) is the most common type of kidney cancer, comprising approximately 85% of all renal malignancies.[1,2] Risk factors for RCC include smoking, obesity, hypertension and acquired cystic kidney disease.[1,3,4]

There are a number of RCC histological subtypes,[5] the most common being clear cell RCC, which accounts for between 70% and 90% of all cases of RCC.[1-4] Non-clear cell RCC is a heterogeneous group of kidney cancers with distinct histologies, diverse biologic behaviours and different clinical outcomes.[6,7]

Patients with RCC are often asymptomatic and >50% of cases are diagnosed incidentally.[3,4] At diagnosis, RCC can be categorised into four disease stages. Patients with Stage 1 and Stage 2 RCC are considered to have early-stage disease, and those with Stage 3 and Stage 4 RCC are considered to have advanced RCC (aRCC).[3,4,8] In Stage 1 and Stage 2 RCC, the tumour is confined to the kidney.[3,4,8] The difference between the two early stages is the size of the tumour. A diagnosis of Stage 3 (locally advanced) disease is made when the tumour is growing into a major vein or has spread to regional lymph nodes.[3,4,8] A diagnosis of Stage 4 (metastatic) disease is made when the tumour is growing into one of the adrenal glands (these are situated on top of the kidneys) or has spread to distant lymph nodes and/or other organs.[3,4,8]

Patients with Stage 3 or Stage 4 aRCC are the focus of this NICE Multiple Technology Appraisal (MTA).

1.2 Epidemiology

1.2.1 Incidence of disease

Between 2015 and 2017, there were 19,973 new cases of kidney cancer in the UK (England: 10,759; Wales: 631).[9] Worldwide, kidney cancer is twice as common in men than in women.[1] In the UK, between 2015 and 2017, there were 1.7 times more new cases in men than in women;[9] a quarter of cases were diagnosed in people aged 60 to 69 years, with nearly half of cases (49%) diagnosed in people aged ≥70 years.[9]

1.2.2 Incidence and death rates by stage of disease

In England, between 2013 and 2017, 43.0% of all cases of kidney cancer with a known stage at diagnosis were classified as being aRCC, i.e., Stage 3 or Stage 4 (Table 1). During this period, the 5-year relative survival rates by stage of disease were markedly lower for patients

with Stage 4 (metastatic) disease than for patients with the other stages of kidney cancer, including Stage 3 (locally advanced) RCC (Table 1).

Table 1 Number, proportion and 5-year survival of people diagnosed with kidney cancer by stage (England, 2013 to 2017)

Disease stage	Number diagnosed	Proportion with a known diagnosis	Proportion alive ≥5 years
Stage 1	17,708	48.0%	86.8%
Stage 2	3346	9.1%	76.6%
Stage 3	6829	18.5%	74.2%
Stage 4	9024	24.5%	12.4%
All	36,907*	100.0%	63.8%

* In addition, 7112 patients were diagnosed with kidney cancer with an unknown stage of disease (total=44,019 cases)
Source: Public Health England – National Cancer Registration and Analysis Service, Office for National Statistics[10]

1.2.3 Incidence and death rates by disease risk status

Two models commonly used to classify risk status are the Memorial Sloan Kettering Cancer Center (MSKCC) risk stratification model[11,12] and the International Metastatic RCC Database Consortium (IMDC) model.[13,14] As highlighted in the Eisai company submission (CS)[15] (p19):

> "The MSKCC system was originally the gold standard method for assessing risks associated with targeted treatment in metastatic RCC, and is still considered relevant by UK clinicians today to estimate patient prognosis. The IMDC system was developed to extend the MSKCC criteria to increase concordance, and is primarily applied in UK clinical practice."

Both models[11-14] calculate patient risk of progression based on number of specific prognostic risk factors. Common to both models[11-14] are the following risk factors: time from diagnosis to treatment, haemoglobin levels, calcium levels and Karnofsky performance status (KPS). The MSKCC model also includes lactate dehydrogenase concentration, and the IMDC model also considers absolute neutrophil count and platelet count.[11-14] Both models[11-14] classify risk as favourable (no adverse prognostic risk factors), intermediate risk (one or two adverse prognostic risk factors) or poor (three or more adverse prognostic risk factors). In a study to validate the IMDC, Heng et al 2013[14] reported that 83% of patients were classified into the same risk subgroup by both models.

The proportions of patients with metastatic RCC who belong to each risk subgroup in eight population-based studies[14,16-22] are presented in Table 2.

Table 2 Proportion of patients with metastatic RCC by risk subgroup in population studies

Study authors	Study type	Risk model n[a]	Favourable risk	Intermediate risk		Poor risk
Heng et al 2013[14]	International study validating IMDC, 2004-2010	IMDC n=849	18%	52%		30%
Gore et al 2015[19]	Global expanded access programme of sunitinib, 2005-2007	IMDC n=4065	24%	54%		22%
Kubackcova et al 2015[16]	Czech Republic population-based study, 2006-2013	IMDC[b] n=495	22%	62%		16%
Schwab et al 2018[21]	Germany single-centre study, 2006-2013	IMDC n=104	14%	63%		23%
Savard et al 2020[20]	International, population-based study, 2010-2013	IMDC n=1769	18%	58%		24%
				I1: 26%[c]	I2: 24%[c]	
de Groot et al 2016[17]	Netherlands population-based study, 2008-2010	MSKCC n=645 [n=210][d]	0	42% [69%][d]		58% [31%][d]
de Groot et al 2016[17]	Netherlands population-based study, 2011-2013	MSKCC n=233 [n=181][d]	58% [76%][d]			42% [24%][d]
Fiala et al 2020[18]	Czech Republic registry, 2006-2018	MSKCC n=2390	34%	61%		6%
				I1: 41%	I2: 21%	
Tamada et al 2018[22]	Consecutively treated patients in Japan	MSKCC n=225[e]	22%	56%		22%
				I1: 28%	I2: 28%	
Kubackcova et al 2015[16]	Czech Republic population-based study, 2006-2013	Modified MSKCC[b,f] n=495	12%	61%		27%

[a] n denotes number of participants with a defined risk subgroup
[b] Using the IMDC criteria, 54.1% of MSKCC poor risk patients were reclassified as intermediate risk and 20.2% of MSKCC intermediate risk patients were reclassified as favourable risk
[c] Number of risk factors not available for 146 (8%) patients classified as intermediate risk
[d] Numbers and proportions of patients in square brackets are those who fulfilled the SUTENT trial[23] criteria
[e] Excludes 9 patients for whom risk subgroup was not determined
[f] Modified model developed by Mekhail et al 2005[24] includes two additional prognostic factors (prior radiotherapy and sites of metastasis) and was found to increase the number of patients classified as favourable risk and poor risk compared to the original model[11,12]
I1=1 risk factor; I2=2 risk factors; IMDC= International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan Kettering Cancer Center

Overall survival (OS) estimates are reported by risk subgroup in six population-based studies[14,16-20] of patients with metastatic RCC who received sunitinib as a first-line treatment and are presented in Table 3. The more recently published studies[18,20,22] also considered prognosis based on whether patients with intermediate risk status had one or two prognostic factors.

Table 3 IOUs Overall survival by risk subgroup in population-based studies of patients with metastatic RCC (all patients received first-line sunitinib)

Study authors	Study type	Median OS, months (95% CI)			
		Risk model, n[a]	Favourable risk	Intermediate risk	Poor risk
Gore et al 2015[19]	International study validating IMDC, 2004-2010	IMDC n=4065	45.5[b]	18.9[b]	6.2[b]
Heng et al 2013[14]	Global expanded access programme of sunitinib, 2005-2007	IMDC n=849	43.2 (31.4 to 50.1)	22.5 (18.7 to 25.1)	7.8 (6.5 to 9.7)
Kubackcova et al 2015[16]	Czech Republic population-based study, 2006-2013	IMDC n=495	44.3 (31.6 to 56.9)	24.8 (19.8 to 29.8)	9.3 (5.1 to 13.5)
Savard et al 2020[20]	International, population-based study, 2010-2013	IMDC n=1769	52.1 (43.4 to 61.2)	31.5 (28.9 to 33.9)[c]	9.8 (8.3 to 11.4)
de Groot et al 2016[17]	Netherlands population-based study, 2008-2010	MSKCC n=210	NA	14.6 (11.5 to 16.0)	6.1 (4.9 to 7.7)
	Netherlands population-based study, 2011-2013	MSKCC n=181	16.6 (10.1 to NR)		6.5 (3.4 to 10.0)
Fiala et al 2020[18]	Czech Republic registry, 2006-2018	MSKCC n=2390	44.7 (40.9 to 50.5)	24.1 (21.9 to 26.0)[d]	9.5 (7.2 to 14.1)
Kubackcova et al 2015[16]	Czech Republic population-based study, 2006-2013	Modified MSKCC[e] n=495	39.5 (23.9 to 55.2)	28.5 (20.1 to 36.8)	10.6 (6.3 to 14.8)

[a] n denotes number of participants it was possible to classify risk for which may not be the same as the number of all-risk participants in the study
[b] Confidence intervals not presented
[c] OS for patients with one risk factor was 35.1 (95% CI: 31.7 to 39.6) months versus 21.9 (95: CI: 18.5 to 25.8) months for those with two risk factors (no statistical significance test reported)
[d] OS for patients with one risk factor was 28.2 (95% CI: 25.9 to 30.7) months versus 16.2 (95% CI: 14.5 to 20.2) months for those with two risk factors ($p < 0.001$)
[e] Modified model developed by Mekhail et al 2005[24] includes two additional prognostic factors (prior radiotherapy and sites of metastasis) and was found to increase the number of patients classified as favourable risk and poor risk compared to the original model[11,12]
CI=confidence interval; IMDC= International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan Kettering Cancer Center; NA=not applicable; NR=not reached; OS=overall survival

Some drugs are only recommended by NICE[25,26] for patients with IMDC intermediate or poor (intermediate/poor) risk. Only one of the population studies (Savard et al 2020[20]) listed in Table 3 reported OS for the combined IMDC intermediate/poor risk subgroup. The reported median OS for this subgroup was 23.2 (95% CI: 21.0 to 25.8) months. In the total (all-risk) population, median OS was 28.6 (95% CI: 25.9 to 31.0) months whereas median OS for the IMDC favourable risk population was 52.1 (95% CI: 43.4 to 61.2) months. Information on treatment options for patients in different IMDC risk subgroups is provided in Section 1.3.

1.3 Current service provision

1.3.1 Surgery

Surgery is usually possible, and is the preferred treatment, for patients with early RCC and patients with locally advanced RCC[27] and is usually curative. However, results from two studies[28,29] that have explored disease progression following surgery suggest that approximately 30% of patients who have received surgery subsequently develop metastatic RCC. Surgery is rarely a treatment option for patients with metastatic RCC.

1.3.2 NICE guidance for first-line drug treatment

Clinical advice to the Assessment Group (AG) is that in NHS clinical practice, patients with aRCC receive the treatments recommended in NICE guidance[25,26,30-33] (see Table 4) and that treatment decisions are made based on histological subtype, IMDC disease risk category, patient age and co-morbidities, patient fitness, disease aggressiveness/biology and patient preference.

Currently, the NICE recommended treatments are systemic vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine-kinase inhibitor (TKI) agents (sunitinib,[30] pazopanib,[31] tivozanib[32] and cabozantinib[25]). However, two drug combination treatments are currently available to patients via the Cancer Drugs Fund (CDF): avelumab plus axitinib[33] (a programmed-death ligand1 [PD-L1] checkpoint inhibitor in combination with a VEGFR-TKI) and nivolumab plus ipilimumab[26] (a programmed death cell protein 1 [PD-1] inhibitor and a cytotoxic T-lymphocyte antigen 4 [CTLA-4] checkpoint inhibitor). Treatment options which are now rarely used due to their associated toxicities[3] are cytokines (interferon alpha and high-dose interleukin-2).

Table 4 Previous NICE appraisals of first-line treatments for advanced RCC

NICE TA	Intervention(s)	NICE recommendation
Recommended for use as a first-line treatment		
TA169 (2009)[30]	Sunitinib	Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG PS of 0 or 1
TA215 (2011/2013)[31]	Pazopanib	Pazopanib is recommended as a first-line treatment option for people with aRCC who have not received prior cytokine therapy and have an ECOG PS of 0 or 1
TA512 (2018)[32]	Tivozanib	Tivozanib is recommended for treating aRCC in adults who have had no previous treatment, only if the company provides tivozanib with the discount stated in the patient access scheme agreement
TA542 (2018)[30]	Cabozantinib	Cabozantinib is recommended, within its marketing authorisation, for adults with untreated aRCC that is **intermediate/poor risk** as defined in the IMDC criteria. It is recommended only if the company provides cabozantinib according to the commercial arrangement
Recommended for use as a first-line treatment within the CDF		
TA581 (2019)[26]	Nivolumab plus ipilimumab	Nivolumab with ipilimumab is recommended for use within the CDF as an option for adults with untreated advanced RCC that is **intermediate/poor risk** as defined in the IMDC criteria. It is recommended only if the conditions in the managed access agreement for nivolumab with ipilimumab are followed
TA645 (2020)[33]	Avelumab plus axitinib	Avelumab with axitinib is recommended for use within the CDF as an option for untreated aRCC in adults. It is recommended only if the conditions in the managed access agreement for avelumab with axitinib are followed
Not recommended for use as a first-line treatment		
TA178 (2009)[34]*	Bevacizumab Sorafenib Temsirolimus	Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic RCC
TA650 (2020)[35]	Pembrolizumab plus axitinib	Pembrolizumab with axitinib is not recommended, within its marketing authorisation, for untreated aRCC in adults

*Also considered sorafenib and sunitinib as second-line treatments as part of this appraisal, neither treatment was recommended
aRCC=advanced renal cell carcinoma; CDF=Cancer Drugs Fund; ECOG PS=Eastern Cooperative Oncology Group performance status; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; RCC=renal cell carcinoma; TA=technology appraisal

1.3.3 European clinical guidelines for first-line drug treatment

Clinical practice guidelines published by the European Association of Urology[36] and the European Society for Medical Oncology[37] recommend three combination treatments for the all-risk population: pembrolizumab plus axitinib (not recommended by NICE[35]), nivolumab plus cabozantinib (not yet appraised by NICE; the planned Single Technology Appraisal [STA] was suspended[38]), and lenvatinib plus pembrolizumab (the focus of this MTA). Both sets of guidelines[36,37] also recommend nivolumab plus ipilimumab as an option for patients in the intermediate/poor risk subgroup (nivolumab plus ipilimumab is currently only recommended by NICE for use within the CDF for this subgroup[26]).

1.3.4 First-line drug treatments for the all-risk population

Three VEGFR-TKIs, sunitinib, pazopanib and tivozanib, are recommended by NICE[30-32] as treatment options for patients with untreated aRCC irrespective of risk status. Avelumab plus axitinib is also recommended as an option for untreated aRCC in adults, but only for use within the CDF.[33] Previous NICE Appraisal Committees[25,26,32,33] have concluded that sunitinib and pazopanib are of equivalent clinical effectiveness and that, "At best, tivozanib may have a similar effect to sunitinib or pazopanib."[32] Clinical advice to the AG is that generally, tivozanib is better tolerated than sunitinib or pazopanib and so now tends to be the preferred VEGFR-TKI monotherapy for the first-line treatment of aRCC.

1.3.5 First-line drug treatments for patients with intermediate/poor risk disease

In line with recommendations in NICE guidance,[25,39] clinical advice to the AG is that, in general, nivolumab plus ipilimumab is the preferred first-line treatment option for patients with intermediate/poor risk disease and that cabozantinib is the preferred treatment option for fitter patients in this subgroup who have rapidly progressing disease (approximately 20%). Clinical advice to the AG is also that patients unable to tolerate either of these treatments receive sunitinib, pazopanib or tivozanib.

1.3.6 First-line drug treatments for patients with favourable risk disease

Neither NICE guidance[26] nor European clinical guidelines[36,37] make specific recommendations for patients with favourable risk disease. The treatment options available in NHS clinical practice to patients with favourable risk disease are sunitinib, pazopanib or tivozanib and, via the CDF, avelumab plus axitinib.[33] Where available, clinical advice to the AG is that avelumab plus axitinib is the preferred first-line treatment option for patients with favourable risk disease who can tolerate this combination, and tivozanib is the favoured treatment option for patients who are only able to tolerate VEGFR-TKI monotherapy.

1.3.7 Subsequent lines of drug treatment

NICE has recommended five treatment options[25,26,30-32] for previously treated patients with aRCC (Table 5).

Table 5 NICE recommended treatments for previously treated aRCC

NICE TA	Drug(s)	Type of drug(s)	Specified previous treatments
TA333 (2015)[40]	Axitinib	VEGFR-TKIs	VEGFR-TKI or cytokine
TA417 (2016)[41]	Nivolumab	PD-1 inhibitor	None specified
TA432 (2017)[42]	Everolimus	mTOR inhibitor	VEGFR-TKI
TA463 (2017)[43]	Cabozantinib	VEGFR-TKIs	VEGFR-TKI
TA498 (2018)[44]*	Lenvatinib plus everolimus	multiple receptor TKI plus mTOR inhibitor	VEGFR-TKI

* Lenvatinib plus everolimus is only recommended for patients with ECOG PS 0 or 1
aRCC=advanced renal cell carcinoma; ECOG PS=Eastern Cooperative Oncology Group performance status; mTOR=mammalian target of rapamycin; PD-1=programmed cell death protein 1; VEGF=vascular endothelial growth factor receptor

All of these subsequent treatments are recommended for patients regardless of their risk status. Clinical advice to the AG is that cabozantinib and nivolumab monotherapy are the most commonly used second-line treatments; lenvatinib plus everolimus is not a treatment option for patients who have previously received lenvatinib.

1.4 Description of technology under assessment

The technology under assessment in this MTA is lenvatinib plus pembrolizumab. In November 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) granted UK marketing authorisation for the use of lenvatinib plus pembrolizumab for untreated aRCC.[45,46] Information about lenvatinib plus pembrolizumab is provided in Table 6.

As noted in the Eisai CS[15] (p18):

> "It has been proposed that combining an immune checkpoint inhibitor (pembrolizumab) with the simultaneous inhibition of angiogenesis and VEGF-mediated immune suppression (lenvatinib), i.e., co-inhibition of PD-1 and VEGF, may offer complimentary modulation of different aspects of tumour immunobiology and potentially improve survival in patients with aRCC."

Eisai also highlights that lenvatinib plus pembrolizumab may be a more convenient treatment for patients than the alternative combination therapies currently recommended by NICE[26,33] as lenvatinib can be taken with or without food and the capsules swallowed whole or ingested by dissolving the capsule(s) in water or apple juice (although using the dissolving route to administer the drugs is not a straightforward process), and pembrolizumab only requires a 30-minute infusion once every 3 or 6 weeks. In contrast, both cabozantinib[47] and axitinib[48] must be swallowed whole (and cabozantinib must be administered after a ≥2 hour fast[47]) and other checkpoint inhibitors[49,50] require longer infusions, for example, treatment with avelumab requires a 60-minute infusions every 2 weeks.[49]

Table 6 Summary of the technology

Feature	Lenvatinib	Pembrolizumab
Brand name	Kisplyx	Keytruda
Manufacturer	Eisai Ltd	Merck Sharp & Dohme (MSD)
Class of drug	Multiple receptor tyrosine kinase inhibitor	Monoclonal antibody
Mechanism of action	Inhibits the activity of VEGFR	Blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2
Dose information for treating aRCC	20mg (oral) once daily until disease progression or unacceptable toxicity	200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes Maximum duration of 2 years
List price per pack	30 capsules (4mg)=£1,437 30 capsules (10mg)=£1,437	100mg vial=£2,630 A single administration of 200mg=£5,260 A single administration of 400mg=£10,520
PAS	Simple discount PAS	Simple discount PAS

aRCC=advanced renal cell carcinoma; PAS=Patient Access Scheme; VEGFR=vascular endothelial growth factor receptor; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; PD-L2=programmed death-ligand 2
Source: Eisai CS,[15] Table 2; MSD CS,[51] Table 2

1.5 Systematic reviews of lenvatinib plus pembrolizumab for aRCC

A substantial number of systematic reviews that compare the clinical effectiveness of first-line treatments for aRCC have been published; however, the AG has only identified seven reviews[52-58] that include patients treated with lenvatinib plus pembrolizumab. The focus and results of these reviews are summarised in Sections 1.5.1 and 1.5.2 respectively, and further details are presented in Appendix 1 (Section 9.1), Table 77.

1.5.1 Focus of the systematic reviews of lenvatinib plus pembrolizumab

In six of the reviews,[52-56,58] the focus was on the efficacy and safety of treatment. In one review,[57] the focus was on safety only.

One review[55] compared lenvatinib plus pembrolizumab versus other combination therapies and versus sunitinib. Six other reviews[52-54,56-58] assessed the evidence for lenvatinib plus pembrolizumab and other combination therapies versus sunitinib; three reviews[53,54,58] only presented pooled results and two reviews[56,57] compared lenvatinib plus pembrolizumab versus other combination therapies by ranking the probability of maximal efficacy.

The therapies included in the seven reviews[52-58] were a combination of PD-1 and CTL-4 checkpoint inhibitors (nivolumab plus ipilimumab),[53,55-58] a PD-L1 checkpoint inhibitor in combination with an angiogenesis inhibitor (atezolizumab plus bevacizumab[53,54,56-58]), a PD-L1 checkpoint inhibitor in combination with a VEGFR-TKI (avelumab plus axitinib[52-54,56-58]) or a PD-1 checkpoint inhibitor in combination with a VEGFR-TKI (pembrolizumab plus axitinib[52-58] or nivolumab plus cabozantinib[52-58]). Three reviews[54,56,58] included subgroup analyses by risk subgroup and one review[52] only included favourable risk patients.

1.5.2 Results from the systematic reviews of lenvatinib plus pembrolizumab

All-risk population results

Five reviews[53-56,58] showed that combination therapies (including lenvatinib plus pembrolizumab) statistically significantly improved progression-free survival (PFS) and ORR versus sunitinib. Massari et al 2021[53] also showed that combination therapies statistically significant improved OS versus sunitinib; however, Mori et al 2021[54] showed that this finding was only applicable to PD-1 checkpoint inhibitors (including lenvatinib plus pembrolizumab) and was not applicable to PD-L1 checkpoint inhibitors.

Four reviews[53-55,58] showed that lenvatinib plus pembrolizumab statistically significantly improved OS versus sunitinib, and one review[56] showed that OS may favour lenvatinib plus pembrolizumab but the result was not statistically significant. In the two reviews[55,56] that ranked the probability of most effective treatment, lenvatinib plus pembrolizumab ranked highest for PFS and ORR in both reviews[55,56] and second highest for OS in both reviews,[55,56] whilst nivolumab plus cabozantinib ranked highest for OS in both reviews.[55,56]

Compared with other PD-1 checkpoint inhibitors,[54] lenvatinib plus pembrolizumab was less well tolerated; patients receiving lenvatinib plus pembrolizumab experienced the highest proportion of Grade ≥3 AEs[55-57] and treatment discontinuations due to AEs.[56,57] Treatment with lenvatinib plus pembrolizumab was also shown to have the highest likelihood of all-grade adrenal insufficiency and the highest likelihood of high-grade aspartate aminotransferase increase.[57]

Intermediate/poor risk subgroup results

Three reviews[54,56,58] compared PFS and OS for combination therapies versus sunitinib and reported statistically significant evidence that combination therapies improved efficacy. The two reviews[54,56] that also compared ORR for combination therapies versus sunitinib found statistically significant evidence that combination therapies improved this outcome.

Favourable risk subgroup results

Three reviews[52,54,58] identified statistically significant evidence that, compared to sunitinib, combination therapies improved PFS but not OS. A fourth review[56] identified statistically significant evidence that four out of six combination therapies studied (including lenvatinib plus pembrolizumab) improved PFS compared to sunitinib. Only two of the six combination therapies (nivolumab plus ipilimumab and pembrolizumab plus axitinib) resulted in statistically significantly improved OS versus sunitinib. The two reviews[54,56] that also compared ORR for combination therapies versus sunitinib found statistically significant evidence that combination

therapies improved this outcome (the exception being atezolizumab plus bevacizumab in the network meta-analysis [NMA][56]).

2 DEFINITION OF THE DECISION PROBLEM

2.1 Decision problem

The key elements of the decision problem for this appraisal, as defined in the final scope[27] issued by NICE are presented in Table 7. Further information is presented in Sections 2.1.1 to 2.1.3.

Table 7 The decision problem

Parameter	Final scope issued by NICE	Addressed by AG
Intervention	Lenvatinib plus pembrolizumab	As per scope
Patient population	Adults with untreated aRCC	Most patients considered in the AG analyses had clear cell aRCC The AG considered the following groups of patients: • intermediate/poor risk subgroup • favourable risk subgroup • all-risk population
Comparators	• Sunitinib • Pazopanib • Tivozanib • Cabozantinib (only for intermediate- or poor-risk disease as defined in IMDC criteria) • Nivolumab plus ipilimumab (only for intermediate- or poor-risk disease as defined in IMDC criteria) - subject to ongoing appraisal	Direct evidence is only available versus sunitinib (CLEAR trial) Some indirect evidence is available for all relevant comparators from Eisai, MSD and AG NMAs
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope for the comparison of lenvatinib plus pembrolizumab versus sunitinib. Some indirect evidence was available for some outcomes for some subgroups
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 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 should be considered from an NHS and PSS perspective The availability of any commercial arrangements for the interventions, comparators and subsequent treatments should be taken into account. The availability of any managed access arrangement for the intervention should be taken into account	As per scope
Other considerations	If the evidence allows the following subgroups should be considered: • People with aRCC that is intermediate/poor risk as defined in IMDC criteria Guidance will only be issued in accordance with the marketing authorisations	As per scope

AG=Assessment Group; aRCC=advanced renal cell carcinoma; IMDC=International Metastatic RCC Database Consortium; NHS=National Health Service; NICE=National Institute for Clinical and Care Excellence; PSS=Personal and Social Services

2.1.1 Patient population

In previous NICE appraisals of treatments for untreated aRCC,[26,33] NICE ACs noted that there was a lack of evidence to guide treatment decisions for patients with non-clear cell RCC. This is primarily due to non-clear cell RCC being (i) heterogeneous (up to 15 different subtypes are listed in the most recent World Health Organisation classification of RCC[6]) and (ii) less common[6,7] than clear cell RCC. The AG made no attempt to provide evidence separately for patients with clear cell and non-clear cell histologies.

As noted in Sections 1.3.2 to 1.3.6, decisions about the most appropriate first-line treatments for patients with aRCC are now typically made based on patient risk subgroup. Therefore, the AG conducted subgroup analyses for intermediate/poor risk and favourable risk subgroups.

Unless otherwise stated, risk subgroup within this report refers to IMDC model risk stratification subgroups.

2.1.2 Comparators

Four of the five comparators listed in the final scope[27] issued by NICE (sunitinib, pazopanib, tivozanib, and cabozantinib for patients with intermediate/poor risk aRCC) are all used in current NHS clinical practice. Nivolumab plus ipilimumab is also listed as a comparator; however, at the time of writing this AG report, nivolumab plus ipilimumab was subject to an ongoing CDF review[26] and was not available for routine use in the NHS. Following advice from the NICE technical team, the AG has included nivolumab plus ipilimumab as a relevant comparator.

2.1.3 Subgroup analyses

In line with the final scope[27] issued by NICE, the AG carried out clinical and cost effectiveness analyses of lenvatinib plus pembrolizumab for the subgroup of patients with intermediate/poor risk disease. Whilst it is stated in the AG protocol that analyses would be undertaken separately for the two subgroups, the AG has only carried out analyses for the combined intermediate/poor risk subgroup; clinical advice to the AG is that, in line with NICE guidance,[25,39] treatment decisions are based on the combined intermediate/poor risk disease category (one category, not two categories). If a patient does not have intermediate/poor risk disease then, by definition, the patient has favourable risk disease; hence the AG has carried out subgroup analysis for the subgroup of patients with favourable risk.

Intermediate/poor risk

Clinical advice to the AG is that, in line with NICE guidance,[25,39] cabozantinib and nivolumab plus ipilimumab are first-line treatment options for patients with intermediate/poor risk aRCC;

in the first-line setting sunitinib, pazopanib or tivozanib are only considered for individuals in this subgroup who are unable to tolerate cabozantinib or nivolumab plus ipilimumab. Clinical advice to the AG is that patients unable to tolerate cabozantinib or nivolumab plus ipilimumab would be unlikely to tolerate lenvatinib plus pembrolizumab. Therefore, the AG does not consider that sunitinib, pazopanib and tivozanib are relevant comparators to lenvatinib plus pembrolizumab for patients with intermediate/poor risk disease.

Avelumab plus axitinib is also an option for patients with intermediate/poor risk disease; as this treatment is in the CDF but is not subject to an ongoing CDF review, it is not a relevant comparator.

Favourable risk

Sunitinib, pazopanib and tivozanib are NICE recommended treatment options[30-32] for patients who are not specifically categorised as having intermediate/poor risk aRCC, i.e., for those with favourable risk disease. The AG has, therefore, carried out subgroup analyses to compare lenvatinib plus pembrolizumab versus sunitinib, versus pazopanib and versus tivozanib for the subgroup of patients with favourable risk disease.

2.2 Overall aims and objectives of assessment

The overall aim of this MTA is to appraise the clinical and cost effectiveness of lenvatinib plus pembrolizumab within its MHRA marketing authorisation[45,46] for patients with untreated aRCC.

Lenvatinib plus pembrolizumab is licensed to treat all patients with aRCC irrespective of risk status. However, two of the comparators listed in the final scope[27] issued by NICE (cabozantinib and nivolumab plus ipilimumab) are only recommended for patients with intermediate/poor risk disease. Therefore, the objectives of this assessment are to appraise the clinical and cost effectiveness of lenvatinib plus pembrolizumab versus:

- cabozantinib or nivolumab plus ipilimumab for the intermediate/poor risk subgroup
- sunitinib, pazopanib and tivozanib for the favourable risk subgroup
- sunitinib, pazopanib and tivozanib for the all-risk population.

3 ASSESSMENT OF CLINICAL EFFECTIVENESS: DIRECT EVIDENCE

3.1 Methods for reviewing effectiveness

A systematic review of clinical effectiveness evidence was undertaken by the AG following the general principles outlined by the Centre for Reviews and Dissemination (CRD).[59] The review is reported using the criteria recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[60] Searches were conducted in accordance with the general principles recommended by the European network for Health Technology Assessment.[61] The protocol is registered with PROSPERO (registration number: CRD42021285879), an international database of prospectively registered systematic reviews in health and social care.[62]

3.1.1 Search strategies

The clinical effectiveness search strategy was designed to identify RCTs that met the inclusion criteria for the review of direct clinical effectiveness evidence, and to identify RCTs that could potentially be used to populate AG NMAs. The AG identified clinical effectiveness studies by searching relevant major medical databases, trial registries, conference abstracts, the NICE technology appraisal website and grey literature websites (Table 8). The search terms used to search the database are presented in Appendix 2 (Section 9.2).

As part of the MTA process, companies were invited to submit evidence to NICE to inform this appraisal. Direct and indirect evidence was provided by two companies: Eisai,[15] the sponsor of lenvatinib, and Merck Sharpe and Dohme (MSD),[51] the sponsor of pembrolizumab. The AG screened the reference lists of the Eisai CS[15] and the MSD CS[51] alongside all other included reports for relevant studies and consulted with the AG clinical experts to identify any relevant studies that may have been missed.

Table 8 Sources searched for clinical effectiveness studies

Search type	Sources	Dates searched
Databases	MEDLINE, EMBASE, PubMed, CENTRAL, INAHTA	From inception to 11 October 2021
Trial registries	clinicaltrials.gov, ICTRP	From inception to 11 October 2021
Conference proceedings	ASCO, ASCO-GU, ESMO, HTAi	From 1 January 2019 to 19 November 2021
NICE technology appraisals	TA169,[30] TA178,[34] TA215,[31] TA512,[32] TA542,[25] TA581,[26] TA650,[35] TA645[33]	From inception to 18 November 2021
Grey literature websites	EMA, CADTH, HAS, FDA, MHRA, PBAC, SMC	Searched on 22 November 2021
Other	Company submissions[15,51] for this appraisal[63]	Received 16 November 2021

ASCO=American Society of Clinical Oncology; ASCO-GU=ASCO-Genitourinary; CADTH=Canadian Agency for Drugs and Technologies in Health; EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; FDA=Food and Drug Administration (United States); HAS=Haute Autorité de Santé (France); HTAi=Health Technology Assessment International; ICTRP=International Clinical Trials Registry Platform; INAHTA=International Network of Agencies for Health Technology Assessment's International Health Technology Assessment Database; MHRA=Medicines and Healthcare products Regulatory Agency; MSD=Merck Sharp & Dohme; NICE=National Institute for Health and Care Excellence; PBAC=Pharmaceutical Benefits Advisory Committee (Australia); SMC=Scottish Medicines Consortium

A database of identified published literature was compiled. MEDLINE, EMBASE, PubMed, CENTRAL, INAHTA, clinicaltrials.gov and International Clinical Trials Registry Platform data were collated in a bibliographic database (Endnote X9 software package[64]) and exported to a specialist systematic review management system (Covidence systematic review software[65]). Conference abstracts results were screened on organisations' websites. The search terms used to search each of the databases and the websites are presented in Appendix 2 (Section 9.2).

3.1.2 Inclusion and exclusion criteria: direct evidence

The eligibility criteria used to identify studies for the review of direct clinical effectiveness are listed in Table 9.

Table 9 Inclusion and exclusion criteria for direct clinical effectiveness review

Criteria	Inclusion	Exclusion
Limits	• English language	• Not English language
Patient population	• Adults with untreated aRCC. If a study included a mixed population and provided subgroup analysis results for the population with untreated aRCC, then this study was included in the review	• Publications which do not include analyses of adults with untreated aRCC
Study design	• RCTs	• Non-RCTs
Intervention	• Lenvatinib plus pembrolizumab for previously untreated aRCC	• Lenvatinib monotherapy • Pembrolizumab monotherapy
Comparators	• Sunitinib • Pazopanib • Tivozanib • Cabozantinib (only for intermediate- or poor-risk disease as defined by IMDC criteria[b]) • Nivolumab plus ipilimumab (only for intermediate/poor risk disease as defined in the IMDC criteria)[c]	• Avelumab plus axitinib[a] • Any other treatment that is not recommended by NICE for adults with untreated aRCC
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Not applicable – no exclusions were made based on outcomes reported

[a] Avelumab plus axitinib is only available to NHS patients via the CDF;[33] it is not subject to an ongoing CDF review, and therefore is not a relevant comparator[66]
[b] Cabozantinib is only recommended by NICE[25] for intermediate/poor risk disease as defined in the IMDC criteria
[c] Nivolumab plus ipilimumab is only recommended by NICE[26] for intermediate/poor risk disease as defined in the IMDC criteria; it is currently only available to NHS patients via the CDF but is currently subject to an ongoing CDF review and is therefore considered by NICE to be a relevant comparator[39]
aRCC=advanced renal cell carcinoma; CDF=Cancer Drugs Fund; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; RCT=randomised controlled trial

Titles and abstracts identified by the electronic searches were uploaded to Covidence and screened by two reviewers (NF and either JG or KE). Full-text articles of any titles and abstracts that were considered potentially eligible for inclusion were obtained via online resources, or through the University of Liverpool libraries, and uploaded to Covidence. These full-text articles were assessed for inclusion by two reviewers (NF and either JG or KE). Discrepancies at each stage of screening were resolved via discussion between the three reviewers. Full-text articles that did not meet the inclusion criteria were excluded with reasons for exclusion noted.

In addition to screening the articles exported to Covidence, two out of three reviewers (RH, JG and KE) screened the conference proceedings independently, using the eligibility criteria shown in Table 9.

3.1.3 Data extraction and quality assessment strategy: direct evidence

Data relating to study characteristics, population characteristics and outcomes were extracted by one reviewer (NF) into tables and independently checked for accuracy by a second reviewer (SN or KE). Data from multiple publications of the same study were extracted and reported as a single study.

Study quality was assessed using the criteria published in the Centre for Review and Dissemination (CRD) Guidance for Undertaking Reviews in Healthcare[59] independently by two reviewers (JG and KE). Disagreements were resolved through discussion and, when necessary, a third reviewer (SN) was consulted.

3.1.4 Statistical approaches for the conduct and analysis of RCTs: direct evidence

The AG assessed the pre-specified statistical approach of the only included RCT.[67] This assessment considered:

- analysis populations
- trial design and sample size
- amendments to the protocol and statistical analysis plan
- definition and analysis approach for primary and secondary efficacy outcomes
- definition and analysis approach for patient reported outcomes (PROs)
- definition and analysis approach for safety outcomes and adverse events
- validity of modelling assumptions (e.g., proportional hazards [PH])
- approach to handling missing data
- subgroup and sensitivity analyses.

The AG also performed an assessment of specific statistical approaches, where appropriate for any relevant study (e.g., analyses to adjust for treatment switching).

3.1.5 Data analysis/synthesis: direct evidence

Meta-analysis

Only one RCT[67] was identified for inclusion in the review and, therefore, a meta-analysis was not required.

Presentation of results

Descriptive information, quality assessment results and statistical assessment results from the included RCT[67] are presented in structured tables and as a narrative summary.

Direct treatment effect estimates are presented as HRs for time-to-event data (i.e., OS and PFS) and odds ratios (ORs) for dichotomous data (i.e., ORR and adverse events [AE]s), or as mean differences (MDs) for continuous data (i.e., health-related quality of life (HRQoL) outcomes). All treatment effect estimates are presented with 95% confidence intervals (CIs).

3.2 Results of search for direct evidence: included and excluded studies

The AG study selection process is shown in Figure 1.

At the title and abstract stage, the AG included any study report that appeared to be an RCT that considered a relevant intervention or comparator. Such a broad approach to inclusion was carried out to aid the identification and selection of studies that provided data that could be used in AG NMAs. This approach resulted in the retrieval of 694 reports (577 via searches of databases and registries, and 117 via other searches). After applying inclusion/exclusion criteria, a total of 20 reports[15,51,67-84] describing one RCT (CLEAR/KEYNOTE-581 trial [NCT02811861], hereafter referred to as the CLEAR trial), was included in the review.

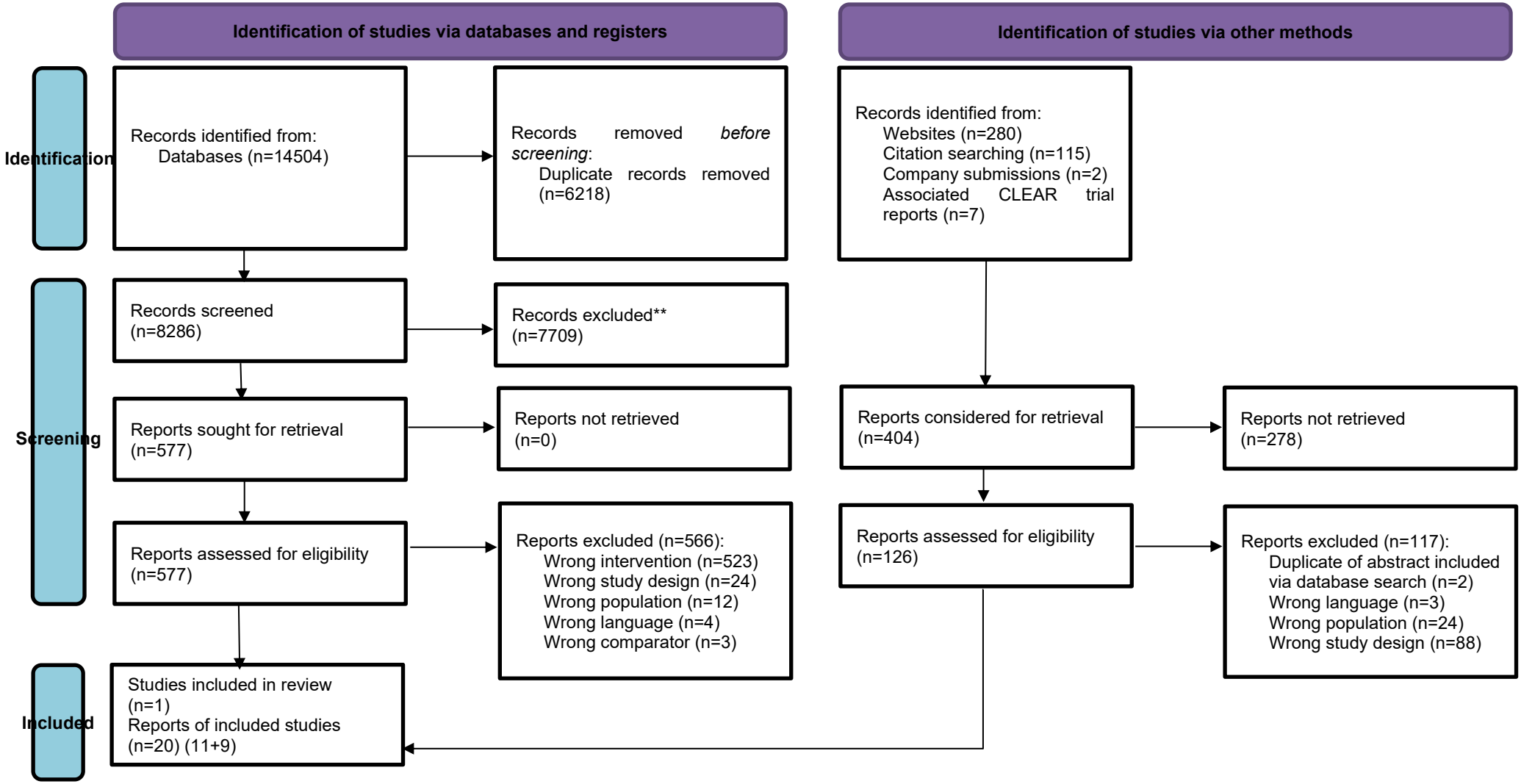

Figure 1 PRISMA flow diagram: direct clinical effectiveness evidence*

* Reports exclude information provided by Eisai and MSD as part of the NICE MTA clarification process

3.3 Sources of CLEAR trial data

The AG review of direct evidence included one RCT, the CLEAR trial; this trial was jointly sponsored by Eisai and MSD. While 20 study reports[15,51,67-84] were included in the review, data were only extracted from the sources listed in Table 10. After reviewing the companies' submissions, the AG requested additional information via the NICE MTA clarification process. The companies' responses to the AG clarification letters were used by the AG as sources of evidence.

The AG employed a hierarchical approach to data extraction. The initial source of data was the published paper,[67] including the online appendix and accompanying trial statistical analysis plan (TSAP).[75] Additional data were extracted first from the Eisai CS[15] and then cross checked with data in the MSD CS.[51] Finally, the Clinical Study Report (CSR)[71] and other CLEAR trial documents provided as part of the companies' submissions to NICE[69-74] were consulted and additional data extracted.

Table 10 Sources of CLEAR trial clinical effectiveness data used in this report

Source	Note
Motzer et al 2021a[67]	Published paper, including the online appendix and protocol
Motzer et al 2021b[82]	HRQoL data reported in conference abstract
Eisai CS[15] and response to AG clarification letter	CS received 15 November 2021; response to the AG clarification letter received 20 December 2021
MSD CS[51] and responses to AG clarification letters	CS received 15 November 2021; initial response to the AG clarification letter received 20 December 2021; additional response to the AG clarification letter received 11 January 2022
Protocol v7[74]	Final protocol (Amendment 7), 6 August 2020
TSAP, v3.0	14 August 2020, available online as appendix to published paper[67]
CSR[71]	28 August 2020, provided by both companies
Updated OS report[72]	20 May 2021, provided by both companies
HRQoL analysis plan, v2.1[69] and HRQoL report[73]	Additional source of HRQoL data (13 February 2021 and 28 August 2020, respectively) provided by Eisai (with Eisai response to the AG clarification letter)

AG=Assessment Group; ASCO=American Society of Clinical Oncology; ASGO-GU=American Society of Clinical Oncology Genitourinary; CS=company submission; CSR=Clinical Study Report; HRQoL=health-related quality of life; OS=overall survival; TSAP=trial statistical analysis plan

3.4 CLEAR trial design and characteristics

The CLEAR trial is a phase III, multi-centre, open-label RCT (with an ongoing extension phase) that was designed to compare the efficacy of lenvatinib plus pembrolizumab versus sunitinib, and lenvatinib plus everolimus versus sunitinib. Patients (n=1069) were randomised 1:1:1 to the treatment arms. Randomisation was stratified according to geographic region (Western Europe and North America, or the rest of the world) and MSKCC prognostic risk subgroup (favourable, intermediate, or poor risk). The treatment combination of lenvatinib plus everolimus is not relevant to this appraisal and is not discussed further in this AG report.

A summary of CLEAR trial design and conduct details is provided in Table 11.

Table 11 A summary of CLEAR trial design and conduct details

Parameter	CLEAR trial
Key eligibility criteria	Inclusion: • Aged ≥18 years • Previously untreated aRCC with a clear-cell component • ≥1 measurable lesion according to RECIST version 1 • KPS score ≥70 (scores range from 0 to 100, lower scores mean greater disability) • Adequately controlled blood pressure, with or without medications • Adequate organ function Patients with CNS metastasis were excluded unless they had completed local therapy and discontinued corticosteroids for this indication for ≥4 weeks before study treatment
Recruitment period	13 October 2016 to 24 July 2019
Number of centres (patients)	All: 181 sites in 20 countries, including 93 sites in Europe (407 patients) UK: 8 sites (26 patients)
Drug doses and schedule	Lenvatinib plus pembrolizumab: • Lenvatinib administered at a dose of 20mg orally once daily for each 21-day treatment cycle. Pembrolizumab administered at a dose of 200mg intravenously on day 1 of each 21-day cycle Sunitinib: • Sunitinib administered at a dose of 50mg orally once daily for 4 weeks of treatment followed by 2 weeks with no treatment (4/2 schedule) In both arms, patients continued to receive study treatment until disease progression was confirmed by BIRC, development of unacceptable toxicity, patient request, withdrawal of consent, completion of 35 treatments (2 years) for pembrolizumab or study termination by the sponsor All patients could continue treatment beyond initial RECIST v1.1-defined progression at the investigator's discretion
Dose modifications	Dose interruptions were permitted for all study drugs Dose reductions were not permitted for pembrolizumab If one drug in the combination treatment arm was discontinued (e.g., due to toxicity), the other drug could be continued

* The most common reasons for screen failures included active central nervous system metastases (n=59), inadequate bone marrow function (n=22), no measurable target lesion (n=21), or cardiovascular impairment (n=21).
aRCC=advanced renal cell carcinoma CNS=central nervous system; KPS=Karnofsky performance status; RECIST=Response Evaluation Criteria in Solid Tumors
Source: Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51]

The CLEAR trial primary outcome was PFS assessed by Blinded Independent Review Committee (BIRC), using the censoring method preferred by the FDA. All other outcomes relevant to the decision problem were reported (OS, ORR, AEs and HRQoL). Pre-specified subgroup analyses, by IMDC and MSKCC risk subgroups, were:

- age (<65 years, ≥65 years)
- sex (male, female)
- race (White, Asian)
- geographic region (Western Europe or North America, Rest of the world)
- MSKCC risk subgroup (Favourable, Intermediate, Poor)
- IMDC risk subgroup (Favourable, Intermediate, Poor)

- baseline KPS score (100-90, 80-70)
- number of organs with metastases (1, 2, ≥3)
- baseline bone, liver, and lung metastasis (yes, no)
- programmed death-ligand 1 (PD-L1) combined positive score (≥1, <1)
- prior nephrectomy (yes, no)
- clear cell histology with sarcomatoid features (yes, no).

Analyses of MSKCC intermediate/poor risk subgroup PFS, OS and ORR data were also presented in the Eisai CS.[15]

The CLEAR trial has an ongoing OS extension phase and timing of the final data cut is event driven. Eisai[15] (p67) and MSD[51] (p66) estimate that the final OS analysis will be carried out in the third quarter of 2022 (estimated study completion date is 31 July 2022). To date, OS has been reported at two different time points: (i) at the time of the third interim analysis (IA3 data cut-off), which was also the final data-cut for PFS and the time at which all other outcomes were reported, and (ii) at the time of the updated OS analysis (see Table 12 for details). As patients could receive subsequent anti-cancer treatment on disease progression, company post-hoc analyses were also performed excluding patients who received subsequent treatment from the analysis and by adjusting for subsequent anti-cancer treatment using the two-stage estimation method[85] (see also Appendix 3, Section 9.3.2, Table 80).

Table 12 CLEAR trial follow-up periods

Parameter	IA3 data cut-off	Updated OS analysis
Data cut-off date	28 August 2020	31 March 2021
Duration of follow-up	Median OS follow-up: 26.6 months. All efficacy, safety and patient reported outcomes were reported at this time point	Median OS follow-up: ~33 months Only OS was assessed at this follow-up
Number (%) of patients still on study treatment	Lenvatinib plus pembrolizumab: 142 (40.0%) Sunitinib: 67 (18.8%)	Lenvatinib plus pembrolizumab: 114 (32.1%) Sunitinib: 49 (13.7%)

IA3=third interim analysis; OS=overall survival
Source: Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51]

Analyses of efficacy outcomes were undertaken using data from the Full Analysis Set (FAS) population, which is also the intention-to-treat (ITT) population and the all-risk population. Safety analyses were undertaken using data from the randomised population who received at least one dose of a study drug and who had at least one post-baseline safety evaluation (safety population).

3.5 CLEAR trial participant characteristics

A summary of baseline characteristics is presented in Table 13. There were 2.9 times as many men as women. Only one patient had clear cell aRCC; a small number of patients also had additional non-clear cell and/or sarcomatoid features. The lenvatinib plus pembrolizumab arm included a higher proportion of patients aged ≥65 years; the median age of patients in this arm was higher than the median age of patients in the sunitinib arm (64 years versus 61 years).

In both trial arms, more patients were categorised as having favourable risk disease using the IMDC classification than using the MSKCC classification, and fewer patients were categorised as having intermediate risk disease using the IMDC classification than using the MSKCC classification. Six patients were not assigned a risk category according to the IMDC classification.

Generally, the baseline characteristics of patients included in the CLEAR trial were balanced between treatment arms. However, while the proportions of patients classified in each MSKCC risk subgroup were the same across the trial arms, there were slight imbalances between arms in terms of IMDC risk status.

Table 13 Participant characteristics in the CLEAR trial, FAS (all-risk) population

Characteristic	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
Mean (SD) age, years	[redacted]	[redacted]
Median (range) age, years	64 (34, 88)	61 (29, 82)
<65 years, n (%)	194 (54.6)	225 (63.0)
Male, n (%)	255 (71.8)	275 (77.0)
Region, n (%)		
Western Europe or North America	198 (55.8)	199 (55.7)
Rest of the world	157 (44.2)	158 (44.3)
KPS, n (%)		
90-100	295 (83.1)	294 (82.4)
70-80	60 (16.9)	62 (17.4)
Missing	0	1 (0.3)
MSKCC risk subgroup, n (%)		
Favourable	96 (27.0)	97 (27.2)
Intermediate	227 (63.9)	228 (63.9)
Poor	32 (9.0)	32 (9.0)
IMDC risk subgroup, n (%)		
Favourable	110 (31.0)	124 (34.7)
Intermediate	210 (59.2)	192 (53.8)
Poor	33 (9.3)	37 (10.4)
Could not be evaluated	2 (0.6)	4 (1.1)
RCC diagnosis classification, n (%) Clear cell with additional features, n (%)		
Papillary	[redacted]	[redacted]
Chromophobe	[redacted]	[redacted]
Sarcomatoid	28 (7.9)	21 (5.9)
Other	[redacted]	[redacted]
Not clear cell	[redacted]	[redacted]
Number of metastatic organs or sites*		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Prior-nephrectomy, n (%)	262 (73.8)	275 (77.0)

* Lesion organs/sites involved were derived from independent imaging review; kidney is not included in the number of metastatic organs/sites; the number or organs/sites reported by Motzer et al 2021a,[67] differs to that reported in the Eisai CS[15]
FAS=Full Analysis Set; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; KPS=Karnofsky performance status; MSKCC=Memorial Sloan-Kettering Cancer Center; PD-L1=programmed death-ligand 1; RCC=renal cell carcinoma; SD=standard deviation
Source: Motzer et al 2021a,[67] Eisai CS,[15] MSD CS[51] and CSR[71]

3.6 Quality assessment of the CLEAR trial

The AG conducted a quality assessment of the CLEAR trial using the criteria published in the CRD's Guidance for undertaking reviews in healthcare.[59] The results of the assessment are presented in Table 14. The AG considers that the CLEAR trial is a good quality trial.

Table 14 Assessment Group quality assessment of the CLEAR trial

Quality assessment item	AG assessment
Was the method used to assign participants to treatment arms really random?	✓
Was the allocation of treatment concealed?	✓
Was the number of participants randomised stated?	✓
Were details of baseline comparability presented in terms of prognostic factors?	✓
Was baseline comparability achieved in terms of prognostic factors?	✓
Were the eligibility criteria for study entry specified?	✓
Were any co-interventions identified that may influence the outcomes for each group?	✕
Were the outcome assessors blinded to the treatment allocation?	✓
Were the individuals administering the intervention blinded to treatment allocation?	✕
Were the participants receiving the intervention blinded to treatment allocation?	✕*
Was the success of the blinding procedure assessed?	NA
Were at least 80% of the participants included in the randomisation process followed up in the final analysis?	✓
Were the reasons for patient withdrawals stated?	✓
Was an intention to treat analysis included?	✓
Is there any evidence that more outcomes were measured than were reported?	✕

* The CLEAR trial was an open-label trial; however, blinded independent review of radiologic outcomes was conducted
✓ yes (item properly addressed) ✕ no (item not properly addressed) NA=not applicable

3.7 Statistical approach used to analyse CLEAR trial data

A summary of the AG checks of the CLEAR trial pre-planned statistical approach is provided in Appendix 3 (Section 9.3.1, Table 79). The AG highlights that in cases where the PH assumption is violated, the estimated HR is not applicable to all time points across the observed CLEAR trial follow-up period. In the context of a single trial, where violations of the PH assumption are demonstrated, visual inspection of the Kaplan-Meier (K-M) data may provide some insight into the likely direction of relative effect at different time points, and changes in the direction or magnitude of relative effect over the time period of the trial (i.e., where K-M curves cross, or diverge).

3.8 CLEAR trial results

3.8.1 Progression-free survival results from the CLEAR trial

Key PFS results from the CLEAR trial are summarised in Table 15.

Table 15 CLEAR trial PFS (FDA censoring rules and BIRC) for the FAS (all-risk) population and IMDC subgroups (IA3 data cut-off)

Characteristic/outcome	All-risk (FAS)		Intermediate/poor risk		Favourable risk	
	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)	Lenvatinib + pembrolizumab (N=110)	Sunitinib (N=124)
Number of events (%)	160 (45.1)	205 (57.4)	115 (47.3)	136 (59.4)	43 (45.1)	67 (54.0)
Death from PFS (%)	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Median PFS in months (95% CI)	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified HR (95% CI) p-value	0.39 (0.32 to 0.49) p<0.001		[redacted]		0.41 (0.28 to 0.62) p<0.001	
PFS rates (%) (95% CI) at: 12 months 18 months 24 months 36 months	[redacted]	[redacted]	 Not reported Not reported Not reported Not reported	 Not reported Not reported Not reported Not reported	 Not reported Not reported Not reported Not reported	 Not reported Not reported Not reported Not reported

Note: Six patients (two in the lenvatinib plus pembrolizumab arm and four in the sunitinib arm) were not assigned a risk category according to the IMDC risk classification
BIRC=Blinded Independent Review Committee; CI=confidence interval; FAS=Full Analysis Set; FDA=Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium PFS=progression-free survival
Source: Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS population data) and Eisai CS,[15] Appendix E1.1 (subgroup data)

PFS: FAS population (ITT population, all-risk population)

In the CLEAR trial, median PFS was statistically significantly longer in the lenvatinib plus pembrolizumab arm than in the sunitinib arm (median 23.9 months, 95% CI: 20.8 to 27.7 months versus 9.2 months, 95% CI: 6.0 to 11.0; HR=0.39 [95% CI: 0.32 to 0.49]; p<0.001). In addition,

[redacted]

Exploratory subgroup analyses: PFS assessed by BIRC by risk subgroup

Subgroup results by MSKCC and IMDC risk subgroups for PFS assessed by BIRC using both the FDA and EMA preferred censoring methods are provided in Appendix 4 (Section 9.4), Table 81 to Table 88. Key PFS results for the intermediate/poor risk and favourable risk subgroups, using the FDA preferred censoring method, are presented in Table 15, and show that:

- Intermediate/poor risk subgroup: median PFS for patients treated with lenvatinib plus pembrolizumab was [redacted] months as compared with 23.9 months in the FAS population. For patients treated with sunitinib, median PFS was [redacted] than reported in the FAS population ([redacted] months versus 9.2 months, respectively). The HR between arms in the intermediate/poor risk subgroup [redacted] was [redacted] to the HR reported between arms for patients in the FAS population (HR=0.39, 95% CI: 0.32 to 0.49).[redacted]
- Favourable risk subgroup: median PFS for patients treated with lenvatinib plus pembrolizumab was [redacted] than the median PFS reported in the FAS population, for lenvatinib plus pembrolizumab ([redacted] months versus 23.9 months) and for sunitinib ([redacted] months versus 9.2 months). However, the HR between arms in the favourable risk subgroup [redacted] was [redacted] to the HR reported in the FAS population (HR=0.39, 95% CI: 0.32 to 0.49).

Other exploratory subgroup analyses of PFS assessed by BIRC

All results from CLEAR trial PFS subgroup analyses for the comparison of lenvatinib plus pembrolizumab versus sunitinib were statistically significantly in favour of lenvatinib plus pembrolizumab (Motzer et al 2021a,[67] Figure 1B).

3.8.2 Overall survival results from the CLEAR trial

Key OS results from the CLEAR trial are presented in Table 16.

Table 16 OS results from the CLEAR trial, FAS (all-risk) population and IMDC subgroups, IA3 data cut-off and updated OS analysis

Characteristic/outcome	All-risk (FAS)		Intermediate/poor risk		Favourable risk	
	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)	Lenvatinib + pembrolizumab (N=110)	Sunitinib (N=124)
OS – IA3 data cut-off						
Number of deaths (%)	[redacted]	[redacted]	66 (27.2)	85 (37.1)	14 (12.7)	15 (12.1)
Median OS in months (95% CI)	NE (33.6 to NE)	NE (NE to NE)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified HR (95% CI)	0.66 (0.49 to 0.88)[a]		[redacted]		1.15 (0.55 to 2.40)	
p value	p=0.005[a]		[redacted]		[redacted]	
OS rate (%) (95% CI) at: 12 months 18 months 24 months	[redacted]	[redacted]	 Not reported Not reported Not reported	 Not reported Not reported Not reported	 Not reported Not reported Not reported	 Not reported Not reported Not reported
OS – updated OS analysis						
OS – updated OS analysis						
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	Not reported	Not reported	[redacted]	[redacted]
Stratified HR (95% CI)	[redacted][a]		[redacted]		[redacted]	
p value	Not reported[a]		Not reported		Not reported	
OS rate (%) (95% CI) at: 12 months 18 months 24 months 36 months	[redacted]	[redacted]	 Not reported Not reported Not reported Not reported	 Not reported Not reported Not reported Not reported	 Not reported Not reported Not reported Not reported	 Not reported Not reported Not reported Not reported

Note: Six patients (two in the lenvatinib plus pembrolizumab arm and four in the sunitinib arm) were not assigned a risk category according to the IMDC risk classification
[a] Neither the p-value nor the HR (95% CIs) should be used to infer statistical significance where the proportional hazards assumption is violated
Source: Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS population data) and Eisai CS,[15] Appendix D2.4.2, Appendix E2 and CSR,[71] Table 14.2.2.2.2.1.2 (subgroup data)
CI=confidence interval; FAS=Full Analysis Set; HR=hazard ratio; IA3=third interim analysis; NE=not estimable; OS=overall survival; PFS=progression-free survival

Full Analysis Set (ITT population, all-risk population)

Median OS had not been reached in either CLEAR trial arm at the time of the IA3 data cut-off [redacted] (Table 16). As the PH assumption is violated, the HR should not be used to infer statistical significance or the magnitude of treatment effect from the HR. However, MSD OS K-M data (MSD CS,[51] Figure 5 and Figure 6) show early survival differences between patients treated with lenvatinib plus pembrolizumab and those treated with sunitinib; OS rates [redacted] for patients treated with lenvatinib plus pembrolizumab compared with patients treated with sunitinib.

Exploratory subgroup analyses: OS

Subgroup analyses carried out using updated OS analysis data were only presented by risk subgroup. Subgroup results by MSKCC and IMDC risk subgroups for both data cut-offs are presented in Appendix 5 (Section 9.5, Table 89 to Table 96). Key results by intermediate/poor and favourable risk subgroups using updated OS analysis data are presented in Table 16 and show that:

- [redacted]
- [redacted]

Exploratory subgroup analyses of OS

Results from most of the OS subgroup analyses generated using data from the IA3 data cut-off favoured lenvatinib plus pembrolizumab versus sunitinib, except for favourable risk subgroup results which favoured sunitinib (Motzer et al 2021a,[67] Figure S4). Neither Eisai nor MSD submitted OS subgroup results, other than by risk subgroup, using data from the updated OS analysis.

3.8.3 Treatment on disease progression and impact on overall survival in the CLEAR trial

In addition to the effect of the study drug, OS results may be influenced by subsequent anti-cancer treatment(s) received on disease progression. Just under half ([redacted]) of all patients in the CLEAR trial received subsequent treatment (updated OS analysis). Compared with patients in the lenvatinib plus pembrolizumab arm, nearly twice as many patients in the sunitinib arm received subsequent treatment (Table 17).

Table 17 The number of patients who received any subsequent systemic anti-cancer treatment in the CLEAR trial, FAS (all-risk) population

Data cut-off	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)	Pooled (N=712)
IA3 data cut-off, n (%)	117 (33.0)	206 (57.1)	323 (45.4)
Updated OS analysis, n (%)	[redacted]	[redacted]	[redacted]

FAS=Full Analysis Set; IA3=interim analysis 3; OS=overall survival; PFS=progression-free survival
Source: Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51]

OS results (updated OS analysis) for patients who received, and for patients who did not receive subsequent treatment are reported by Eisai[15] (CS, p42). The results are summarised in Table 18. The PH assumption was violated for the analysis of OS data from patients who received subsequent treatment and so the OS HR should not be used to infer magnitude of treatment effect or statistical significance. [redacted]

Table 18 OS results for patients who did and did not receive subsequent treatment in the CLEAR trial, FAS (all-risk) population, updated OS analysis

Characteristic/ outcome	Received subsequent treatment		Did not receive subsequent treatment	
	Lenvatinib + pembrolizumab (N=[redacted])	Sunitinib (N=[redacted])	Lenvatinib + pembrolizumab (N=[redacted])	Sunitinib (N=[redacted])
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

CI=confidence interval; HR=hazard ratio; NE=not estimable; OS=overall survival
Source: Eisai CS,[15] p42

Information about the types of subsequent treatment received by CLEAR trial patients (updated OS analysis, FAS population) was included in the Eisai CS[15] (Eisai CS,[15] Table 15); further details for the FAS population and by risk subgroup were provided in the Eisai response to the AG clarification letter (clarification question B5, Table 10 and Table 11). The subsequent treatments received by the FAS population (all-risk), the intermediate/poor subgroup and the favourable/unknown risk subgroup are listed in Table 19, Table 20 and Table 21 respectively.

Table 19 Summary of subsequent anti-cancer treatment received on disease progression by CLEAR trial patients, FAS (all-risk) population, updated OS analysis

Subsequent treatment	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
Any, n (%)	[redacted]	[redacted]
Treatment received:		
Anti-VEGF therapy, n (%)	[redacted]	[redacted]
PD-1/PD-L1 checkpoint inhibitor, n (%)[a]	[redacted]	[redacted]
- nivolumab, n (%)	[redacted]	[redacted]
- other PD-1/PD-L1 checkpoint inhibitor, n (%)	[redacted]	[redacted]
mTOR inhibitor, n (%)[b]	[redacted]	[redacted]
- everolimus, n (%)	[redacted]	[redacted]
- temsirolimus, n (%)	[redacted]	[redacted]
CTLA-4 inhibitor, n (%)	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]

[a] Some patients received more than one PD-1/PD-L1 checkpoint inhibitor
[b] Some patients received more than one mTOR inhibitor
CTLA-4=cytotoxic T-lymphocyte-associated protein 4; mTOR=mammalian target of rapamycin; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; VEGF=vascular endothelial growth factor
Source: Adapted from Eisai response to the AG clarification letter, question B5, Table 10

Table 20 Summary of subsequent anti-cancer treatment received on disease progression by CLEAR trial patients, intermediate/poor subgroup, updated OS analysis

Subsequent treatment	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)
Any, n (%)	[redacted]	[redacted]
Treatment received:		
Anti-VEGF therapy, n (%)	[redacted]	[redacted]
PD-1/PD-L1 checkpoint inhibitor, n (%)[a]	[redacted]	[redacted]
- nivolumab, n (%)	[redacted]	[redacted]
- other PD-1/PD-L1 checkpoint inhibitor, n (%)	[redacted]	[redacted]
mTOR inhibitor, n (%)[b]	[redacted]	[redacted]
- everolimus, n (%)	[redacted]	[redacted]
- temsirolimus, n (%)	[redacted]	[redacted]
CTLA-4 inhibitor, n (%)	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]

[a] Some patients received more than one PD-1/PD-L1 checkpoint inhibitor
[b] Some patients received more than one mTOR inhibitor
CTLA-4=cytotoxic T-lymphocyte-associated protein 4; mTOR=mammalian target of rapamycin; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; VEGF=vascular endothelial growth factor
Source: Adapted Eisai response to the AG clarification letter, question B5, Table 11

Table 21 Summary of subsequent anti-cancer treatment received on disease progression by CLEAR trial patients, favourable/unknown[a] risk subgroup, updated OS analysis

Subsequent treatments	Lenvatinib + pembrolizumab (N=112)	Sunitinib (N=128)
Any, n (%)	[redacted]	[redacted]
Treatment received:		
Anti-VEGF therapy, n (%)	[redacted]	[redacted]
PD-1/PD-L1 checkpoint inhibitor, n (%)[b]	[redacted]	[redacted]
- nivolumab, n (%)	[redacted]	[redacted]
- other PD-1/PD-L1 checkpoint inhibitor, n (%)	[redacted]	[redacted]
mTOR inhibitor, n (%)[c]	[redacted]	[redacted]
- everolimus, n (%)	[redacted]	[redacted]
- temsirolimus, n (%)	[redacted]	[redacted]
CTLA-4 inhibitor, n (%)	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]

[a] International Metastatic Renal Cell Carcinoma Database Consortium risk status was unknown for 2 patients treated with lenvatinib plus pembrolizumab and for 4 patients treated with sunitinib
[b] Some patients received more than one PD-1/PD-L1 checkpoint inhibitor
[c] Some patients received more than one mTOR inhibitor
CTLA-4=cytotoxic T-lymphocyte-associated protein 4; mTOR=mammalian target of rapamycin; PD-1=programmed cell death protein1; PD-L1=programmed cell-death ligand 1; VEGF=vascular endothelial growth factor
Source: Calculated from Eisai response to the AG clarification letter, question B5, Table 10 and Table 11

Eisai also conducted prespecified analyses to adjust OS for the effect of any subsequent anti-cancer treatment (FAS population, updated OS analysis). These analyses were conducted using the two-stage estimation method with different models (log-normal acceleration factor [AF] with and without re-censoring; log-logistic AF with and without re-censoring; Weibull AF with and without re-censoring). The results are presented in the Eisai CS[15] (Table 16) and [redacted] A summary of the AG checks of the treatment switching analysis methods used by Eisai is provided in Appendix 3 (Section 9.3.2, Table 80).

3.8.4 Objective tumour response results from the CLEAR trial

Key tumour response results, including ORR results, from the CLEAR trial are presented in Table 22.

Table 22 BIRC assessed objective response results from the CLEAR trial, FAS (all-risk) population and IMDC subgroups, IA3 data cut-off

Characteristic / outcome	All-risk (FAS)		Intermediate/poor risk		Favourable risk	
	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)	Lenvatinib + pembrolizumab (N=110)	Sunitinib (N=124)
ORR (CR + PR) by BIRC, % (95% CI)	71.0 (66.3 to 75.7)	36.1 (31.2 to 41.1)	[redacted](Not reported)	[redacted](Not reported)	[redacted](Not reported)	[redacted](Not reported)
Difference, % (95% CI)	[redacted]		[redacted]		[redacted]	
Odds ratio (95% CI)	[redacted]		[redacted]		[redacted]	
p value	[redacted]		[redacted]		[redacted]	
Best objective response:						
Complete response (CR), n (%)	57 (16.1)	15 (4.2)	Not reported	Not reported	Not reported	Not reported
Partial response (PR), n (%)	195 (54.9)	114 (31.9)	Not reported	Not reported	Not reported	Not reported
Stable disease, n (%)	68 (19.2)	136 (38.1)	Not reported	Not reported	Not reported	Not reported
Progressive disease, n (%)	19 (5.4)	50 (14.0)	Not reported	Not reported	Not reported	Not reported
Unevaluable for response / not known, n (%)	16 (4.5)	42 (11.8)	Not reported	Not reported	Not reported	Not reported
No postbaseline tumour assessment	12 (3.4)	38 (10.6)	Not reported	Not reported	Not reported	Not reported
≥1 Lesion NE	1 (0.3)	2 (0.6)	Not reported	Not reported	Not reported	Not reported
Early stable disease (<7 Weeks)	3 (0.8)	1 (0.3)	Not reported	Not reported	Not reported	Not reported
Median time to response, months (range)	1.94 (1.41 to 18.50)	1.94 (1.61 to 16.62)	Not reported	Not reported	Not reported	Not reported
Median duration of response, months (95% CI)	25.8 (22.1 to 27.9)	14.6 (9.4 to 16.7)	Not reported	Not reported	Not reported	Not reported

Note: Six patients (two in the lenvatinib plus pembrolizumab arm and four in the sunitinib arm) were not assigned a risk category according to the IMDC risk classification
*The difference between the treatment arms was tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by geographic region and MSKCC prognostic groups
BIRC=Blinded Independent Review Committee; CI=confidence interval; CR=complete response; ORR=objective response rate; PR=partial response
Source: Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS population data) and Eisai CS,[15] Appendix E4.1

Full Analysis Set population

CLEAR trial ORR assessed by BIRC was statistically significantly higher in the lenvatinib plus pembrolizumab arm than in the sunitinib arm (71.0% [95% CI: 66.3% to 75.7%] versus 36.0% [95% CI: 31.2% to 41.1%]; odds ratio [redacted]). While time to response was 1.94 months in both arms, the duration of response was nearly twice as long for patients treated with lenvatinib plus pembrolizumab (25.8 months) than for patients treated with sunitinib (14.6 months).

Exploratory subgroup analyses: ORR by risk subgroup

ORR results by risk subgroup are summarised in Appendix 6 (Section 9.6, Table 97). Key results for the intermediate/poor risk and favourable risk subgroups using data from the IA3 data cut-off are presented in Table 22 and show that:

- [redacted]

Other exploratory ORR subgroup analyses

[redacted] (CSR Section 11.4.1.6.3).[71]

3.8.5 Safety results

Safety data from the CLEAR trial were reported (IA3 data cut-off). The AEs were graded using CTCAE version 4.03.[86] The safety population included all patients who received at least one dose of either study drug.

The median duration of treatment was longer in the lenvatinib plus pembrolizumab arm than in the sunitinib arm (17.0 months versus 7.8 months). The median relative dose intensity (RDI) of lenvatinib per patient was [redacted] and the median number of pembrolizumab administrations was [redacted]. The median relative dose intensity of sunitinib per patient was [redacted].

A summary of treatment emergent adverse events (TEAEs) is presented in Table 23. Patients in the lenvatinib plus pembrolizumab arm experienced more AE (of any type) than patients in the sunitinib arm. While 37.2% of patients discontinued lenvatinib or pembrolizumab due to TEAEs, 13.4% of patients discontinued both lenvatinib and pembrolizumab due to TEAEs; 14.4% of patients discontinued sunitinib due to TEAEs.

Table 23 Summary of treatment-emergent adverse events in the CLEAR trial, all-risk safety population, IA3 data cut-off

Type of AE, n (%)	Lenvatinib + pembrolizumab (N=352)	Sunitinib (N=340)
Any TEAE	351 (99.7)	335 (98.5)
TRAE	341 (96.9)	313 (92.1)
Any Grade ≥3 TEAE	290 (82.4)	244 (71.8)
Non-fatal serious TEAE	178 (50.6)	113 (33.2)
Non-fatal serious treatment-related TEAE	119 (33.8)	51 (15.0)
TEAE leading to treatment interruption	276 (78.4)	183 (53.8)
Interruption of lenvatinib	257 (73.0)	NA
Interruption of pembrolizumab	194 (55.1)	NA
Interruption of both lenvatinib and pembrolizumab	138 (39.2)	NA
TEAE leading to dose reduction	242 (68.8)	171 (50.3)
TEAEs leading to study drug discontinuation	131 (37.2)	49 (14.4)
Discontinuation of lenvatinib	90 (25.6)	NA
Discontinuation of pembrolizumab	101 (28.7)	NA
Discontinuation of both lenvatinib and pembrolizumab	47 (13.4)	NA
Fatal TEAE	15 (4.3)	11 (3.2)
Fatal TRAE	[redacted]	[redacted]

NA=not applicable; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event
Source: Eisai CS,[15] Table 18, Eisai CS,[15] Appendix F5, Table 61 and MSD CS,[51] Appendix F, Table 6

A summary of TEAEs by IMDC risk subgroups is presented in Table 24. The rates of TEAEs were similar across risk subgroups in both treatment arms, except for TEAEs leading to drug discontinuations.

Table 24 Summary of treatment-emergent adverse events in the CLEAR trial, IMDC risk subgroups safety population, IA3 data cut-off

Type of AE	Intermediate/poor risk, n (%)		Favourable risk, n (%)	
	Lenvatinib + pembrolizumab (N=241)	Sunitinib (N=220)	Lenvatinib + pembrolizumab (N=109)	Sunitinib (N=117)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade ≥3 TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TRAE	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade ≥3 TRAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event
Source: adapted from Eisai CS,[15] Appendix F, Table 64 and Table 65

The AEs of any cause (any grade in ≥25% of patients and Grade ≥3 in ≥5% of patients) that emerged or worsened during the CLEAR are summarised in Table 25 and Table 26 respectively. Nearly all patients in both arms experienced at least one all-grade AE with more Grade ≥3 AEs reported in the lenvatinib plus pembrolizumab arm (82.4%) than in the sunitinib arm (71.8%).

The most commonly occurring all-grade AEs in both arms were diarrhoea (61.4% versus 49.4%) and hypertension (55.4% versus 41.5%). Hypertension was also the most common Grade ≥3 AE in both arms (27.6% versus 18.8%). The other most common Grade ≥3 AEs in the lenvatinib plus pembrolizumab arm were lipase increased (12.8% versus 8.8%), diarrhoea (9.7% versus 5.3%), amylase increased (9.1% versus 2.9%), weight decreased (8.0% versus 0.3%), proteinuria (7.7% versus 2.9%) and asthenia (5.4% versus 4.4%).

MSD[51] (p69) reported a "higher than expected" incidence of Grade ≥3 hepatic AEs. From data presented by the companies (Eisai CS,[15] Table 20 and MSD CS,[51] Appendix F, Table 8), incidences of Grade ≥3 alanine aminotransferase increased and Grade ≥3 aspartate aminotransferase increased were 4.3% and 3.1% respectively in the lenvatinib plus pembrolizumab arm versus 2.4% and 0.9% respectively in the sunitinib arm. Grade ≥3 blood bilirubin increased in 1.1% of patients treated with lenvatinib plus pembrolizumab and in 0.6% of patients treated with sunitinib. It is reported in the summary of product characteristics (SmPC) for lenvatinib that Grade 3 liver-related reactions occurred in 9.9% of patients in the lenvatinib plus pembrolizumab arm and in 5.3% of patients in the sunitinib arm.[45]

Table 25 Any grade adverse events emerging or worsening in ≥25% of patients in either arm of the CLEAR trial, all-risk safety population, IA3 data cut-off

Adverse event	Lenvatinib + pembrolizumab (N=352)	Sunitinib (N=340)
	n (%)	n (%)
Any AE	351 (99.7)	335 (98.5)
Diarrhoea	216 (61.4)	168 (49.4)
Hypertension	195 (55.4)	141 (41.5)
Hypothyroidism	166 (47.2)	90 (26.5)
Decreased appetite	142 (40.3)	105 (30.9)
Fatigue	141 (40.1)	125 (36.8)
Nausea	126 (35.8)	113 (33.2)
Stomatitis	122 (34.7)	131 (38.5)
Dysphonia	105 (29.8)	14 (4.1)
Weight decrease	105 (29.8)	31 (9.1)
Proteinuria	104 (29.5)	43 (12.6)
PPE	101 (28.7)	127 (37.4)
Arthralgia	99 (28.1)	52 (15.3)
Rash	96 (27.3)	47 (13.8)
Vomiting	92 (26.1)	68 (20.0)
Constipation	89 (25.3)	64 (18.8)
Dysgeusia	43 (12.2)	95 (27.9)

AE=adverse event; PPE=Palmar-plantar erythrodysesthesia syndrome
Source: adapted from Motzer et al 2021a,[67] Table 3

Table 26 Grade ≥3 Treatment-emergent adverse events in the CLEAR trial (≥5% of patients in either arm), all-risk safety population, IA3 data cut-off

Adverse event	Lenvatinib + pembrolizumab (N=352)	Sunitinib (N=340)
	n (%)	n (%)
Any Grade ≥3 TEAE	290 (82.4)	244 (71.8)
Hypertension	97 (27.6)	64 (18.8)
Lipase increased	45 (12.8)	30 (8.8)
Diarrhoea	34 (9.7)	18 (5.3)
Amylase increased	32 (9.1)	10 (2.9)
Weight decreased	28 (8.0)	1 (0.3)
Proteinuria	27 (7.7)	10 (2.9)
Asthenia	19 (5.4)	15 (4.4)
Hypertriglyceridaemia	17 (4.8)	22 (6.5)
Hyponatraemia	17 (4.8)	17 (5.0)
Anaemia	7 (2.0)	18 (5.3)
Neutrophil count decreased	6 (1.7)	19 (5.6)
Platelet cell count decreased	4 (1.1)	31 (6.2)
Thrombocytopenia	2 (0.6)	19 (5.6)
Neutropenia	2 (0.6)	20 (5.9)

TEAE=treatment-emergent adverse event
Source: adapted from MSD CS,[51] Appendix F, Table 8

MSD[51] reported that the most common non-fatal serious AEs (SAEs) in the lenvatinib plus pembrolizumab arm were diarrhoea (3.4%), vomiting (2.8%), pneumonitis (2.6%), acute kidney injury (2.3%) and hypertension (2.3%), each of which occurred with an incidence ≤1.2% in the sunitinib arm (MSD CS,[51] Appendix F, Table 3). Pyrexia was the most common SAE in the sunitinib arm (2.1% versus 1.7% in the lenvatinib plus pembrolizumab arm).

Eisai[15] reported that AEs of special interest (AEOSIs) for pembrolizumab were experienced by [redacted]% of patients in the lenvatinib plus pembrolizumab arm and [redacted]% of patients in the sunitinib arm (Eisai CS,[15] Appendix F3.2). According to the CSR,[71] for the comparison of lenvatinib plus pembrolizumab versus sunitinib, the most common AEOSI was hypothyroidism ([redacted]% versus [redacted]% respectively); other AEOSIs reported by ≥5% of patients in the lenvatinib plus pembrolizumab arm (versus AEOSIs reported by ≥5% of patients in the sunitinib arm) were hyperthyroidism ([redacted]% versus [redacted]%), pneumonitis ([redacted]% versus [redacted]%), adrenal insufficiency ([redacted]% versus [redacted]%) and severe skin reactions ([redacted]% versus [redacted]%). [redacted] severe skin reactions were (by definition) Grade ≥3. In total, [redacted]% of patients treated with lenvatinib plus pembrolizumab experienced a Grade ≥3 AEOSI, compared with [redacted]% of patients treated with sunitinib.[71] [redacted] patients experienced Grade ≥3 hypothyroidism ([redacted]% versus [redacted]%), pneumonitis ([redacted]% versus [redacted]%) or adrenal insufficiency ([redacted]% versus [redacted]%).

3.8.6 Health-related quality of life results from the CLEAR trial

In the CLEAR trial, HRQoL was assessed as a secondary endpoint using the following validated questionnaires: (i) the Functional Assessment of Cancer Therapy Kidney Index-Disease-Related Symptoms (FKSI-DRS), (ii) the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), and (iii) the European Quality of Life-5 Dimensions-3 Levels Version (EuroQoL EQ-5D-3L). In summary:

(i) The FKSI-DRS consists of 9-items designed to assess the frequency/severity of symptoms specific to advanced kidney cancer, including fatigue, pain, bone pain, lack of energy, shortness of breath, fevers, weight loss, coughing and blood in the urine. Scores are measured using a 5-point Likert scale, and higher total scores correspond to better HRQoL.

(ii) The EORTC is a cancer-specific questionnaire consisting of function and symptom scales which are scored from 0 to 100. Higher scores on the functional scales reflect better HRQoL, and higher scores on the symptom scales reflect worse symptoms.

(iii) The EQ-5D-3L is used to assess general HRQoL in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 3 levels of response. Responses are used to generate health state index scores, with higher scores indicating better health. The second part of this questionnaire consists of the visual analogue scale (VAS), where patients rate their perceived health on a scale of 0 (worst imaginable health) to 100 (best imaginable health).

HRQoL assessments were performed at baseline, Day 1 of each subsequent treatment cycle, and at the off-treatment visit (30 days after final dose of study drug). As stated in the Eisai HRQoL outcomes study report,[73] completion rates (at least one complete score; FAS population) for all HRQoL instruments were notably different for the two trial arms. The completion rates for any instrument declined below [redacted]% at Cycle 26 for patients treated with lenvatinib plus pembrolizumab, and at Cycle 12 for patients treated with sunitinib. The completion rates at the off-treatment visit were [redacted]% for patients treated with lenvatinib plus pembrolizumab and [redacted]% for patients treated with sunitinib. Compliance was generally greater than [redacted]% in both trial arms during early cycles of treatment; however, at the off-treatment visit compliance had dropped to approximately [redacted]%.

Change from baseline in FKSI-DRS, EORTC QLQ-C30 and EQ-5D-3L score

For each CLEAR trial arm, the overall least squares (LS) mean change was calculated as an average of the change between baseline and each of the time points up until the mean follow up time (Cycle 15). The difference between the arms in the overall LS mean change was interpreted as clinically meaningful if it exceeded the pre-defined minimally important difference (MID) for that outcome. As reported by Motzer et al 2021b[82] and in the MSD CS,[51] only a few statistically significant differences were identified between treatment arms for the overall LS mean change in the EORTC QLQ-C30. Lenvatinib and pembrolizumab resulted in higher physical functioning scores and lower fatigue, dyspnea and constipation scores than

sunitinib; none of these differences exceeded the pre-defined MID. No statistically significant differences were identified between treatment arms for the overall LS mean change in the FKSI-DRS or EQ-5D-3L.

Time to first deterioration and time to definitive deterioration analyses

A deterioration event was defined as a detrimental change in HRQoL score from baseline that exceeded the MID value for that outcome. Two time points were assessed: time to first deterioration (TTD), as the earliest deterioration event during treatment, and time until definitive deterioration (TuDD), as the earliest deterioration event during treatment where there was no subsequent recovery above the deterioration threshold or no subsequent HRQoL data. As reported by Motzer et al 2021b[82] and in the Eisai CS[15] (Appendix M3.1), statistically significant differences were identified in the median TTD in favour of lenvatinib plus pembrolizumab versus sunitinib for the following EORTC QLQ-C30 scales: physical functioning, appetite loss and dyspnea, and the EQ-5D-VAS score. As reported in the Eisai CS[15] (Appendix M3.2), [redacted]. It was not possible to compare the values for the cognitive domain, or constipation and financial difficulties symptom scales, due to no estimable values in one or both of the treatment arms.

Summary of response status during treatment

The proportions of participants in each treatment arm who, relative to baseline, had improved or deteriorated, or who were stable on treatment, were assessed. As reported in the Eisai CS[15] (Appendix M3.3), for all HRQoL scales, [redacted]

3.9 Interpretation of evidence from the CLEAR trial

The CLEAR trial is a well-designed trial and results are generalisable to NHS clinical practice. However, the trial only provided evidence for the comparison of treatment with lenvatinib plus pembrolizumab versus one of the relevant comparators (sunitinib) identified in the final scope[27] issued by NICE. Clinical effectiveness data were available from two data cuts: IA3 (PFS, ORR and AEs) and an updated OS analysis (OS).

CLEAR trial efficacy results suggested that PFS and ORR were statistically significantly improved for patients treated with lenvatinib plus pembrolizumab compared with patients treated with sunitinib (all-risk population, intermediate/poor risk subgroup and favourable risk subgroup). For the intermediate/poor risk and favourable risk subgroups, PFS and ORR differences favoured patients in the lenvatinib plus pembrolizumab arm; all PFS and ORR results were statistically significant, and clinical advice to the AG was that they were also clinically meaningful.

For the all-risk population, OS results were difficult to interpret as the PH assumption was violated over the CLEAR trial follow-up period. Therefore, results should not be used to infer any statistically significant difference (or lack of statistically significant difference) for the comparison of treatment with lenvatinib plus pembrolizumab versus sunitinib. However, the CLEAR trial the OS survival rates at 12 months, 18 months, 24 months and 36 months all favour lenvatinib plus pembrolizumab versus sunitinib.

The CLEAR trial OS PH assumption was not violated for the intermediate/poor risk and favourable risk subgroups. The HR results from the updated OS analysis showed a statistically significant improvement for patients treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib for the intermediate/poor risk subgroup and the all-risk population; there were too few events in the favourable risk subgroup for robust OS conclusions to be drawn.

OS results can be influenced by subsequent anti-cancer treatments received by patients on disease progression. Eisai[15] carried out a treatment-switching analysis to test whether adjusting for the effect of subsequent treatments affected OS results. Results, only generated for the all-risk population, continued to show a statistically significant advantage for lenvatinib plus pembrolizumab versus sunitinib. In addition to a treatment-switching analysis to test whether adjusting for the effect of subsequent treatment affected OS results, Eisai[15] also conducted post-hoc analyses that examined OS for patients who did and did not receive subsequent treatment separately. The PH assumption was violated for patients who received subsequent treatments; the K-M data suggested an

[redacted] and patients treated with sunitinib experienced an OS benefit. Clinical advice to the AG is that patients who do not receive subsequent treatments are a heterogeneous group and, therefore, the results from this post-hoc analysis are difficult to interpret.

More patients treated with lenvatinib plus pembrolizumab experienced Grade ≥3 AEs than patients treated with sunitinib.[15,51,67] Nonetheless, both companies[15,51] highlighted that evidence from the CLEAR trial showed that, in general, lenvatinib plus pembrolizumab was well tolerated in patients with aRCC; generally, the AEs experienced by patients were consistent with the known safety profile of each drug. However, both companies[15,51] highlighted that there was a higher than expected incidence of Grade 1 and Grade 2 hypothyroidism, a known AE associated with both lenvatinib and pembrolizumab.[51] MSD[51] also highlighted there was a higher than expected incidence of Grade ≥3 hepatic AEs.

When compared to treatment with sunitinib, treatment with lenvatinib plus pembrolizumab appeared to neither improve or worsen HRQoL, as measured by the FKSI-DRS, EORTC QLQ-C30 and EQ-5D-3L instruments.[15,51,82]

As the CLEAR trial only provided clinical effectiveness evidence for the comparison of lenvatinib plus pembrolizumab versus sunitinib, it was necessary to generate indirect evidence to compare lenvatinib plus pembrolizumab versus other relevant comparators (see Section 4).

4 ASSESSMENT OF CLINICAL EFFECTIVENESS: INDIRECT EVIDENCE

4.1 Limited direct clinical effectiveness evidence

The only direct clinical effectiveness evidence available for the comparison of lenvatinib plus pembrolizumab for patients with untreated aRCC versus any comparator listed in the final scope[27] issued by NICE is from the CLEAR trial (versus sunitinib). To allow comparisons between lenvatinib plus pembrolizumab versus other relevant comparators indirect comparisons were required.

4.2 Eisai and MSD indirect comparisons

A summary and AG critique of the Eisai and MSD NMA statistical approaches are provided in Appendix 7 (Section 9.7, Table 98 and Table 99 respectively). The AG considered that the NMA statistical approaches used by Eisai and MSD were appropriate and appeared to be correctly implemented. However, neither company presented comparative evidence for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab for the intermediate/poor risk subgroup.

The two companies presented results from two different approaches to carrying out NMAs (Bayesian HR and fractional polynomial [FP]) for PFS and OS (Eisai CS[15] and Appendix D.4; MSD CS[51] and Appendix M).

4.3 AG methodological approach to NMAs: feasibility assessment

4.3.1 Studies assessed by the AG for potential inclusion in NMAs

Any study identified by the AG searches for direct evidence that appeared to be designed as an RCT of any drug used to treat adults with untreated aRCC was tagged as 'RCT' within Covidence (n=1129 records). These records were then examined by SN to confirm that the study design and the study population were of interest (i.e., RCTs of adults with untreated aRCC) and to identify the drug treatments included in the studies.

In addition, any study previously identified by the AG searches that appeared to be an NMA of RCTs of drugs used to treat adults with untreated aRCC was tagged as a 'network meta-analysis' within Covidence (n=36, published from 2009 to 2021). The AG examined the reference lists and network structures of recently published NMAs, i.e., those published since 2020, (n=10[56,87-95]) to assess the feasibility of constructing suitable networks for each outcome listed in the final scope[27] issued by NICE.

In total, the AG identified ten RCTs[23,67,96-103] of drug treatments for adults with untreated aRCC that were potentially eligible for inclusion in the AG NMAs.

4.3.2 AG consideration of specific networks

The AG assessment of the feasibility of constructing specific networks considered the following:

- the feasibility of constructing a 'suitable connected network' of relevant treatments for each outcome and for each risk subgroup
- the clinical and methodological heterogeneity of the included studies in terms of (a) study population, (b) interventions and comparators, (c) outcome measures (OS, PFS, ORR, safety and HRQoL), and (d) study quality.

For each outcome listed in the final scope[27] issued by NICE, the AG initially considered a 'suitable connected network' to be a network which only included RCTs of comparators listed in the final scope[27] issued by NICE for the following risk groups, as defined in the IMDC criteria:[13]

- intermediate/poor risk subgroup (network nodes: lenvatinib plus pembrolizumab, cabozantinib and nivolumab plus ipilimumab)
- favourable risk subgroup (network nodes: lenvatinib plus pembrolizumab, sunitinib, pazopanib and tivozanib)
- the all-risk population (network nodes: lenvatinib plus pembrolizumab, sunitinib, pazopanib, and tivozanib)

However, where it was not possible to construct a connected network using only the comparators listed in the final scope[27] issued by NICE, the AG considered introducing additional treatments (i.e., nodes), such as interferon-alpha and sorafenib to form connections. The AG considered that it was not appropriate to attempt to connect comparators listed in the final scope[27] issued by NICE via two or more non-relevant treatments as more uncertainty is introduced with the addition of each irrelevant node.

Following assessment of suitable network structures and consideration of the availability of outcome data from each of the ten RCTs,[23,67,96-103] the AG excluded two trials[23,98] (reasons are listed in Table 27) in at least one of the AG NMAs.

Table 27 RCTs included/excluded from AG NMAs

RCT	Randomised treatments	Notes
RCTs included in the AG NMAS		
CABOSUN[96]	• Cabozantinib • Sunitinib	Included in PFS, OS, ORR and safety NMAs for intermediate/poor risk subgroup only
CheckMate 214[99]	• Nivolumab + ipilimumab • Sunitinib	Included in PFS, OS and ORR NMAs for intermediate/poor risk subgroup only
CLEAR trial	• Lenvatinib + pembrolizumab • Sunitinib	Included in PFS, OS, ORR and safety NMAs for favourable risk and intermediate/poor risk subgroup and all-risk population
COMPARZ[100]	• Pazopanib • Sunitinib	Included in PFS, OS, ORR and safety NMAs for favourable risk subgroup and all-risk population OS data taken from final OS analysis[104]
CROSS-J-RCC[103]	• Sunitinib • Sorafenib	Included in PFS NMAs for all-risk population only
SWITCH[97]	• Sunitinib • Sorafenib	Included in PFS NMAs for all-risk population only
SWITCH II[102]	• Pazopanib • Sorafenib	Included in PFS NMAs for all-risk population only
TIVO-1[101]	• Tivozanib • Sorafenib	Included in PFS NMAs for all-risk population only
RCTs not included in the AG NMAs		
Escudier 2009[98]	• Interferon-alpha • Sorafenib	OS data not reported so cannot be included in OS NMAs Excluded from PFS, ORR and safety NMAs as neither treatment is a relevant comparator and this trial data cannot be used to connect relevant comparators to the network
Motzer 2007[23]	• Interferon-alpha • Sunitinib	Excluded from PFS, OS, ORR and safety NMAs as interferon-alpha is not a relevant comparator and this trial data cannot be used to connect relevant comparators to the network

AG=Assessment Group; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial

Details about the comparators, and a list of the RCTs that provided information to inform the AG PFS, OS and ORR NMAs for the intermediate/poor risk and favourable risk subgroups and all-risk population are presented in Table 28. The AG PFS, OS and ORR network diagrams are presented in Appendix 8 (Section 9.8, Figure 31 to Figure 32) and the outcome data used to populate the AG PFS, OS and ORR NMAs are presented in Appendix 9 (Section 9.9, Table 100 to Table 102).

The AG considered that the different definitions of AEs reported within the trials (i.e., treatment-emergent, treatment-related or all-cause AEs for Grade ≥3 AEs and discontinuations due to AEs) made it difficult to interpret any relative differences between treatments. Furthermore, safety data were not reported separately for subgroups of interest, most notably for the intermediate/poor risk subgroup in the CheckMate 214 trial,[99] and for the

favourable risk subgroup in any trials other than the CLEAR trial. AE data were unavailable for the previously untreated patients in the TIVO-1 trial.[101]

Nonetheless, the AG performed NMAs for Grade ≥3 AEs where either treatment-emergent or all-cause AEs were reported (see Appendix 8, Section 9.8, Figure 30 and Figure 32 for network diagrams and Appendix 9, Section 9.9, Table 103 for outcome data used to populate these NMAs). The AG also considered performing NMAs for discontinuations due to AEs comparing (a) discontinuations of both lenvatinib and pembrolizumab and (b) discontinuations of either lenvatinib or pembrolizumab versus relevant comparators. However, it appeared that only data for (b) were available from the CLEAR trial for risk subgroups (see Table 24). Further, when summing the total of AEs from the two subgroups, there were still many AEs in the all-risk population that appeared to be unaccounted for according to subgroup. i.e., summing the numbers of discontinuations due to AEs in the intermediate/poor and favourable risk subgroups from Table 24 did not sum to the total reported for the all-risk population in Table 23. Therefore, the AG considered the limitations of the data for discontinuations due to AEs prevented meaningful NMAs for discontinuations due to AEs being performed.

It was not possible for the AG to perform any HRQoL NMAs due to the heterogeneity of the HRQoL outcome scales used in the included trials and the sparsity of reported data (i.e., 95% CIs not reported and data not reported separately for subgroups of interest).

Table 28 Summary of AG OS, PFS and ORR NMAs

Outcome	Risk group	Comparators[a]	Trials	Notes[b]
PFS	Intermediate/poor	• Lenvatinib + pembrolizumab • Sunitinib* • Cabozantinib • Nivolumab + ipilimumab	• CLEAR • CABOSUN[96] • CheckMate 214[99]	• BIRC assessed PFS data used for all trials • IMDC risk subgroup data used for all trials Separate NMAs conducted using: • PFS assessed by FDA censoring rule used for the CLEAR trial (primary analysis) • PFS assessed by EMA censoring rule used for the CLEAR trial (sensitivity analysis)
	Favourable	• Lenvatinib + pembrolizumab • Sunitinib • Pazopanib	• CLEAR • COMPARZ[100]	• BIRC assessed PFS data used for both trials Separate NMAs conducted using: • PFS assessed by FDA censoring rule used for the CLEAR trial, IMDC risk subgroup data used for CLEAR trial and MSKCC risk subgroup data used for COMPARZ trial (primary analysis) • PFS assessed by EMA censoring rule used for the CLEAR trial, IMDC risk subgroup data used for CLEAR trial and MSKCC risk subgroup data used for COMPARZ trial (sensitivity analysis). • PFS assessed by FDA censoring rule used for the CLEAR trial, MSKCC risk subgroup data used for both trials (sensitivity analysis) • PFS assessed by EMA censoring rule used for the CLEAR trial, MSKCC risk subgroup data used for both trials (sensitivity analysis)
	All-risk	• Lenvatinib + pembrolizumab • Sunitinib • Pazopanib • Tivozanib • Sorafenib*	• CLEAR • COMPARZ[100] • CROSS-J-RCC[103] • SWITCH[97] • SWITCH II[102] • TIVO-1[101]	• BIRC assessed PFS data used for the CLEAR, COMPARZ and TIVO 1 trials • Investigator assessed PFS data used for CROSS-J-RCC and SWITCH trials. PFS assessment method not stated for SWITCH II trial • PFS on first-line treatment data used for the CROSS-J-RCC, SWITCH and SWITCH II trials[c] • Untreated subgroup data used for the TIVO-1 trial[d] Separate NMAs conducted using: • PFS assessed by FDA censoring rule used for the CLEAR trial (primary analysis) • PFS assessed by EMA censoring rule used for the CLEAR trial (sensitivity analysis)
OS	Intermediate/poor	• Lenvatinib + pembrolizumab • Sunitinib* • Cabozantinib • Nivolumab + ipilimumab	• CLEAR • CABOSUN[96] • CheckMate 214[99]	IMDC risk subgroup data used for all trials

Outcome	Risk group	Comparators[a]	Trials	Notes[b]
	Favourable	• Lenvatinib + pembrolizumab • Sunitinib • Pazopanib	• CLEAR • COMPARZ[100]	Separate NMAs conducted using: • IMDC risk subgroup data used for CLEAR trial and MSKCC risk subgroup data used for COMPARZ trial (primary analysis) • MSKCC risk subgroup data used for both trials (sensitivity analysis) • OS data taken from final OS analysis reported by Motzer et al 2014[104]
	All-risk	• Lenvatinib + pembrolizumab • Sunitinib • Pazopanib	• CLEAR • COMPARZ[100]	• OS data taken from final OS analysis reported by Motzer et al 2014[104]
ORR	Intermediate/poor	• Lenvatinib + pembrolizumab • Sunitinib* • Cabozantinib • Nivolumab + ipilimumab	• CLEAR • CABOSUN[96] • CheckMate 214[99]	• BIRC assessed ORR data used for all trials • IMDC risk subgroup data used for all trials
	All-risk	• Lenvatinib + pembrolizumab • Sunitinib • Pazopanib	• CLEAR • COMPARZ[100]	BIRC assessed ORR data used for both trials
Grade≥3 AEs	Intermediate/poor	• Lenvatinib + pembrolizumab • Sunitinib* • Cabozantinib	• CLEAR • CABOSUN[96]	• IMDC risk subgroup data used for both trials
	All-risk	• Lenvatinib + pembrolizumab • Sunitinib • Pazopanib	• CLEAR COMPARZ[100]	None

[a] Comparators marked with a star (*) are not relevant comparators for the population or subgroup but are included within the network to form connections with relevant comparators
[b] AG preferences for data to include in NMAs: BIRC assessed PFS and ORR data (investigator assessed PFS or ORR data included in BIRC assessed PFS or ORR data not reported), PFS assessed by the FDA censoring rule from the CLEAR tria (PFS assessed by the EMA censoring rule from the CLEAR trial included in sensitivity analysis), risk subgroup data according to IMDC criteria (risk subgroup data according to MSKCC criteria included if IMDC risk subgroup data not reported and/or risk subgroup data according to MSKCC criteria from the CLEAR trial in sensitivity analysis)
[c] The CROSS-J-RCC,[103] SWITCH[97] and SWITCH II[102] trials had a sequential design (patients received first-line therapy with the treatment they were randomised to, and patients who discontinued first-line therapy due to disease progression or toxicity received the other trial treatment second line). PFS data for first-line treatment is extracted
[d] The TIVO-1 trial[101] recruited patients with untreated mRCC and patients who had received prior systematic therapy for mRCC. OS data for the untreated subgroup are extracted from TA512[32]
AE=adverse events; AG=Assessment Group; BIRC=blinded independent review committee; EMA=European Medicines Agency; FDA=Food and Drug Administration; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; PFS=progression-free survival; ORR=objective response rate; OS=overall survival

4.3.3 AG methodological approach: intermediate/poor risk subgroup

The AG was able to construct a suitable network for PFS, OS and ORR including the two relevant comparators for this subgroup (cabozantinib and nivolumab plus ipilimumab); these networks also included sunitinib, a comparator common to the three included RCTs[67,96,99] (Appendix 8; Section 9.8, Figure 29). Safety data were not reported for the intermediate/poor risk subgroup in the CheckMate 214 trial,[99] therefore the AG networks for Grade≥3 AEs due to AEs for this subgroup included only cabozantinib (and sunitinib) as comparators (Appendix 8; Section 9.8, Figure 32).

4.3.4 AG methodological approach: IMDC/MSKCC favourable risk subgroup

The AG PFS and OS networks only included sunitinib and pazopanib as comparators (Figure 30). It was not possible to connect tivozanib to the PFS and OS networks as the only identified trial of tivozanib (TIVO-1 trial[101]) recruited a mixed population of untreated and previously treated patients with metastatic RCC and did not report PFS and OS data separately for the subgroup of untreated patients.

Only the CLEAR trial reported ORR and safety data for the favourable risk subgroup; therefore, it was not possible to carry out NMAs of ORR or safety outcomes for lenvatinib plus pembrolizumab versus pazopanib or tivozanib.

4.3.5 AG methodological approach: all-risk population

The AG PFS all-risk population network included all relevant comparators (sunitinib, pazopanib and tivozanib). This network was constructed by including sorafenib as a node and, by using PFS data relating to first-line treatment from two trials (CROSS-J-RCC[103] and SWITCH[97]) of sunitinib versus sorafenib that used a sequential design to connect tivozanib to the network (Appendix 8; Section 9.8, Figure 31).

It was not possible to connect tivozanib to the OS network as OS data from patients receiving first-line treatment were not available from the CROSS-J-RCC[103] and SWITCH[97] trials and no trials were identified that allowed tivozanib to be included in the OS network via a single additional treatment node. The AG did not consider that it was appropriate to attempt to connect tivozanib to the OS network via two or more non-relevant treatments which were not relevant comparators due to the increased level of uncertainty.

The AG was also unable to connect tivozanib to the ORR network as the only identified tivozanib trial (TIVO-1 trial[101]) recruited a mixed population of untreated and previously treated

patients with metastatic RCC and did not report ORR data separately for the subgroup of untreated patients.

Therefore, for the all-risk population, the AG OS, ORR, Grade≥3 AEs networks only included sunitinib and pazopanib as comparators (Appendix 8; Section 9.8, Figure 30). The AG was not able to indirectly compare the clinical effectiveness of lenvatinib plus pembrolizumab versus tivozanib for OS, ORR or Grade ≥3 AEs for patients in the all-risk population.

4.3.6 Quality assessment of the trials included in AG NMAs

The quality assessment of the CLEAR trial and the seven other RCTs[96,97,99-103] included in the AG NMAs is presented in Appendix 10 (Section 9.10; Table 104).

The AG considers that most of the trials included in the AG NMAs were of good methodological quality. However, due to insufficient information available, the AG was unable to assess the robustness of the randomisation procedures and whether robust procedures were in place to prevent patients or investigators predicting allocation to treatment in one trial.[102] All of the trials were open-label; however, the CLEAR trial and four other trials[96,99-101] reported the use of blinded independent review of radiologic outcomes.

4.3.7 AG summary of patient and trial characteristics and assessment of heterogeneity

Summaries of the design, demographic characteristics and the IMDC and MSKCC risk subgroups of patients enrolled in the CLEAR trial and other seven RCTs[96,97,99-103] included in the AG NMAs are provided in Appendix 11 (Section 9.11, Table 105 and Table 106).

In addition to the CLEAR trial, five of the trials were phase III RCTs[97,99,100,102,103] and two were phase II RCTs.[96,101] Three trials[97,102,103] used a sequential design in which patients were randomised to first-line treatment, and patients who discontinued first-line treatment due to disease progression or toxicity received the alternative trial treatment as a second-line therapy; only data from these trials relating to first-line treatment were extracted. All of the RCTs were designed as open-label trials (Appendix 11 , Section 9.11; Table 104); the CLEAR trial and four other RCTs[96,99-101] used blinded independent review for radiologic outcomes (i.e., PFS and ORR), two RCTs[97,103] used unblinded investigator assessment, and the authors of one RCT[102] did not report method of radiologic outcome assessment.

Two trials[101,103] recruited patients with metastatic RCC only. The CLEAR trial and five other RCTs[96,97,99,100,102,103] recruited untreated patients only, while one trial (TIVO-1[101]) recruited a mix of untreated patients (70%) and patients who had received previous systemic therapy (30%); data were extracted from the TIVO-1[101] trial for the untreated subgroup only.

The CLEAR trial and five other RCTs[96,99-101,103] recruited patients with clear cell RCC only, while 13% of recruited patients in the other two trials[97,102] had non-clear cell histology. Results were not reported separately in the SWITCH trials[97,102] for patients with clear cell histology.

The ages of recruited patients were similar across the RCTs (Appendix 11; Section 9.11,Table 105 and Table 106); across trial arms, the median age ranged from 61 years in the CLEAR trial and two other trials,[99,100] to 68 years.[102] All trials recruited a majority of male patients (71%[99,100] to 84%[96,103]).

In addition to the CLEAR trial, three RCTs[99-101] recruited patients irrespective of disease risk according to IMDC or MSKCC criteria. However, data from the CheckMate 214 trial[99] (nivolumab plus ipilimumab versus sunitinib) were available for the intermediate/poor risk population and were used in the AG NMAs. The cabozantinib RCT[96] only recruited patients with intermediate or poor risk disease. Three RCTs[97,102,103] were designed to only recruit patients with favourable or intermediate risk disease by MSKCC criteria.

Only the CLEAR trial reported disease risk classifications according to both IMDC and MSKCC risk criteria (Appendix 11; Section 9.11, Table 106). Two other RCTs[96,99] reported the proportion of patients classified by IMDC risk subgroup and four other RCTs[97,100,102,103] reported the proportion of patients classified by MSKCC risk subgroup. The remaining RCT (TIVO-1[101]) did not report risk of disease according to IMDC or MSKCC criteria for the subgroup of untreated patients. The proportions of patients classified within each disease risk subgroup according to either IMDC or MSKCC criteria varied across RCTs (Appendix 11; Section 9.11, Table 106).

The following differences between RCTs may have introduced heterogeneity into the AG NMAs:

- populations characteristics (i.e., disease stage [locally advanced and/or metastatic RCC], disease risk criteria and proportions of patients in each risk subgroup)
- PFS and ORR assessment methods (BIRC, investigator, or not reported) and types of AEs (all-cause AE or TEAE)
- patient baseline characteristics (Appendix 11; Section 9.11, Table 105)
- differences in median PFS, OS, ORR abd Grade ≥3 follow-up times (Appendix 9; Section 9.9, Table 100 to Table 103).

The AG is not aware of any statistical methods that can be used to adjust for these differences in patient baseline characteristics and trial design.

4.3.8 AG assessment of proportional hazards assumptions

For time-to-event outcomes presented as HRs (i.e., PFS and OS), the AG assessed the validity of the within trial PFS and OS PH assumptions, for each of the groups (intermediate/poor risk and favourable risk subgroups and all-risk population). The AG PH assessments were carried out by examining the figures (Schoenfeld residuals plots or log cumulative hazard plots) and statistical test results (e.g., Grambsch-Therneau test[105]) presented in the Eisai CS[15] (Section 5.3.1 and Section 5.3.2) and in the Eisai response to clarification, questions A1 and A2.

Data from the CheckMate214 trial[99] (nivolumab plus ipilimumab versus sunitinib) were not included in the company NMAs. The AG, therefore, digitised the published intermediate/poor risk subgroup PFS and OS 42-month K-M data[99] and assessed proportionality by plotting Schoenfeld residuals and performing a Grambsch-Therneau test.[105] The AG OS and PFS PH assessments are presented in Appendix 12 (Section 9.12). Violations of the PH assumption within the studies included in the AG NMAs are listed in Table 29.

Table 29 PH violations within the studies included in the AG NMAs

Risk group	PFS	OS
Intermediate/poor subgroup	CheckMate 214 trial[99]	None
Favourable subgroup	PH could not be assessed within the COMPARZ trial[100] for PFS, or OS[104] (pazopanib versus sunitinib) as no K-M data were presented	
All-risk population	TIVO-1 trial[101]	CLEAR trial

K-M=Kaplan Meier; OS=overall survival; PH=proportional hazards; PFS=progression free survival

If the PH assumption holds, a HR represents an average of the relative treatment effect during the trial follow-up period[106] (or trials, in the context of an NMA) and the HR is proportional over time.[107] When the PH assumption is violated, this means that the HR (whether from a trial or from an NMA including data from one or more trials with PH violations) is not applicable to all time points across the trial follow-up periods. If the PH assumption holds, then it may not be unreasonable to assume that the estimated HRs is valid beyond the trial follow-up periods. However, when the PH assumption is violated, estimated HRs may not produce accurate projections of relative survival between treatment arms beyond the observed trial follow-up periods.

Some PH test results showed (Table 29) that PFS and OS outcome hazards were not proportional. Within any network, if any within trial hazards are not proportional, then Bayesian HR NMA results (i.e., the HRs and 95% CrIs) should not be used to infer statistically significant differences (or lack of statistically significant difference) between treatments.

Where violations of the PH assumption are demonstrated, alternative flexible modelling approaches for NMA which relax the PH assumption, including FP NMAs, have been proposed to aid decision making.[108,109] However, interpretation of the estimates provided by these complex modelling techniques can be difficult and often are not intuitive.[108,109]

The 'best-fitting' FP model (or alternative flexible model) for an NMA which is defined according to model fit statistics, such as the Deviance Information Criterion (DIC), reflects the model which most closely captures the shape of the observed data. However model fit statistics do not provide information about whether a model is a good fit to the data or whether the estimates generated by the model, including projections of results beyond the follow-up times of trials included in the NMA, are clinically plausible.[109] Furthermore, flexible models which appear similar according to model fit (i.e., according to DIC statistics) may generate very different long-term survival estimates; advice from the Medical Research Council Biostatistics Unit[110] is that, "if the difference in DIC is, say, less than 5 and the models make very different inferences, then it could be misleading just to report the model with the lowest DIC" Due to these limitations, the AG does not consider that it is appropriate to use the results of FP NMAs for clinical decision making.

The AG considers that the limitations associated with the interpretation of results from FP NMAs are greater than the limitations of interpretation of the Bayesian HR NMA results when the PH assumption is violated. In addition, for the intermediate/poor risk subgroup (the largest of the two risk subgroups considered) there was no violation of the OS PH assumption within any of the trials included in the AG OS network.

The AG carried out PFS, OS and ORR NMAs for the intermediate/poor risk and the favourable risk subgroups and all-risk population. However, the AG emphasises that where violations of the PH assumption were demonstrated, HRs and 95% CrIs should not be used to infer any statistically significant difference (or lack of statistically significant difference) for the treatment comparisons.

4.3.9 AG statistical approach to Bayesian HR NMAs

The AG performed PFS, OS and ORR NMAs using a Bayesian framework. These were carried out using the multinma R package.[111] This approach is in line with Decision Support Unit (DSU) guidance (documents 2, 3 and 4[112-114]). All results were generated using 100,000 iterations on 3 chains after a burn-in of 100,000 and vague prior distributions were used for intercept, treatment and heterogeneity (for random-effects [RE] models only) parameters.

The AG performed NMAs using fixed-effects (FE) and RE models. As convergence issues occurred due to sparse data, RE NMA results were unusable. Due to a lack of published information to select informative prior distributions to improve convergence of RE models, the AG has only presented results from FE models in the main body of this AG report. The AG has described where important clinical or statistical heterogeneity between RCTs included in the NMA may have had an impact on how NMA results can be interpreted.

For PFS, the only outcome with a closed loop present within the network, the AG assessed inconsistency in the NMAs by applying an unrelated mean effects model[114] and by comparing model fit statistics of inconsistency models with consistency models.

Treatment effect estimates for direct and indirect clinical effectiveness evidence are presented as HRs for time-to-event data (i.e., PFS and OS) and ORs for dichotomous data (i.e., ORR). All treatment effect estimates are presented with 95% CrIs.

An example of the statistical code used by the AG to perform PFS, OS, ORR and safety NMAs is provided in Appendix 13 (Section 9.13).

4.4 Results of the AG NMAs

Results of the AG FE NMAs are presented in this section and results of the AG RE NMAs are presented in Appendix 14 (Section 9.14; Table 108, Table 109 and Table 110 for PFS, OS and ORR respectively and Table 113 for Grade ≥3 AEs). The AG RE NMAs were associated with convergence issues; it is likely that these issues arose due to sparse networks (i.e., a small number of included trials). Due to the convergence issues, 95% CrIs around the HRs are very wide and unstable, these RE NMA results should not be used to inform clinical decision making.

When interpreting AG FE NMA results, it should be noted that the results do not account for the observed heterogeneity between the trials (Section 4.3.7).

4.4.1 Progression-free survival: AG FE NMAs

The AG PFS NMA results for all pairs of treatments for the intermediate/poor risk subgroup and the IMDC/MSKCC favourable risk subgroup and all-risk population are presented in Table 30.

The AG NMAs included PFS data that were assessed using FDA censoring rules. The AG PFS NMA sensitivity analysis included CLEAR trial PFS data assessed using the EMA censoring rules and data from all other included trials using FDA censoring rules (Appendix 14; Section 9.14, Table 112). Results from the two AG PFS NMAs were similar.

Table 30 Results from the AG PFS FE NMAs by risk group (FDA censoring rules)

Treatment	Comparator	Fixed effects HR (95% CrI)[a]
Intermediate/poor risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.36 (0.28 to 0.46)
Lenvatinib + pembrolizumab	Cabozantinib	0.75 (0.45 to 1.25)
Lenvatinib + pembrolizumab	Nivolumab plus ipilimumab	0.48 (0.35 to 0.66)
Cabozantinib	Sunitinib	0.48 (0.31 to 0.74)
Nivolumab plus ipilimumab	Sunitinib	0.75 (0.62 to 0.90)
Nivolumab plus ipilimumab	Cabozantinib	1.57 (0.97 to 2.51)
IMDC/MSKCC favourable risk subgroup[b]		
Lenvatinib + pembrolizumab	Sunitinib	0.41 (0.28 to 0.60)
Lenvatinib + pembrolizumab	Pazopanib	0.40 (0.21 to 0.75)
Pazopanib	Sunitinib	1.02 (0.63 to 1.68)
All-risk population		
Lenvatinib + pembrolizumab	Sunitinib	0.39 (0.32 to 0.48)
Lenvatinib + pembrolizumab	Pazopanib	0.34 (0.26 to 0.43)
Lenvatinib + pembrolizumab	Tivozanib	0.50 (0.34 to 0.73)
Lenvatinib + pembrolizumab	Sorafenib	0.38 (0.29 to 0.50)
Pazopanib	Sunitinib	1.16 (1.01 to 1.34)
Tivozanib	Sunitinib	0.78 (0.57 to 1.07)
Sorafenib	Sunitinib	1.03 (0.86 to 1.22)
Pazopanib	Tivozanib	1.49 (1.07 to 2.05)
Pazopanib	Sorafenib	1.13 (0.94 to 1.35)
Tivozanib	Sorafenib	0.76 (0.58 to 1.00)

[a] HR<1 favours the treatment over the comparator
[b] Favourable risk subgroup data from the COMPARZ trial[100] are defined by MSKCC criteria
AG=Assessment Group; CrI=credible interval; FDA=Food and Drug administration; FE=fixed effects; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloane Keating Cancer Center; NMA=network meta-analysis; PFS=progression-free survival
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 100) of this AG report

Due to PH violations or uncertainty regarding the validity of the PH assumption, the HRs and 95% CrIs shown in Table 30 cannot be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons (Section 4.3.8).

4.4.2 Overall survival: AG FE NMAs

AG OS FE NMA results for all pairs of treatments for the intermediate/poor risk subgroup and the IMDC/MSKCC favourable risk subgroup and all-risk population are presented in Table 31.

Table 31 Results from AG OS fixed effects NMAs by risk group

Treatment	Comparator	Fixed effects HR (95% CrI)[a]
Intermediate/poor risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.62 (0.46 to 0.83)
Lenvatinib + pembrolizumab	Cabozantinib	0.78 (0.47 to 1.28)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.94 (0.66 to 1.32)
Cabozantinib	Sunitinib	0.80 (0.53 to 1.21)
Nivolumab + ipilimumab	Sunitinib	0.66 (0.55 to 0.79)
Nivolumab + ipilimumab	Cabozantinib	0.83 (0.53 to 1.30)
IMDC/MSKCC favourable risk subgroup[b]		
Lenvatinib + pembrolizumab	Sunitinib	1.22 (0.66 to 2.25)
Lenvatinib + pembrolizumab	Pazopanib	1.38 (0.69 to 2.80)
Pazopanib	Sunitinib	0.88 (0.63 to 1.23)
All-risk population		
Lenvatinib + pembrolizumab	Sunitinib	0.72 (0.55 to 0.94)
Lenvatinib + pembrolizumab	Pazopanib	0.79 (0.58 to 1.06)
Pazopanib	Sunitinib	0.92 (0.79 to 1.07)

[a] HR<1 favours the treatment over the comparator
[b] Favourable risk subgroup data from the COMPARZ trial[100] including final OS analysis[104] used in the NMA are defined by MSKCC criteria
AG=Assessment Group; CrI=credible interval; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloane Keating Cancer Center; NMA=network meta-analysis; OS=overall survival
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 101) of this AG report

In the intermediate/poor risk subgroup, a numerical advantage in terms of OS was shown for lenvatinib plus pembrolizumab versus cabozantinib (HR=0.78, 95% CrI: 0.47 to 1.28) and versus nivolumab plus ipilimumab (HR=0.94, 95% CrI: 0.66 to 1.32). However, neither of these numerical advantages was statistically significant. No violations of the PH assumption were observed for OS in this subgroup (Section 4.3.8).

Due to PH violations or uncertainty regarding the validity of the PH assumption, the AG OS NMA HRs and 95% CrIs for the IMDC/MSKCC favourable risk subgroup and all-risk population (Table 31) cannot be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons (Section 4.3.8).

4.4.3 Objective response rate: AG FE NMAs

AG ORR NMA results for all pairs of treatments for the intermediate/poor risk subgroup and all-risk population and are presented in Appendix 14 (Section 9.14, Table 110).

In the intermediate/poor risk subgroup, ORR was statistically significantly higher for lenvatinib plus pembrolizumab compared to nivolumab plus ipilimumab (OR=3.19, 95% CrI: 1.95 to 5.26), however, no statistically significant difference was shown between lenvatinib plus pembrolizumab and cabozantinib (OR=2.46, 95% CrI: 0.84 to 6.82). In the all-risk population, ORR was statistically significantly higher for lenvatinib plus pembrolizumab compared to

sunitinib (OR=4.35, 95% CrI: 3.16 to 5.99) and compared to pazopanib (OR=3.22, 95% CrI: 2.14 to 4.85).

4.4.4 Grade ≥3 AEs: AG FE NMAs

AG Grade ≥3 FE NMA results for all pairs of treatments for the intermediate/poor risk subgroup and the all-risk population are presented in Appendix 14 (Section 9.14, Table 113).

In the intermediate/poor risk subgroup, for the comparison of lenvatinib plus pembrolizumab versus cabozantinib, there were no statistically significant differences in Grade ≥3 AEs (OR=1.80, 95% CrI: 0.79 to 4.10). In the all-risk population, there were statistically significantly more Grade ≥3 AEs for lenvatinib plus pembrolizumab compared to sunitinib (OR=1.84, 95% CrI: 1.28 to 2.66) and compared to pazopanib (OR=1.86, 95% CrI: 1.17 to 2.94).

4.4.5 AG sensitivity analysis NMAs: favourable risk subgroup

The COMPARZ trial[100] reported PFS and OS results (including a separately reported final OS analysis[104]) for the MSKCC favourable risk subgroup (not for the IMDC favourable risk subgroup). Therefore, the AG performed sensitivity analyses including MSKCC favourable risk subgroup data from the CLEAR trial and the COMPARZ trial[100] for the PFS (FDA and EMA censoring rules) and the OS NMAs (using COMPARZ trial final OS analysis[104]). Results of the MSKCC/MSKCC favourable risk subgroup PFS and OS NMAs are presented in Appendix 14 (Section 9.14; Table 111). Numerical results (i.e., HRs and 95% CrIs) were similar for the IMDC/MSKCC and the MSKCC/MSKCC favourable risk subgroup analyses, and also using the two different censoring rules.

4.4.6 Assessment of inconsistency for OS, PFS and ORR NMAs

AG assessments of inconsistency for PFS in the all-risk population, the only NMA with a closed loop present within the network, are presented in Appendix 15 (Section 9.15). Although a model which accounts for inconsistency in the NMA provides a better statistical model fit compared to a model which assumes consistency, results of AG FE NMAs which assumed consistency or accounted for inconsistency were very similar. Therefore, any inconsistency present between direct and indirect evidence for PFS in the all-risk population does not seem to have had an important impact on AG PFS NMA results.

Due to the lack of closed loops in any of the other AG networks, the consistency of indirect estimates of OS, ORR and AEs are unknown.

4.5 Interpretation of the indirect evidence from AG NMAs

The CLEAR trial only provided evidence for the comparison of lenvatinib plus pembrolizumab versus one of the relevant comparators (sunitinib). Therefore, indirect treatment comparisons were carried out to provide evidence for the comparison of lenvatinib plus pembrolizumab versus cabozantinib, nivolumab plus ipilimumab, pazopanib and tivozanib. The AG was unable to consider the impact of observed heterogeneity between the trials when carrying out NMAs.

Due to limited data availability and within trial PFS and OS PH violations (or uncertainty regarding the validity of the PH assumption), AG NMA HRs and 95% CrIs can only be used to infer a statistically significant OS difference for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab for patients in intermediate/poor risk subgroup. Results demonstrated a numerical advantage for lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab; these results were not statistically significant.

For any treatment comparisons that include sunitinib, pazopanib and tivozanib, where it is not possible to draw conclusions from NMA results about statistical significance, the AG highlights that previous NICE ACs[25,26,32,33] have concluded that sunitinib and pazopanib are of equivalent clinical effectiveness in the all-risk population and that: “At best, tivozanib may have a similar effect to sunitinib or pazopanib.”[32]

AG ORR NMA results for the intermediate/poor risk subgroup suggested that treatment with lenvatinib plus pembrolizumab only led to a statistically significant improvement in ORR versus nivolumab plus ipilimumab. It was not possible to generate results for the IMDC/MSKCC favourable risk subgroup due to data limitations. AG ORR NMA results for the all-risk population suggested that treatment with lenvatinib plus pembrolizumab led to a statistically significantly improvement in ORR versus sunitinib and versus pazopanib.

AG Grade ≥3 AE NMA results for the intermediate/poor risk subgroup suggested that treatment with lenvatinib plus pembrolizumab led to statistically significantly more Grade ≥3 AEs versus cabozantinib. It was not possible to generate results for the IMDC/MSKCC favourable risk subgroup. AG Grade ≥3 AE NMA results for the all-risk population suggested that treatment with lenvatinib led to statistically significantly more Grade ≥3 AEs versus sunitinib and versus pazopanib.

5 ASSESSMENT OF COST EFFECTIVENESS

5.1 Systematic review of existing cost effectiveness evidence

The AG conducted a systematic review of the economic literature to identify the existing evidence base assessing the cost effectiveness of treatment with lenvatinib plus pembrolizumab for patients with untreated aRCC versus five different treatments (sunitinib, pazopanib, tivozanib, cabozantinib and nivolumab plus ipilimumab).

The AG critiqued the companies' systematic reviews (Section 5.3) and the companies' economic analyses (Section 5.4). The companies' cost effectiveness results are presented and discussed by the AG in Section 5.5.

5.2 AG review of cost effectiveness evidence

5.2.1 AG search strategy

The AG searched the electronic sources listed in Table 32. Full search strategies are presented in Appendix 1. As lenvatinib was first approved for the treatment of aRCC by the FDA in 2016, the AG considered that searching databases from 2006 onwards would allow all relevant economic evidence to be identified. In addition, the reference lists of all included publications were assessed for relevance. The results of the searches were entered into an Endnote (X9 software package[64]) library, de-duplicated, and then exported into Covidence systematic review software.[65]

Table 32 Sources searched for cost effectiveness studies

Search type	Sources	Dates
Databases	MEDLINE, EMBASE, PubMed, CENTRAL, INAHTA, NHS EED, EconLit, CEA Registry	From 1 January 2006 to 11 October 2021
Trial registries	clinicaltrials.gov, ICTRP	From 1st January 2006 to 11 October 2021
Conference proceedings	ASCO, ASCO-GU, ESMO and HTAi, ISPOR	From 2019 to 22 November 2021
Websites	SMC, CADTH, HAS, PBAC	Searched on 22 November 2021

ASCO=American Society of Clinical Oncology; ASCO-GU=ASCO-Genitourinary; CADTH=Canadian Agency for Drugs and Technologies in Health; CEA Registry=Cost Effectiveness Analysis Registry; ESMO=European Society for Medical Oncology; HAS=Haute Autorité de Santé; HTAi=Health Technology Assessment international; ICTRP=International Clinical Trials Registry Platform; INAHTA=International Network of Agencies for Health Technology Assessment's International Health Technology Assessment Database; ISPOR=International Society for Pharmacoeconomics and Outcomes Research; NHS EED=National Health Service Economic Evaluation Database; PBAC=Pharmaceutical Benefits Advisory Committee; SMC=Scottish Medicines Consortium

5.2.2 AG study selection and inclusion criteria

Records were selected for inclusion in the review based on the criteria shown in Table 33. The criteria were developed to ensure that the included studies would provide information to help address the AG decision problem which aligns to the final scope[27] issued by NICE, i.e., to assess the cost effectiveness of treatment with lenvatinib plus pembrolizumab for patients with untreated aRCC versus sunitinib, pazopanib, tivozanib, cabozantinib and nivolumab plus ipilimumab.

Table 33 Inclusion criteria for cost effectiveness evidence

Hierarchical order	Inclusion criteria
1. Language	English language only
2. Population	Adults with untreated aRCC
3. Study design	Full economic evaluations that consider both costs and consequences (cost effectiveness analysis, cost utility analysis, cost minimisation analysis and cost benefit analysis)
4. Intervention	Lenvatinib plus pembrolizumab
5. Comparators	Sunitinib Pazopanib Tivozanib Cabozantinib (only for intermediate/poor risk disease as defined in IMDC criteria) Nivolumab with ipilimumab (only for intermediate/poor risk disease as defined by IMDC criteria)
6. Costs	Direct healthcare costs
7. Outcomes	Incremental cost per LY gained and/or incremental cost per QALY gained
8. Date span	2006 to present

aRCC=advanced renal cell carcinoma; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; LY=life year; QALY=quality adjusted life year

Two reviewers (RH/DB) independently screened the titles and abstracts of all records identified by the searches. Full-text versions of all studies considered potentially relevant were obtained. The same two reviewers then independently assessed the relevance of these full-text publications and reasons for exclusion were assigned based on the hierarchical order as shown in Table 33. Disagreements about inclusion were resolved through discussion and, in all cases, a consensus was reached.

5.2.3 Quantity of cost effectiveness evidence

The AG searches identified 3127 records. Of these, 2742 records were obtained from the database searches and 385 records were identified from other sources, i.e., from conference proceedings (n=129) and website searches (n=256). Once duplicates were removed, 1899 records remained. Following screening of titles and abstracts, 47 full-text publications were retrieved (one potentially relevant report could not be retrieved) and checked for eligibility using pre-specified inclusion criteria. The AG study selection process is shown in Figure 2.

Included study

Only one cost effectiveness study[115] was included in the AG review. Using this study, forward citation searches were carried out; however, no additional studies were identified. As the included study was published in 2021, this was to be expected.

Excluded studies

In total, 46 reports were excluded from the review at the full-text stage. Reasons for exclusion were wrong population (n=4), wrong study design (n=15), wrong intervention (n=25) and duplicate publications (n=2).

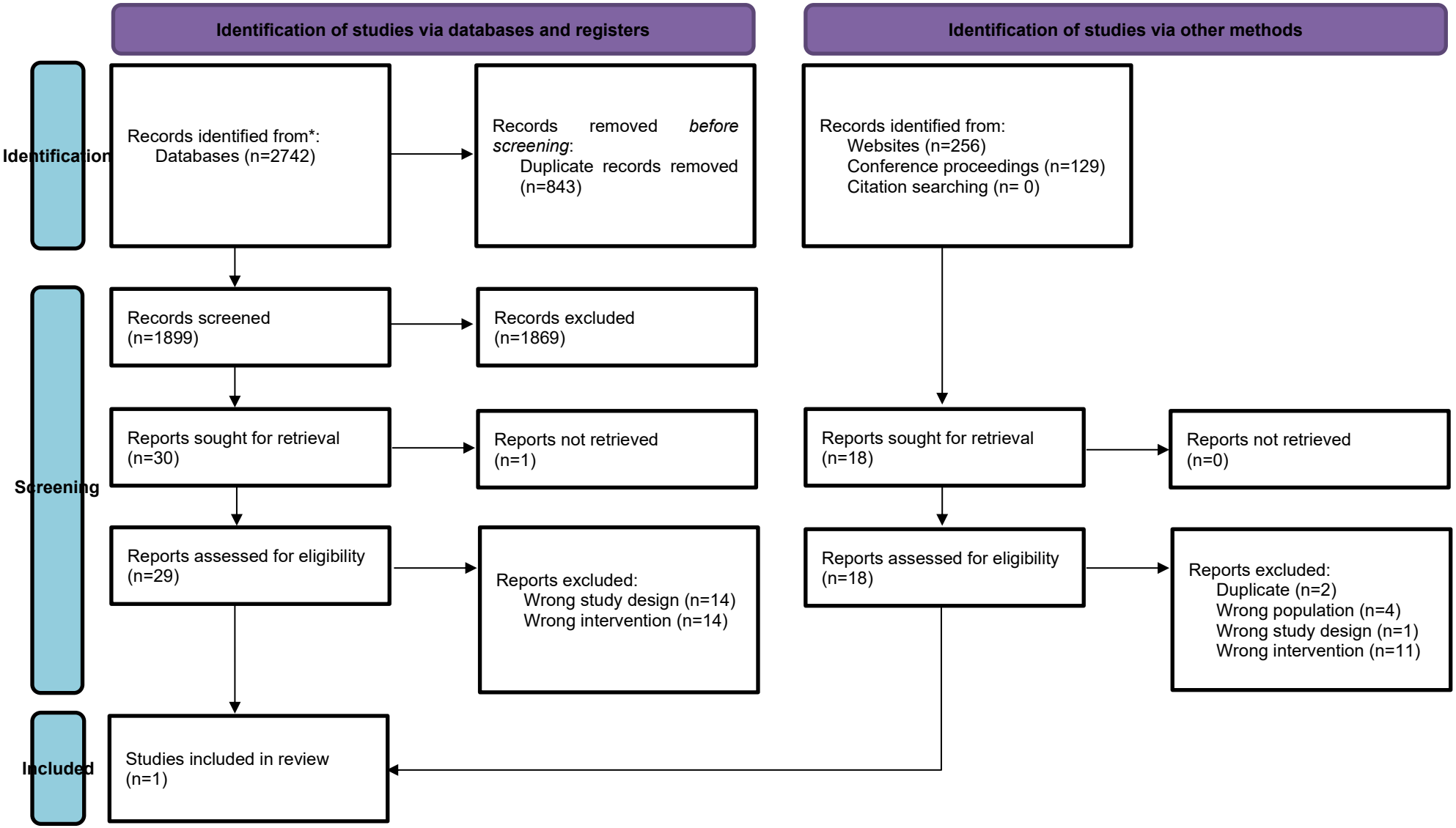

Figure 2 PRISMA 2020 flow diagram for cost effectiveness systematic review

5.2.4 AG data extraction

A data extraction form was designed in MS Excel. Extracted data included bibliographic information (e.g., authors and title) and details of the type of analyses conducted. Details about the economic model were also extracted (e.g., parameters used and their sources, results of the analyses, authors' conclusions and limitations reported by the authors). Information from the included study was extracted independently by two reviewers (RH/DB).

5.2.5 Quality of cost effectiveness evidence

The AG assessed the quality of the included cost effectiveness study[115] using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist[116] (Appendix 16, Section 9.16, Table 116). Two reviewers (RH/DB) independently carried out the quality assessment. The reviewers agreed that, except for resource use items, Li et al 2021[115] had transparently reported the methods used to conduct their cost effectiveness analysis.

5.2.6 Key information from the included cost effectiveness study

The data extracted by the AG from the included cost effectiveness study[115] are provided in Table 34.

Table 34 Key information from the included cost effectiveness study

Author	Li et al 2021[115]
Year	2021
Type of economic evaluation	Cost utility analysis
Population	Adults aged 62 years with aRCC, all-risk population
Intervention(s) & comparator(s)	Sunitinib, avelumab+axitinib,* nivolumab+ipilimumab,* lenvatinib+pembrolizumab, pembrolizumab+axitinib,* nivolumab+cabozantinib*
Model structure	Microsimulation
Health states	First-line treatment, second-line treatment, third-line treatment, discontinued treatment due to AEs, BSC, dead
Time horizon	Lifetime
Cycle length	42 days
Discount rates for costs and benefits	3% for costs and benefits
Perspective used (country, healthcare system, societal)	US payer (direct costs only)
Sources of clinical evidence	Kaplan-Meier data from the key trials (the CLEAR trial, CheckMate 9ER trial,[117] CheckMate 214 trial,[99] KEYNOTE-426 trial,[118] and JAVELIN Renal 101 trial[119])
Sources of utilities evidence	Published sources: Cella et al 2018;[120] de Groot et al 2018;[121] Wan et al 2019;[122] Patel et al 202[123]
Sources of costs evidence	Published sources include Centres for Medicare and Medicaid Services 2021;[124] Agency for Healthcare Research and Quality US Dept of Health & Human Services 2021;[125] Motzer et al 2018;[126] Perrin et al 2015[127]
Currency used	US $
Year to which costs apply	2021
Total costs	LEN+PEM=$562,080.09 SUN=$239,257.68
Total QALYs	LEN+PEM=2.61 SUN=2.42
Total LYs	LEN+PEM=3.44 SUN=3.21
Incremental costs	LEN+PEM versus SUN=$322,822.41
Incremental QALYs	LEN+PEM versus SUN=0.19
Incremental LYs	LEN+PEM versus SUN=0.23
ICER per LY gained	LEN+PEM versus SUN=$1,403,575.70
ICER per QALY gained	LEN+PEM versus SUN=$172,749.53
Sensitivity analysis results	The time horizon varied to 5, 10 and 20 years. A time horizon of 5 years significantly increased the ICER per QALY gained as most of the costs occurred in the first 5 years but the period over which benefits accrued exceeded 5 years
Conclusions of cost effectiveness results	Pembrolizumab plus axitinib* is the best option at a WTP threshold of $100,000
Limitations	Indirect comparisons include bias of different patient characteristics, lack of long-term OS data for patients treated with immune checkpoint inhibitors to validate model estimates, estimates of treatment discontinuation do not extend beyond the trial periods studied and the utility estimates come from a range of sources that may not accurately reflect clinical reality, the model is designed to represent the US health system so estimates may not be transferable to other health care systems.

*Not a relevant comparator or not used in a relevant population in this appraisal, therefore full results are not presented
AEs=adverse events; aRCC=advanced renal cell carcinoma; BSC=best supportive care; OS=overall survival; QALY=quality adjusted life years; WTP=willingness to pay

The cost effectiveness results generated by the Li et al 2021[115] economic model show that lenvatinib plus pembrolizumab generates more life years (LYs) and more quality adjusted life years (QALYs) than sunitinib. However, incremental costs are high and the base case incremental cost effectiveness ratio (ICER) for this comparison is over US$100,000 per QALY, a level that the authors report is an acceptable willingness to pay threshold.

5.2.7 AG systematic review conclusions

The Li et al 2021[115] cost effectiveness study includes estimates of the comparative cost effectiveness of lenvatinib plus pembrolizumab versus sunitinib. However, the study was undertaken from the perspective of the US health care system and, therefore, the extent to which resource use and results are generalisable to the NHS is unclear. Further, the study is limited to the all-risk population and includes comparators that are not recommended by NICE for patients with untreated aRCC.

5.3 AG assessment of the companies' systematic review of cost effectiveness evidence

The searches for cost effectiveness studies carried out by Eisai and MSD were very similar. The AG appraisal of the review methods described by the authors was based on information provided in the Eisai[15] and MSD[51] company submissions.

The date span for both of the companies' searches was from the inception of relevant databases to the date on which the searches were conducted. Both first searches were carried out in March 2019 and both companies conducted an updated search in January 2021. No relevant studies were identified. As the companies' searches were last updated in January 2021, the only cost effectiveness study included in the AG review was not identified.

The AG assessed the companies' literature review using the LRiG in-house systematic review checklist. Details of this assessment are provided in Table 35.

Table 35 AG appraisal of companies' cost effectiveness systematic review methods

Review process	AG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Partially
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	NA
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	NA
Was the quality assessment conducted by two or more reviewers independently?	NA
Were attempts to synthesise evidence appropriate?	NA

AG=Assessment Group; NA=not applicable
Source: LR*i*G in-house checklist

5.3.1 AG conclusions

The AG considers that the companies used appropriate methods to identify potentially relevant cost effectiveness studies for inclusion in their systematic reviews. However, the final searches were undertaken in January 2021, and therefore the cost effectiveness study[115] included in the AG systematic review was not identified.

5.4 AG summary and critique of companies' economic analyses

5.4.1 AG summary of companies' economic models

Table 36 Key information about the companies' models

Parameter	Eisai CS	MSD CS
Type of economic evaluation	Cost utility analysis	Cost utility analysis
Population	People with untreated advanced renal cell carcinoma Subgroups: intermediate/poor risk	People with untreated advanced renal cell carcinoma Subgroups: intermediate/poor risk and favourable risk*
Intervention(s) & comparator(s)	Pembrolizumab in combination with: Lenvatinib Sunitinib Pazopanib Tivozanib Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria)	Pembrolizumab in combination with: Lenvatinib Sunitinib Pazopanib Tivozanib Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria)
Model structure	Partitioned survival model	Partitioned survival model
Health states	PFS, PPS, OS	PFS (on and off tx), PPS (on and off tx), OS
Time horizon	40 years	40 years
Cycle length	7 days	7 days
Discount rates for costs and benefits	3.5%	3.5%
Perspective used (country, healthcare system, societal)	NHS and Personal Social Services perspective	NHS and Personal Social Services perspective
Sources of clinical evidence	CLEAR trial data and Eisai NMA results	CLEAR trial data and MSD NMA results
Sources of utilities evidence	CLEAR trial EQ-5D-3L data	CLEAR trial EQ-5D-3L data
Sources of costs evidence	Resource use was based on current clinical practice, previous HTAs in advanced/metastatic RCC and published literature. Unit costs were informed by recognised national databases	Resource use was based on current clinical practice, previous HTAs in advanced/metastatic RCC and published literature. Unit costs were informed by recognised national databases
Currency used	GBP 2019/2020	GBP 2019/2020

* Data provided in MSD initial and additional responses to the AG clarification letters
CS=company submission; HTA=health technology assessment; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life years; RCC=renal cell carcinoma; TTD=time to treatment discontinuation; tx=treatment
Source: Eisai CS[15] and MSD CS[51]

5.4.2 Critical appraisal of the companies' economic analyses

The AG critical appraisal of the companies' economic analyses was carried out using the Drummond checklist (Table 37) and the NICE Reference Case checklist (Table 38).

Table 37 Critical appraisal checklist for the companies' economic analyses (Drummond check list)

Question	Eisai model	MSD model
Was a well-defined question posed in answerable form?	✓	✓
Was a comprehensive description of the competing alternatives given?	✓	✓
Was the effectiveness of the programme or services established?	✓	✓
Where all the important and relevant costs and consequences for each alternative identified?	✓	✓
Were costs and consequences measured accurately in appropriate physical units?	✓	✓
Were the cost and consequences valued credibly?	✓	✓
Were costs and consequences adjusted for differential timing?	✓	✓
Was an incremental analysis of costs and consequences of alternatives performed?	✓	✓
Was allowance made for uncertainty in the estimates of costs and consequences?	✓	✓
Did the presentation and discussion of study results include all issues of concern to users?	✓/✗	✓/✗

✓ yes (item properly addressed) ✗ no (item not properly addressed) ✓/✗ partially (item partially addressed)
Source: Drummond and Jefferson 1996[128]

Table 38 NICE Reference Case checklist

Element of health technology assessment	Reference Case	MSD and Eisai models
Defining the decision problem	The scope developed by NICE	Yes
Comparators	As listed in the scope developed by NICE	Partly - nivolumab+ipilimumab was not included as a comparator
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review and NMA	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
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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: NICE Reference Case[129]

5.5 Eisai and MSD cost effectiveness results

Due to differences in the companies' modelling approaches, there are differences between the Eisai and MSD cost effectiveness results. Eisai and MSD pairwise cost effectiveness results for the intermediate/poor risk subgroup are presented in Table 39. MSD pairwise base case and fully incremental cost effectiveness results for the favourable risk subgroup are presented in Table 40 and Table 41 respectively. Eisai did not present any cost effectiveness results for the favourable risk subgroup.

Table 39 Companies' pairwise base case results, intermediate/poor risk subgroup (list prices)

Treatment	Total			Incremental			
	Costs	LYs	QALYs	Costs	LYs	QALYs	Cost per QALY gained
Eisai							
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£118,571
MSD							
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£77,730

ICER=incremental cost effectiveness ratio; LYs=life years gained; QALYs=quality adjusted life years
Source: Eisai CS,[15] Table 63 and MSD CS,[51] Table 65

Table 40 MSD's pairwise base case results, favourable risk subgroup (list prices)

Treatment	Total			Incremental			
	Costs	LYs	QALYs	Costs	LYs	QALYs	Cost per QALY gained
Gamma distribution for comparator OS							
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]				
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£354,839
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£359,052
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£350,580
Weibull distribution for comparator OS							
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]		NR		
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£225,227
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£227,898
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£222,527

ICER=incremental cost effectiveness ratio; LYs=life years gained; NR=not reported; OS=overall survival; QALYs=quality adjusted life years
Source: MSD additional response to the AG clarification letter, Table 12 and Table 13, and MSD favourable risk model

Table 41 MSD fully incremental base case results, favourable risk subgroup (list prices)

Treatment	Total		Incremental		
	Costs	QALYs	Costs	QALYs	Cost per QALY gained
Gamma distribution for comparator OS					
Pazopanib	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	[redacted]	-	SUN dominated by PAZO
Tivozanib	[redacted]	[redacted]	[redacted]	-	TIV dominated by PAZO
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£357,332
Weibull distribution for comparator OS					
Pazopanib	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	[redacted]		SUN dominated by PAZO
Tivozanib	[redacted]	[redacted]	[redacted]		TIV dominated by PAZO
Lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£229,186

ICER=incremental cost effectiveness ratio; LYs=life years gained; NR=not reported; OS=overall survival; QALYs=quality adjusted life years
Source: MSD additional response to the AG clarification letter, Table 12 and Table 13, and MSD model

5.6 AG economic evaluation and description of company models

The Eisai and MSD company submissions to NICE included economic models built in Microsoft Excel. The AG considers that results from both models can be used to inform decision making; however, in some instances, the companies could have made more appropriate assumptions and parameter choices. The AG has not developed a de novo economic model; instead, the AG has modified the model provided by MSD (referred to in this report from now on as the MSD/AG model). The main reason for modifying the MSD model rather than the Eisai model was that MSD provided cost effectiveness analyses for the favourable risk subgroup and, therefore, fewer modifications to this model were needed. Neither of the companies produced cost effectiveness results for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab (intermediate/poor risk subgroup), despite both models having the functionality for this comparison. Furthermore, Eisai did not generate any cost effectiveness results for the favourable risk subgroup.

5.7 Overview of clinical effectiveness evidence used to populate the models

Direct clinical evidence from the CLEAR trial is available for the comparison of lenvatinib plus pembrolizumab versus sunitinib and is the primary source of clinical effectiveness data used to populate the Eisai, MSD and MSD/AG models. The CLEAR trial is a good quality, phase III, multi-centre, open-label RCT. The final analysis of PFS was carried out using data from the IA3 data cut-off (28 August 2020); EQ-5D-3L and TTD data were also reported at this time point. OS data are available from an updated OS analysis (31 March 2021) at which point median OS follow-up was 33 months. At the time of the updated OS analysis, 114 (32.1%)

and 49 (13.7%) patients in the lenvatinib plus pembrolizumab and sunitinib arms respectively were still receiving their randomised treatment.

For the comparison of lenvatinib plus pembrolizumab versus comparator treatments, the AG considered the following three approaches to generate model inputs:

1. Use direct clinical evidence

Direct clinical evidence is available from the CLEAR trial to allow comparison of the efficacy of lenvatinib plus pembrolizumab versus sunitinib.

2. Use results from NMAs

PFS and OS NMA results were generated by Eisai, MSD and the AG for the comparison of lenvatinib plus pembrolizumab versus sunitinib, pazopanib and tivozanib. However, violations of the PH assumption within some of the studies included within the AG NMAs were observed (Table 42). As previously stated (Section 4.3.8), when the PH assumption is violated, NMA results (HRs and 95% CrIs) cannot be used to infer any statistically significant difference (or lack of statistically significant difference).

Table 42 Observed proportional hazard violations in the studies included in the AG NMAs

Risk group	PFS	OS
Intermediate/poor subgroup	CheckMate 214 trial[99] (nivolumab plus ipilimumab versus sunitinib)	NA*
Favourable subgroup	Unclear if HRs were proportional COMPARZ trial[100] information (including final OS analysis[104] information) did not include K-M data for this subgroup (pazopanib versus sunitinib)	
All-risk population	TIVO-1 trial[101] (tivozanib versus sorafenib)	CLEAR trial (lenvatinib plus pembrolizumab versus sunitinib)

* Proportional hazards assumption holds for OS in all trials included within the AG OS NMAs
AG=Assessment Group; HR=hazard ratio; K-M=Kaplan-Meier; NA=not applicable; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival

3. **Assume clinical equivalence/similarity**

Assume that sunitinib, pazopanib and tivozanib are clinically similar and use CLEAR trial sunitinib data to reflect the effectiveness of pazopanib and tivozanib. The assumption that pazopanib and tivozanib have equivalent efficacy to sunitinib is supported by the conclusions reached by NICE ACs,[25,26,32,33] namely that sunitinib and pazopanib are of equivalent clinical effectiveness and that, “At best, tivozanib may have a similar effect to sunitinib or pazopanib.”[32] No robust evidence to dispute these conclusions was generated by the Eisai, MSD or AG NMAs. This assumption was made based on all-risk population data; the AG has, however, assumed that it also holds for the intermediate/poor risk and favourable risk subgroups.

5.8 Model structure

The Eisai and MSD economic models are partitioned survival models with the same three health states: pre-progression, post-progression and death. The pre-progression and post-progression health states in the MSD model also include on-treatment and off-treatment substates. These models use the same structure as models previously submitted to inform NICE appraisals of treatments for untreated aRCC (Figure 3).

The cycle length used in both company models was 1 week. Eisai implemented a half-cycle correction but neither MSD nor the AG considered that this was necessary due to the short cycle length and therefore did not implement a half-cycle correction.

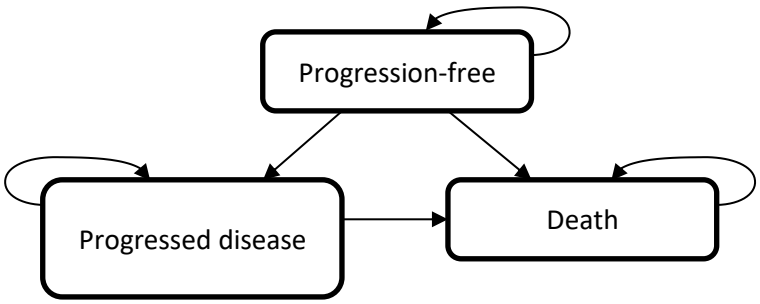

Figure 3 Structure of MSD and MSD/AG company model

Source: MSD company model

5.9 Population characteristics

In the Eisai model, the mean age (61.2 years) and proportion of males (74.5%) reflect the characteristics of all patients recruited to the CLEAR trial (Eisai CS,[15] Section 5.2.1). In the MSD (and MSD/AG) model, the mean age, proportion of males and weight of patients vary by subgroup and reflect the baseline age, proportion of males, and mean weight of patients in the CLEAR trial who were recruited from European sites only (Table 43).

Table 43 MSD population characteristics by risk group

Risk groups	Mean age	Proportion males	Weight
Intermediate/poor	[redacted]	[redacted]	[redacted]
Favourable	[redacted]	[redacted]	[redacted]
All-risk	61.7	74.5%	81.1kg

kg=kilograms
Source: MSD CS[51] and MSD model

5.9.1 Prognostic risk subgroups

IMDC prognostic risk subgroup data are available from the CLEAR trial:

- intermediate/poor risk (n=472, 66.3%
- intermediate risk (n=402, 56.5%)
- poor risk (n=70, 9.8%)
- favourable risk (n=234, 32.9%)

Previous NICE technology appraisals[25,26,30-32,39] have produced treatment recommendations for patients with untreated aRCC for the combined intermediate/poor risk subgroup (TA542,[25] TA581[26] [and TA645[39] for use within the CDF]) and all-risk population (TA169,[30] TA215[31] and TA512[32]). As some treatments are only available for the intermediate/poor risk subgroup, the AG considers that cost effectiveness results for the all-risk population (CLEAR trial FAS/ITT population) are not relevant to this appraisal. The AG has therefore conducted separate cost effectiveness analyses for the intermediate/poor risk and favourable subgroups using relevant comparator data for each subgroup (i.e., intermediate/poor risk: cabozantinib or nivolumab plus ipilimumab; favourable risk: sunitinib, pazopanib or tivozanib). For completeness, cost effectiveness results for the all-risk population are provided in Appendix 17 (Section 9.17). As cabozantinib and nivolumab plus ipilimumab are only recommended by NICE for treating patients with intermediate/poor risk disease, the AG does not consider that cost effectiveness results for the poor risk subgroup only are relevant and so has not generated any cost effectiveness results for this subgroup.

5.10 Intervention and comparator treatments

The intervention is lenvatinib plus pembrolizumab. The comparators listed in the final scope issued by NICE are shown in Table 44. For patients with intermediate/poor risk disease, clinical advice to the AG is that sunitinib, pazopanib and tivozanib are treatments that are generally reserved for use as later lines of treatment and would only be offered as first-line treatments to patients who were unable to tolerate cabozantinib, nivolumab plus ipilimumab or lenvatinib plus pembrolizumab (if recommended by NICE). Therefore, the AG considers that sunitinib, pazopanib and tivozanib are not relevant comparators for the intermediate/poor risk subgroup.

Table 44 Comparator treatments considered by the AG for each risk subgroup

Subgroup	Comparators
Intermediate/poor risk	Cabozantinib Nivolumab plus ipilimumab
Favourable risk	Sunitinib Pazopanib Tivozanib

Source: Final scope[27] issued by NICE

Eisai and MSD did not include nivolumab plus ipilimumab as a comparator (Eisai CS,[15] Table1; MSD CS,[51] Table 1). However, as nivolumab plus ipilimumab is a comparator listed in the final scope[27] issued by NICE, the AG has included it as a comparator in the MSD/AG model.

5.11 Discounting, time horizon and perspective

In line with the NICE Reference Case,[129] in the Eisai and MSD (and MSD/AG) models, costs and benefits were discounted at a rate of 3.5%. In the MSD model, discounting was incorrectly applied from the first cycle; in the MSD/AG model, this error was corrected and discounting now starts at the beginning of the second year. Scenario analyses were performed by the AG using annual discount rates of 0% and 6%for costs and benefits.

The time horizon used in the Eisai, MSD and MSD/AG models is 40 years. The AG considers that this is sufficient to capture all relevant costs and benefits. The perspective of all three models is the NHS and PSS.

5.12 Populating the model with clinical effectiveness data: general methods

Direct clinical effectiveness evidence (PFS, OS and TTD) is only available from the CLEAR trial for the comparison of the efficacy of lenvatinib plus pembrolizumab versus sunitinib.

In line with Decision Support Unit (DSU) guidance,[130] Eisai, MSD and the AG assessed the goodness-of-fit to PFS, OS and TTD K-M data of standard distributions (exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, Weibull) using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) statistics. The distribution producing the lowest AIC and BIC statistics is considered the best fitting (i.e., highest ranking); however, Eisai suggests that other distributions may be as good as the highest ranking distribution (Table 45). The AG highlights that, for PFS and OS, Eisai only provided AIC and BIC statistics for the all-risk population.

Table 45 AIC and BIC rule of thumb for goodness-of-fit

Difference in points from distribution with lowest AIC and BIC	**Rule of thumb**	
	AIC	**BIC**
0 to 4 points	Good	Acceptable
4 to 7 points	Reasonable	
7 to 10 points	Acceptable	
>10 points	Poor	Poor

AIC=Akaike information criterion; BIC=Bayesian information criterion
Source: Eisai CS,[15] Table 23

As well as the visual fit of the seven distributions to the K-M data, the AG also assessed the:

- clinical plausibility of long-term projections (i.e., whether the mortality rate rapidly fell below background mortality)
- whether the distribution used to model PFS led to higher mortality than the distribution chosen to model OS
- whether survival projections for the intermediate/poor risk subgroup were more/less optimistic than those for the favourable risk subgroup.

5.13 Populating the MSD/AG model: progression-free survival

Eisai and MSD fitted distributions to CLEAR trial BICR assessed PFS data (FDA censoring rules). The PFS distributions chosen by Eisai, MSD and the AG are shown in Table 46. The PFS distributions chosen by the AG are shown graphically for the intermediate/poor and favourable risk subgroups in Figure 4 and Figure 5 respectively.

Table 46 Modelling progression-free survival

Treatment	**Eisai**	**MSD**	**AG**
	Modelling		
Intermediate/poor risk subgroup			
Lenvatinib plus pembrolizumab	Exponential		
Cabozantinib	Eisai NMA result: LEN+PEM vs cabozantinib [redacted]	MSD NMA result: first-order fractional polynomial model	AG NMA result: LEN+PEM vs cabozantinib HR=[redacted]
Nivolumab plus ipilimumab	No results generated		AG NMA result: LEN+PEM vs nivolumab plus ipilimumab HR=[redacted]
Favourable risk subgroup			
Lenvatinib plus pembrolizumab	No results generated	Generalised gamma	
Sunitinib		Log-normal	
Pazopanib/tivozanib		Equal to sunitinib	

AG=Assessment Group; HR=hazard ratio; NMA=network meta-analysis
Source: Eisai CS,[15] MSD CS,[51] AG PFS NMA

Figure 4 AG base case PFS distributions, intermediate/poor risk subgroup

AG=Assessment Group; PFS=progression-free survival
Source: MSD/AG model

Figure 5 AG base case PFS distributions, favourable risk subgroup

AG=Assessment Group; PFS=progression-free survival
Source: MSD/AG model

5.13.1 Intermediate/poor risk subgroup (PFS)

Lenvatinib plus pembrolizumab

All the MSD AIC statistics for the distributions fitted to CLEAR trial lenvatinib plus pembrolizumab data lie within five AIC points of each other (Table 47). The distributions are shown visually against the CLEAR trial PFS-K-M data in Figure 6. Eisai and MSD chose to model PFS using similar exponential distributions. The AG considered that it was appropriate to use the exponential distribution with the parameters estimated by MSD.

Table 47 MSD CLEAR trial PFS data goodness-of-fit statistics, intermediate/poor subgroup (IA3 data cut)

Distribution	Lenvatinib + pembrolizumab	
	AIC [rank]	BIC [rank]
Exponential	[redacted] [1]	[redacted] [1]
Gamma	[redacted] [2]	[redacted] [2]
Generalised gamma	[redacted] [6]	[redacted] [7]
Gompertz	[redacted] [5]	[redacted] [5]
Log-logistic	[redacted] [4]	[redacted] [4]
Log-normal	[redacted] [7]	[redacted] [6]
Weibull	[redacted] [3]	[redacted] [3]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion
Source: Adapted from MSD model

Figure 6 PFS distributions for lenvatinib plus pembrolizumab, intermediate/poor risk subgroup

PFS=progression-free survival
Source: MSD model

Cabozantinib and nivolumab plus ipilimumab

Eisai and MSD used results from their respective PFS NMAs and applied these to their chosen lenvatinib plus pembrolizumab distribution to generate results for lenvatinib plus pembrolizumab versus cabozantinib. No NMA results were presented by Eisai or MSD for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab.

For the comparison of lenvatinib plus pembrolizumab versus cabozantinib, the AG adopted the same approach as Eisai and MSD and applied the HR generated by the AG PFS NMA (lenvatinib plus pembrolizumab versus cabozantinib) to the distribution chosen for lenvatinib plus pembrolizumab. For the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab, the AG applied the HR generated by the AG PFS NMA (lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab) to the distribution chosen for lenvatinib plus pembrolizumab.

Eisai NMAs did not include data from the CheckMate 214 trial;[99] nevertheless, the Eisai and AG NMA results were very similar for the comparison of lenvatinib plus pembrolizumab versus cabozantinib. This suggests that the AG PFS NMA results (lenvatinib plus pembrolizumab versus cabozantinib) are not substantially affected by the inclusion of data from the

CheckMate 214 trial.[99] As shown in Table 42 the CheckMate 214 trial[99] PFS PH assumption is violated; this means that the CheckMate 214 trial[99] PFS HR is not applicable to all time points across the observed follow-up period. Therefore, the AG PFS NMA HRs are not applicable to all time points across the observed follow-up of the trials included in the NMAs.

5.13.2 Favourable risk subgroup (PFS)

Eisai did not generate any cost effectiveness estimates for the favourable risk subgroup.

Lenvatinib plus pembrolizumab

MSD chose the generalised gamma distribution to model PFS for patients receiving lenvatinib plus pembrolizumab (ranked 5/7 using AIC statistics, Table 48). The distributions are shown visually against the CLEAR trial PFS-K-M data in Figure 7. The generalised gamma distribution's AIC statistic lies within five points of the AIC statistic for the highest ranking distribution. The AG agrees with MSD that the higher ranking distributions are either a poor visual fit to the PFS K-M data for patients receiving lenvatinib plus pembrolizumab or produce unrealistic long-term extrapolations, i.e., patients either progress very rapidly or experience very little progression. The generalised gamma distribution, on visual inspection, seemed to offer long-term projections that were clinically plausible; the AG therefore considered that the generalised gamma distribution was an appropriate choice of distribution to use in the base case analysis.

Figure 7 PFS distributions for lenvatinib plus pembrolizumab, favourable risk subgroup

PFS=progression-free survival
Source: MSD model

Sunitinib (pazopanib and tivozanib)

MSD chose the distribution with the lowest AIC statistic (log-normal) to model PFS for patients in the favourable risk subgroup receiving sunitinib, pazopanib and tivozanib. As shown in Table 48, there is little to choose between the alternative distributions. The distributions are shown visually against the CLEAR trial PFS-K-M data in Figure 8. The AG considered that as the log-normal distribution was the highest ranking distribution based on AIC and BIC statistics, was a good visual fit to sunitinib CLEAR trial PFS K-M data, and the long-term projections appeared clinically plausible, the log-normal distribution was an appropriate choice to use in the base case analysis.

Table 48 MSD CLEAR trial PFS data goodness-of-fit statistics, favourable risk subgroup, IA3 data cut

Distribution	Lenvatinib + pembrolizumab [rank]		Sunitinib [rank]	
	AIC	BIC	AIC	BIC
Exponential	[redacted] [7]	[redacted] [5]	[redacted] [7]	[redacted] [6]
Gamma	[redacted] [2]	[redacted] [2]	[redacted] [4]	[redacted] [3]
Generalised gamma	[redacted] [5]	[redacted] [7]	[redacted] [2]	[redacted] [5]
Gompertz	[redacted] [6]	[redacted] [6]	[redacted] [6]	[redacted] [7]
Log-logistic	[redacted] [1]	[redacted] [1]	[redacted] [3]	[redacted] [2]
Log-normal	[redacted] [3]	[redacted] [3]	[redacted] [1]	[redacted] [1]
Weibull	[redacted] [4]	[redacted] [4]	[redacted] [5]	[redacted] [4]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion
Source: Adapted from MSD model

Figure 8 PFS distributions for sunitinib, pazopanib and tivozanib, favourable risk subgroup

PFS=progression-free survival
Source: MSD model

5.13.3 AG scenario analyses: intermediate/poor and favourable risk subgroups (PFS)

Intermediate/poor risk subgroup

The AG explored the effect on cost effectiveness results of using the parametric distributions that had AIC statistics that were within five points of the AIC statistic for the distribution used to model PFS for patients treated with lenvatinib plus pembrolizumab; distributions for cabozantinib and nivolumab plus ipilimumab changed automatically.

The AG also explored the effect on cost effectiveness results of using the MSD FP NMA results to model PFS for patients treated with cabozantinib PFS.

Favourable risk subgroup

The AG explored the effect on cost effectiveness results of using the parametric distributions that had AIC statistics that were within five points of the AIC statistic for the distribution used to model PFS for patients treated with lenvatinib plus pembrolizumab; distributions for sunitinib, pazopanib and tivozanib were unchanged.

The AG explored the effect on cost effectiveness results of using the parametric distributions that had AIC statistics that were within five points of the AIC statistic for the distribution used to model PFS for patients treated with sunitinib (pazopanib and tivozanib); distributions for lenvatinib plus pembrolizumab were unchanged.

5.14 Populating the MSD/AG model: overall survival

The distributions chosen by Eisai, MSD and the AG for OS are shown in Table 49. The OS distributions chosen by the AG are shown graphically for the intermediate/poor and favourable risk subgroups in Figure 9 and Figure 10 respectively.

Table 49 Modelling overall survival (updated OS analysis)

Treatment	Eisai	MSD	AG
Intermediate/poor risk			
Lenvatinib plus pembrolizumab	Exponential	Exponential	K-M+exponential
Cabozantinib	Eisai NMA: LEN+PEM vs cabozantinib [redacted]	MSD NMA: first-order fractional polynomial model	AG NMA: LEN+PEM vs cabozantinib HR=[redacted]
Nivolumab plus ipilimumab	No results presented		AG NMA: LEN+PEM vs nivolumab plus ipilimumab HR=[redacted]
Favourable risk			
Lenvatinib plus pembrolizumab	No results presented	Exponential	Log-logistic
Sunitinib		Gamma or Weibull*	Gamma
Pazopanib		Equal to sunitinib	Equal to sunitinib
Tivozanib		Equal to sunitinib	Equal to sunitinib

* MSD presented two sets of results
AS=Assessment Group; HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival
Source: Eisai CS,[15] MSD CS,[51] AG OS NMA

Figure 9 AG base case OS distributions, intermediate/poor risk subgroup

AG=Assessment Group; OS=overall survival
Source: MSD model

Figure 10 AG base case OS distributions, favourable risk subgroup

AG=Assessment Group; OS=overall survival
Source: MSD model

5.14.1 Intermediate/poor risk subgroup (OS)

Lenvatinib plus pembrolizumab

Both companies chose the exponential distribution (ranked 6/7 using AIC statistics) to estimate OS for patients in the intermediate/poor subgroup receiving lenvatinib plus pembrolizumab despite this not being the highest ranking distribution based on AIC statistics or within five points of the highest ranking distribution (Table 50). Their choice was based on good visual fit to CLEAR trial OS K-M data and the fact that higher ranking distributions generated implausible long-term OS estimates.

Although the AG was satisfied that the companies followed DSU guidance,[130] the AG did not consider that any of the distributions considered by Eisai or MSD provided a good visual fit to the available CLEAR trial OS K-M data available. The AG examined the CLEAR trial OS K-M data received during the NICE MTA clarification process and observed that the lenvatinib plus pembrolizumab OS hazard was constant beyond 50 weeks. The AG therefore considered that the companies' choice of an exponential distribution was appropriate, but that K-M data should be used up to the point that censoring and small numbers of events rendered the data too uncertain (the AG considered that this occurred at 120 weeks). The AG appended the

exponential distribution (based on the hazard between 50 and 120 weeks) to the CLEAR trial OS K-M data from 120 weeks onwards.

The distributions considered by Eisai, MSD and the AG are shown visually against the CLEAR trial OS K-M data in Figure 11.

Figure 11 OS distributions for lenvatinib plus pembrolizumab, intermediate/poor risk subgroup

OS=overall survival
Source: MSD model

Table 50 MSD CLEAR trial OS goodness-of-fit statistics, intermediate/poor risk subgroup, updated OS analysis

Distribution	Lenvatinib plus pembrolizumab	
	AIC [rank]	BIC [rank]
Exponential	[redacted] [6]	[redacted] [2]
Gamma	[redacted] [4]	[redacted] [4]
Generalised gamma	[redacted] [3]	[redacted] [6]
Gompertz	[redacted] [1]	[redacted] [1]
Log-logistic	[redacted] [5]	[redacted] [5]
Log-normal	[redacted] [7]	[redacted] [7]
Weibull	[redacted] [2]	[redacted] [3]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; OS=overall survival
Source: Adapted from MSD model

Cabozantinib and nivolumab plus ipilimumab

For the comparison of lenvatinib plus pembrolizumab versus cabozantinib, Eisai and MSD applied the HRs generated by their OS NMAs (lenvatinib plus pembrolizumab versus cabozantinib) to the OS distributions chosen for lenvatinib plus pembrolizumab.

For the comparison of lenvatinib plus pembrolizumab versus cabozantinib, the AG applied the HR generated by the AG OS NMA (lenvatinib plus pembrolizumab versus cabozantinib) to the OS distribution chosen for lenvatinib plus pembrolizumab.

No NMA results were presented by Eisai or MSD for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab.

For the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab, the AG applied the HR generated by the AG OS NMA (lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab) to the distribution chosen for lenvatinib plus pembrolizumab.

As described in Section 4.4.2, the AG concluded that, for the intermediate/poor risk subgroup, the OS PH assumption was not violated in the CLEAR trial or either of the two other trials[96,99] included in the AG OS NMA.

5.14.2 Favourable risk subgroup (OS)

For patients in the favourable risk subgroup, there was considerable uncertainty around the validity of the CLEAR trial OS estimates due to the low number of events experienced by these patients; over [redacted] of patients were alive at the end of the trial follow up period.

Lenvatinib plus pembrolizumab

MSD chose the exponential distribution (ranked 7/7 using AIC statistics) to model OS for patients treated with lenvatinib plus pembrolizumab (Table 51). The AG considered that the exponential distribution generated OS estimates that were too optimistic ([redacted]% of patients were still alive after 14 years) and was a poor fit to the CLEAR trial OS K-M data. The AG considered that survival in the favourable risk subgroup should be no worse than survival in the intermediate/poor risk subgroup. Four of the seven distributions considered by MSD (i.e., Gompertz, generalised gamma, Weibull and gamma) produced 10-year survival estimates that were above the AG 10-year survival estimates for the intermediate/poor risk subgroup (Figure 12). The AG therefore chose the Gompertz distribution which was the highest ranking, based on AIC and BIC statistics, of the four distributions that the AG considered clinically plausible.

Sunitinib (pazopanib and tivozanib)

To model OS for patients in the favourable risk subgroup who received sunitinib, MSD used two distributions (gamma and Weibull) that they considered were equally plausible.

During the NICE MTA clarification process, MSD provided CLEAR trial OS K-M and HR data that suggested improved survival for patients in the sunitinib arm versus patients in the lenvatinib plus pembrolizumab arm. Similarly, AG OS NMA results suggested improved survival for patients treated with sunitinib versus patients treated with lenvatinib plus pembrolizumab (although the difference was not statistically significant). The MSD model predicted a survival benefit that was greater for patients treated with lenvatinib plus pembrolizumab than for patients treated with sunitinib. As the CLEAR trial evidence does not support such a benefit, a benefit should not be modelled.

Given the AG's chosen survival distribution for lenvatinib plus pembrolizumab, the AG considered that the gamma distribution was the appropriate distribution to use to model OS for patients treated with sunitinib (and therefore also for patients treated with pazopanib and tivozanib). The gamma distribution was the highest ranking distribution, based on AIC and BIC statistics (Table 51) that produced survival estimates that were consistent with a sustained survival benefit for patients treated with sunitinib versus patients treated with lenvatinib plus pembrolizumab whilst not producing implausibly long survival estimates (Figure 13).

Table 51 MSD CLEAR trial OS data goodness-of-fit statistics, favourable risk subgroup, updated OS analysis

Distribution	Lenvatinib plus pembrolizumab		Sunitinib	
	AIC [rank]	BIC [rank]	AIC [rank]	BIC [rank]
Exponential	[redacted] [7]	[redacted] [5]	[redacted] [1]	[redacted] [1]
Gamma	[redacted] [4]	[redacted] [4]	[redacted] [4]	[redacted] [4]
Generalised gamma	[redacted] [5]	[redacted] [7]	[redacted] [6]	[redacted] [7]
Gompertz	[redacted] [1]	[redacted] [1]	[redacted] [7]	[redacted] [6]
Log-logistic	[redacted] [3]	[redacted] [3]	[redacted] [3]	[redacted] [3]
Log-normal†	[redacted] [6]	[redacted] [6]	[redacted] [2]	[redacted] [2]
Weibull	[redacted] [2]	[redacted] [2]	[redacted] [5]	[redacted] [5]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; OS=overall survival
Source: Adapted from MSD model

Figure 12 OS distributions for lenvatanib plus pembrolizumab, favourable risk subgroup
OS=overall survival
Source: MSD model

Figure 13 OS distributions for sunitinib, pazopanib or tivozanib, favourable risk subgroup

OS=overall survival

Source: MSD model

5.14.3 AG scenario analyses: intermediate/poor and favourable risk subgroups (OS)

Intermediate/poor risk subgroup

The AG carried out scenario analyses that employed Eisai and MSD base case approaches to modelling OS:

- use the exponential distribution (Eisai and MSD preferred distribution) to model OS for lenvatinib plus pembrolizumab
- apply Eisai and MSD OS NMA HRs to the AG lenvatinib plus pembrolizumab distribution to generate cabozantinib OS estimates
- apply the MSD FP NMA HR to the AG lenvatinib plus pembrolizumab distribution to generate cabozantinib OS estimates.

The AG OS NMA HRs for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab and for the comparison of lenvatinib plus pembrolizumab versus cabozantinib were not statistically significantly different from 1. The AG, therefore, carried out a scenario analysis using a HR equal to 1 for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab and for the comparison of lenvatinib plus pembrolizumab versus cabozantinib (i.e., the OS distributions for nivolumab plus ipilimumab and for cabozantinib were assumed to be the same as that for lenvatinib plus pembrolizumab).

Favourable risk subgroup

The AG carried out a scenario analysis using the AG OS NMA HR for the comparison of lenvatinib plus pembrolizumab versus sunitinib (HR=[redacted]) applied to the log-logistic distribution used to represent OS for patients treated with lenvatinib plus pembrolizumab in the AG base case.

As the AG NMA OS HR for the comparison of lenvatinib plus pembrolizumab versus sunitinib was not statistically significantly different from 1, the AG carried out a scenario analysis using an OS HR=1 (i.e., the OS distribution for sunitinib was assumed to be the same as that for lenvatinib plus pembrolizumab).

In two other scenarios, the AG used an OS HR=1 for the comparison of lenvatinib plus pembrolizumab versus pazopanib and versus tivozanib.

5.15 Populating the model: time to treatment discontinuation

The parametric distributions chosen by Eisai, MSD and the AG to model TTD for all treatments are shown in Table 52. The TTD distributions chosen by the AG are shown graphically for the intermediate/poor and favourable risk subgroups in Figure 14 and Figure 15 respectively.

Table 52 Modelling time to treatment discontinuation

Treatment	Eisai	MSD	AG
Intermediate/poor risk subgroup			
Lenvatinib	Generalised gamma	Generalised gamma	Generalised gamma (Eisai)
Pembrolizumab	Weibull	K-M data (CLEAR trial data are complete)	
Cabozantinib	Generalised gamma	MSD NMA: first-order fractional polynomial model	Log-logistic (Eisai)
Nivolumab plus ipilimumab	Not estimated		Set equal to lenvatinib
Favourable risk subgroup			
Lenvatinib	Not estimated	Exponential	
Pembrolizumab		K-M data (CLEAR trial data are complete)	
Sunitinib		Exponential	
Pazopanib		Equal to sunitinib	
Tivozanib		Equal to sunitinib	

AG=Assessment Group; K-M=Kaplan-Meier; NMA=network meta-analysis
Source: Eisai CS,[15] MSD CS[51]

Figure 14 AG base case TTD distributions, intermediate/poor risk subgroup

AG=Assessment Group; TTD=time to treatment discontinuation
Source: MSD/AG model

Figure 15 AG base case TTD distributions, favourable risk subgroup

AG=Assessment Group; TTD=time to treatment discontinuation
Source: AG model

5.15.1 Intermediate/poor risk subgroups (TTD)

The AG considered that TTD for patients receiving lenvatinib should be modelled by fitting a distribution to CLEAR trial TTD K-M data and, for patients receiving pembrolizumab, the CLEAR trial TTD K-M data should be used directly.

Lenvatinib

Eisai and MSD provided CLEAR trial lenvatinib TTD K-M data during the NICE MTA clarification process. However, the two datasets differed slightly (by 24 months there was a clear gap between the two datasets). The AG concluded that as safety data from the CLEAR trial suggested a lower level of treatment discontinuation due to lenvatinib than due to pembrolizumab (25.6% versus 28.7%[67]), the Eisai lenvatinib TTD K-M data were likely to be the most accurate as they followed a trajectory that was consistently above the pembrolizumab TTD K-M data until 24 months, i.e., until the time when the pembrolizumab stopping rule was activated. In contrast, the MSD lenvatinib TTD K-M data crossed the pembrolizumab TTD K-M data at 20 months.

Both companies chose to use generalised gamma distributions to model TTD for patients treated with lenvatinib (this was the highest ranking distribution using AIC statistics [MSD CS[51]]) (Table 53). The distributions considered by MSD and the AG are shown visually against the CLEAR trial PFS-K-M data in Figure 16. The AG considered that the Eisai generalised gamma distribution provided a good visual fit to lenvatinib TTD K-M data and did not cross the pembrolizumab TTD K-M data until 24 months. The AG therefore chose to use Eisai's generalised gamma distribution to model lenvatinib K-M TTD data.

Table 53 MSD CLEAR trial TTD data goodness-of-fit statistics, intermediate/poor risk subgroup, IA3 data cut

Distribution	Lenvatinib	
	AIC [rank]	BIC [rank]
Exponential	[redacted] [3]	[redacted] [1]
Gamma	[redacted] [5]	[redacted] [5]
Generalised gamma	[redacted] [1]	[redacted] [3]
Gompertz	[redacted] [2]	[redacted] [2]
Log-logistic	[redacted] [6]	[redacted] [6]
Log-normal	[redacted] [7]	[redacted] [7]
Weibull	[redacted] [4]	[redacted] [4]

Source: Adapted from MSD model

Figure 16 TTD distributions for lenvatanib, intermediate/poor risk subgroup

TTD=time to treatment discontinuation
Source: MSD model

Pembrolizumab

MSD modelled pembrolizumab TTD by directly using the K-M data from the CLEAR trial and applied a 2-year stopping rule in line with the CLEAR trial protocol. Eisai modelled pembrolizumab TTD by fitting a Weibull distribution to the CLEAR trial K-M data; it is clear from the Eisai model outputs that a stopping rule for pembrolizumab at 2 years had been applied. The CLEAR trial pembrolizumab TTD K-M data are almost complete ([redacted]) and so the AG used the TTD K-M data directly to estimate the cost of treatment with pembrolizumab for patients in the intermediate/poor risk subgroup. As the AG used the K-M data directly, an enforced 2 year stopping rule was not implemented; however, this did mean that some patients remained on pembrolizumab for a short period of time beyond 2 years.

Cabozantinib

MSD modelled cabozantinib TTD using results from their FP TTD NMA. Eisai digitised the (intermediate/poor risk subgroup) cabozantinib TTD K-M data used to inform NICE TA542[25] and selected a distribution based on AIC and BIC statistics, visual fit and clinical plausibility (Table 54). The distributions considered by Eisai and the AG are shown visually in Figure 17. The generalised gamma distribution was not the highest ranking distribution based on AIC statistics or BIC statistics. However, the generalised gamma distribution AIC statistic was within five points of the lowest AIC statistic (log-logistic distribution). In addition, the generalised gamma distribution was the same distribution as the one Eisai used to model TTD for patients receiving lenvatinib, which has a similar mode of action to cabozantinib.

The AG considered that the Eisai approach to modelling cabozantinib TTD was more robust than the MSD approach. Whilst the Eisai approach was essentially a naïve between trial analysis, the AG considered that Eisai's transparent approach was preferable to the largely arbitrary parameterisation of MSD's FP TTD model. All six distributions assessed by Eisai had AIC statistics that were within five points of each other, were broadly similar in terms of visual fit and generated similar long-term estimates. The AG chose to use the log-logistic distribution as this was the distribution with the lowest AIC statistic.

Table 54 TTD data goodness-of-fit statistics, intermediate/poor risk subgroup

Distribution*	Cabozantinib	
	AIC [rank]	BIC [rank]
Exponential	633.61 [4]	635.91 [1]
Generalised gamma	633.58 [3]	640.33 [6]
Gompertz	635.34 [5]	639.89 [4]
Log-logistic	631.66 [1]	636.21 [2]
Log-normal	631.80 [2]	636.35 [3]
Weibull	635.64 [6]	640.19 [5]

* Distributions fitted to digitised TA542[25] data
AIC=Akaike information criterion; BIC=Bayesian information criterion
Source: Adapted from Eisai CS,[15] Appendix O

Figure 17 TTD distributions for cabozantinib, intermediate/poor risk subgroup

TTD=time to treatment discontinuation
Source: Eisai model

Nivolumab plus ipilimumab

Nivolumab plus ipilimumab TTD K-M data from the CheckMate 214 trial[99] are not in the public domain. The AG considered using pembrolizumab CLEAR trial TTD K-M data to model TTD for patients treated with nivolumab plus ipilimumab as both treatments are immunotherapies. However, the effect of the pembrolizumab 2 year stopping rule on TTD data is unclear. Therefore, in the absence of an alternative data source, the AG used the approach that was used to model TTD for patients treated with lenvatinib (generalised gamma distribution) to model TTD for patients treated with nivolumab plus ipilimumab.

In the MSD/AG model, treatment with ipilimumab was restricted to four cycles, i.e., was stopped at 12 weeks (in line with information provided in the nivolumab plus ipilimumab SmPC[50]).

5.15.2 Favourable risk subgroup

Of the two companies, only MSD provided cost effectiveness results for the favourable risk subgroup.

Pembrolizumab

The CLEAR trial pembrolizumab TTD K-M data are complete. Therefore, MSD and the AG used pembrolizumab TTD K-M data directly in the MSD and MSD/AG models to estimate the cost of treatment with pembrolizumab for the favourable risk subgroup. MSD applied a 2-year stopping rule in line with the CLEAR trial protocol. The AG used the TTD K-M data directly to estimate the cost of treatment with pembrolizumab for patients in the favourable risk subgroup. As the AG used the K-M data directly, an enforced 2 year stopping rule was not fully implemented; some patients remained on pembrolizumab for a short period of time beyond 2 years.

Lenvatinib, sunitinib, pazopanib and tivozanib

MSD fitted exponential distributions to the lenvatinib and sunitinib CLEAR trial TTD K-M data; these were the highest ranking distributions based on AIC statistics and BIC statistics (Table 55). The distributions considered by MSD and the AG are shown visually against the CLEAR trial TTD-K-M data in Figure 18 for lenvatinib and Figure 19 for sunitinib, pazopanib and tivozanib. MSD and the AG used these distributions to model TTD for patients treated with lenvatinib and sunitinib as they were also a good visual fit to the CLEAR trial TTD K-M data. MSD and the AG assumed that TTD for patients treated with pazopanib and tivozanib was the same as TTD for patients treated with sunitinib.

Table 55 MSD CLEAR trial TTD data goodness-of-fit statistics, favourable risk subgroup, IA3 data cut

Distribution	Lenvatinib		Sunitinib	
	AIC [rank]	BIC [rank]	AIC [rank]	BIC [rank]
Exponential†	[redacted] [1]	[redacted] [1]	[redacted] [1]	[redacted] [1]
Gamma	[redacted] [3]	[redacted] [3]	[redacted] [4]	[redacted] [4]
Generalised gamma	[redacted] [5]	[redacted] [6]	[redacted] [6]	[redacted] [7]
Gompertz	[redacted] [2]	[redacted] [2]	[redacted] [7]	[redacted] [6]
Log-logistic	[redacted] [6]	[redacted] [5]	[redacted] [3]	[redacted] [3]
Log-normal	[redacted] [7]	[redacted] [7]	[redacted] [2]	[redacted] [2]
Weibull	[redacted] [4]	[redacted] [4]	[redacted] [5]	[redacted] [5]

† Distribution used by MSD and the AG to model TTD for patients receiving lenvatinib and those receiving sunitinib
AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion.
Source: Adapted from MSD additional response to the AG clarification letter, Table 9 and Table 10

Figure 18 TTD distributions for lenvatinib, favourable risk subgroup

TTD=time to treatment discontinuation
Source: MSD model

Figure 19 TTD distributions for sunitinib, pazopanib and tivozanib, favourable risk subgroup

TTD=time to treatment discontinuation
Source: MSD model

5.15.3 AG scenario analyses: intermediate/poor and favourable risk subgroups (TTD)

Intermediate/poor risk subgroup

The AG explored the effect on cost effectiveness results of using the parametric distributions that had AIC statistics that were within five points of the AIC statistic for the distribution used to model TTD for patients receiving lenvatinib. The cabozantinib distribution was unchanged and the nivolumab plus ipilimumab distribution automatically updated as it was the same as the lenvatinib TTD distribution.

The AG explored the effect on cost effectiveness results of using alternative parametric distributions (i.e., the five distributions that had not been used in the AG base case analysis) to model TTD for patients treated with cabozantinib. The distribution for lenvatinib, and consequently for nivolumab plus ipilimumab, was unchanged.

The AG explored the effect on cost effectiveness results of using the MSD TTD FP NMA results applied to the AG TTD lenvatinib distribution to model TTD for patients treated with cabozantinib.

The AG explored the effect on cost effectiveness results of using the distribution used in the base case to model TTD for patients treated with pembrolizumab (Weibull) to model TTD for patients treated with nivolumab plus ipilimumab.

Favourable risk subgroup

The AG explored the effect on cost effectiveness results of using the parametric distributions that had AIC statistics that were within five points of the AIC statistic for the distribution used to model TTD for patients treated with lenvatinib; distributions for sunitinib, pazopanib and tivozanib were unchanged.

The AG explored the effect on cost effectiveness results of using the parametric distributions that had AIC statistics that were within five points of the AIC statistic for the distribution used to model TTD for patients treated with sunitinib and consequently for patients treated with pazopanib and tivozanib. The distribution for lenvatinib was unchanged.

5.16 Utility values

Eisai and MSD used EQ-5D-3L data (IA3 data cut) collected as part of the CLEAR trial to estimate utility values. In the CLEAR trial, the EQ-5D-3L questionnaire was administered at baseline (prior to first dose) on day 1 of each subsequent cycle until treatment discontinuation, at the discontinuation visit, at time of withdrawal and at the off-treatment visit (i.e., within 30 days of the final dose of study treatment). Thus, the data used to inform post-progression utility values were limited. The UK scoring functions were developed based on the time trade off technique. Values were calculated using safety population data; they were not calculated for the different risk subgroups.

Eisai used the health state utility value approach, with treatment specific utilities in the progression-free health state; CLEAR trial data showed that the utility values for patients treated with lenvatinib plus pembrolizumab and patients treated with sunitinib utility were statistically significantly different ([redacted]).

MSD used a time to death approach in their base case and carried out a scenario that explored the impact on cost effectiveness results of using the health state utility approach. In the scenario analysis, utility values varied depending on whether the patient was on- or off-treatment.

The AG considered that the MSD time to death approach provided the best reflection of the HRQoL of long-term survivors and used this approach in the MSD/AG model (Table 56).

Table 56 MSD time to death utility values (excluding AE disutilities)

Risk subgroup	Time to death (days)					
	360+	270-359	180-269	90-179	30-89	0-29
Intermediate/poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Favourable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Adapted from MSD response to additional clarification questions, Table 1

5.16.1 AG scenario analyses (utility values)

The AG carried out two scenario analyses. One scenario analysis used the Eisai treatment dependent health state utility values and the other used the MSD treatment independent health state utility values (Table 57).

Table 57 Eisai and MSD health state utility values

Company	Health state	Treatment	Intermediate/poor risk subgroup	Favourable risk subgroup
			Mean	
Pre-progression				
Eisai	Progression-free	LEN+PEM	[redacted]	NA
		Sunitinib	[redacted]	NA
		Pazopanib		
		Tivozanib		
		Cabozantinib		
MSD	Pre-progression (on-treatment)		[redacted]	[redacted]
	Pre-progression (off-treatment)		[redacted]	[redacted]
Post-progression				
Eisai	Post-progression (all treatments)		[redacted]	NA
MSD	Progressed (on-treatment)		[redacted]	[redacted]
	Progressed (off-treatment)		[redacted]	[redacted]

NA=not applicable
Source: Eisai CS,[15] Table 33 and MSD response to additional clarification questions, Table 2

5.17 Health state resource use and unit costs

Levels of health state resource use (outpatient consultations, CT scans and blood tests) modelled by Eisai and MSD differed. Eisai implemented the resource use estimates that were used to inform the NICE appraisal of pembrolizumab plus axitinib for untreated aRCC (TA650[35]) and MSD used the resource estimates that were used to inform the NICE appraisal of cabozantinib for untreated aRCC (TA542[25]).

Clinical advice to the AG was that:

- an initial CT scan was not necessary as scans would have previously been conducted to determine that the RCC needed treatment and the disease stage
- all patients would have an initial appointment with a consultant which would include blood tests

- patients would subsequently be seen monthly by a consultant, although, in the longer-term, some patients might be seen less frequently
- it was appropriate for resource use to be the same for patients in the pre-progression health sate (after the first visit) and patients in the post-progression health state as monitoring remained broadly the same regardless of treatment
- that the resource use estimates in the MSD economic model appeared too low.

Clinical advice to the AG was that the estimates used by Eisai were a better reflection of clinical practice than the estimates used by MSD; however, all patients would receive a blood test as part of the initial outpatient consultation (Table 58).

Table 58 Health state resource use

Health state	Resource	Eisai	MSD	AG
Progression-free: first week	Outpatient consultation	100%	100%	100%
	Computed tomography	0%	3%	0%
	Blood tests	0%	8%	100%
Progression-free: subsequent weeks	Outpatient	25%	8%	25%
	Computed tomography	8%	3%	8%
	Blood tests	25%	8%	25%
Post-progression	Outpatient	25%	8%	25%
	Computed tomography	8%	3%	8%
	Blood tests	25%	8%	25%

Source: Eisai CS,[15] Table 50 and MSD CS,[51] Table 48

Eisai, MSD and the AG sourced unit costs for all modelled health state resources from the National Schedule of NHS Costs 2019/2020[131] (Table 59).

Table 59 Health state unit costs used in MSD/AG model

Resource		Unit cost	HRG	Type of visit
Consultation	First visit	£253.20	WF01B (service code 370)	Non-Admitted Face-to-Face Attendance, First
	Subsequent visits	£200.20	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up
Computed tomography		£120.55	RD22Z	Outpatient
Blood test		£1.81	DAPS03	Integrated blood services

HRG=healthcare resource group; NA=not applicable
Source: National Schedule of NHS Costs 2019/2020[131]

5.18 Drug costs

Lenvatinib

Eisai and MSD estimated drug acquisition costs for lenvatinib and pembrolizumab based on the dosing schedules for each drug as described in the CLEAR trial protocol. Eisai calculated the cost of lenvatinib using a weighted average cost per mg based on the average dose received by CLEAR trial patients and MSD used weekly CLEAR trial dosing data. These data

were provided for the all-risk population and not separately by risk subgroups. Clinical advice to the AG was that dosing was unlikely to vary by risk subgroup.

Lenvatinib tablets are available in two strengths (4mg and 10mg); the cost of a 30-tablet pack is the same irrespective of dose. Clinical advice to the AG was that, in NHS clinical practice, a patient's dose of lenvatinib varies in line with the CLEAR trial protocol descriptions, i.e., a patient will start on a dose of 20mg per day and then their dose will be reduced to 14mg, then to 10mg, and finally to 8mg, with reductions ceasing once a level that the patient can tolerate has been reached. Further, clinical advice to the AG was that:

- a dose of 8mg per day was quite rare as patients unable to tolerate a 10mg per day dose were unlikely to be able to tolerate an 8mg per day dose
- in the short term, 14mg per day was the dose that most patients were titrated to from 20mg
- in the longer term, approximately 25% of patients were prescribed a 10mg per day dose.

As the cost per pack of lenvatinib is the same for a 20mg per day dose and a 14mg per day dose, the proportion of people prescribed a 10mg dose (i.e., one capsule) is important.

The AG has used the weekly lenvatinib CLEAR trial dosing data (available from the MSD model). The AG highlights that after 120 weeks, patient CLEAR trial data are limited and, therefore, are unreliable. The AG has costed lenvatinib using CLEAR trial data (tablets per week) over the first 120 weeks and, for the remainder of the model timeframe, used the average weekly number of lenvatinib tablets patients received between weeks 94 and 120 (i.e., the 6 months prior to the end of the reliable data). This approach meant that use of an RDI was not relevant.

Pembrolizumab

In the CLEAR trial, treatment with pembrolizumab was available for a maximum of 2 years. Based on CLEAR trial data, Eisai and MSD used an RDI multiplier (based on all-risk population data) to account for 'delays in drug administration' ([redacted]% and [redacted]% respectively). Eisai and MSD used the same methods to estimate RDI values and therefore it is unclear why the values presented by Eisai and MSD differ. Eisai did not provide the values used in their calculation; however, MSD did provide this detail and the AG was able to verify the MSD RDI value. Therefore, the AG used the MSD value in the MSD/AG model.

Sunitinib

Eisai, MSD and the AG estimated the cost of sunitinib using the CLEAR trial dosing schedule. Eisai and MSD used an RDI multiplier (estimated using CLEAR trial data) to adjust the cost of

sunitinib. Eisai used a mean value of [redacted]% (Eisai CS,[15] Table 38) and MSD used the published median value of 83.2%.[67] The AG has used the mean value ([redacted]%).

Pazopanib, tivozanib, cabozantinib and nivolumab plus ipilimumab

Eisai and MSD estimated the costs of treatment with pazopanib, tivozanib and cabozantinib using dosing schedules published in the relevant SmPCs (Table 60). Eisai and MSD used RDI multipliers published in previous NICE TAs to adjust the costs of pazopanib (86%), tivozanib (94%) and cabozantinib (94%) (Table 61). The AG considered that the approach used by the companies were appropriate and used the same dosing schedules and RDI values in the MSD/AG model.

The AG used the published dosing schedule for nivolumab plus ipilimumab[50] (Table 60). No RDI multiplier information was available for nivolumab plus ipilimumab and therefore the AG used the MSD pembrolizumab RDI multiplier ([redacted]%), based on CLEAR trial data, to adjust the cost of nivolumab plus ipilimumab.

Table 60 Treatment dosing schedules

Regimen	Treatment	Dose per administration	Frequency	Administration method
Pembrolizumab plus lenvatinib	Pembrolizumab	200mg	Every 3 wks	Intravenous
	Lenvatinib	Varies	Once daily	Oral
Sunitinib	Sunitinib	50mg	Once daily (4 wks on, 2 wks off)	Oral
Pazopanib	Pazopanib	800mg	Once daily	Oral
Tivozanib	Tivozanib	1.34mg	Once daily (3 wks on, 1 wk off)	Oral
Cabozantinib	Cabozantinib	60mg	Once daily	Oral
Nivolumab plus ipilimumab	Nivolumab	3mg/kg	Every 3 wks (4 doses)	Intravenous
	Ipilimumab	1mg/kg	Every 3 wks (4 doses)	Intravenous
	Nivolumab (monotherapy)	480mg	Every 4 wks	Intravenous

Source: Eisai CS,[15] Table 37, MSD CS,[51] Table 45 and nivolumab plus ipilimumab SmPC[50]

Table 61 Relative dose intensity multipliers used in the Eisai, MSD and MSD/AG model

Drug	Eisai		MSD		AG
	RDI	Source	RDI	Source	
Lenvatinib	69.7%	CLEAR trial	Used weekly dosing data from CLEAR trial		Used weekly dosing data from CLEAR trial
Pembrolizumab	[redacted]%	CLEAR trial	[redacted]%	CLEAR trial	[redacted]%
Sunitinib	[redacted]%	CLEAR trial mean	83.2%	CLEAR trial median	[redacted]%
Pazopanib	86%	NICE TA215[31]	86%	NICE TA215[31]	86%
Tivozanib	94%	NICE TA512[32]	94%	NICE TA512[32]	94%
Cabozantinib	94%	NICE TA542[25]	94.3%	NICE TA542[25]	94.3%
Nivolumab	NA		NA		Equal to pembrolizumab
Ipilimumab					Equal to pembrolizumab

AG=Assessment Group; NA=not applicable; TA=technology appraisal

For all first-line treatments (intervention and comparators), costs per cycle were calculated using published British National Formulary prices (online database) (Table 62).

Table 62 Drug acquisition costs (list prices)

Treatment	mg per unit	Pack size	Cost per pack
Lenvatinib	10mg/4mg	30	£1,437.00
Pembrolizumab	100mg	1 vial	£2,630.00
Sunitinib	12.5mg	28	£784.70
Pazopanib	200mg	30	£560.50
Tivozanib	1.3mg	21	£2,052.00
Cabozantinib	60mg	30	£5,143.00
Nivolumab	240mg	1	£2,633.00
Ipilimumab	50mg	1	£3,750.00

Source: Eisai CS,[15] Table 39, MSD CS,[51] Table 45 and nivolumab plus ipilimumab SmPC[50]

5.18.1 Drug administration costs

Drug administration costs are presented in Table 63. Eisai and MSD estimated chemotherapy administration costs using the National Schedule of NHS Costs 2019/2020 (SB12Z Simple parenteral chemotherapy at first attendance).[131] However, the costs associated with this code differ as Eisai has assumed that administration is an outpatient appointment (£221.35) and MSD has assumed that administration is a day case appointment (£299.61). Clinical advice to the AG is that chemotherapy infusions are delivered as part of an outpatient appointment and, therefore, the AG has used the same administration cost as Eisai (£221.35) for first attendance and SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle for all other attendances (£253.77).

Eisai and MSD assumed that the cost of administering oral drugs was zero. The AG considered that this was a conservative assumption and therefore included the cost of the delivery of oral chemotherapy for the first cycle and the cost of a hospital-based pharmacist dispensing the drugs for the subsequent cycles. These assumptions are the same as the assumptions used in TA645[33] (Table 63).

As nivolumab and ipilimumab are both IV drugs, the AG assumed that for the period patients received both drugs (first four cycles), the most appropriate administration cost was Deliver Complex Chemotherapy at First Attendance (SB14Z) – outpatient. For the subsequent cycles, when patients only received nivolumab, the administration cost used was Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z) – outpatient.

Table 63 National Schedule of NHS Costs 2019/20 drug administration codes and costs

Drug	Eisai	MSD	AG
Lenvatinib	Assume no administration costs for oral treatments		Deliver Exclusively Oral Chemotherapy (SB11Z) – Day case and Reg Day/Night £226.45 Hospital-based staff – Pharmacist [Band 6 radiographer - £55 per hour (assumed 12 minutes)] £11.00*
Pembrolizumab	Deliver Simple Parenteral Chemotherapy at First Attendance – outpatient (SB12Z) £221.35	Simple parenteral chemotherapy at first attendance – day case (SB12Z) £299.61	Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z) – outpatient £221.35
Sunitinib	Assume no administration costs for oral treatments		Deliver Exclusively Oral Chemotherapy (SB11Z) – Day case and Reg Day/Night £226.45 – first cycle only Hospital-based staff – Pharmacist [Band 6 radiographer - £55 per hour (assumed 12 minutes)] £11.00*
Pazopanib	Assume no administration costs for oral treatments		Same as sunitinib
Tivozanib			
Cabozantinib			
Nivolumab	NA**		Deliver Complex Chemotherapy at First Attendance (SB14Z) – outpatient £352.24 (for first 4 cycles when niv+ipi are delivered jointly) Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z) – outpatient £221.35 (from the 5th cycle – nivolumab maintenance)
Ipilimumab			

* Assumption based on administration costs used in TA645[33]
** Cost effectiveness results not presented for nivolumab plus ipilimumab
AG=Assessment Group; NA=not applicable
Source: National Schedule of NHS Costs 2019/20[131]

5.19 End of life costs

Eisai and MSD models included a fixed cost to cover end of life care (applied at death). Both companies used a published cost (inflated to 2019/20 prices) associated with delivering end of life care in hospital (Nuffield Trust report [132]). MSD also included costs for local authority funded social care, district nursing and GP visits (Nuffield Trust report [132]); these additional costs were considered relevant during NICE TA542[25] and TA650.[35] The AG considered that it was appropriate to include the additional costs associated with end of life care and has, therefore, used the MSD end of life costs in the MSD/AG model (£8,442.02).

5.20 Adverse events

Eisai and MSD assumed that the frequency of AEs did not vary by risk subgroup and used all-risk population AE rates for all risk groups. Clinical advice to the AG was that this approach was appropriate.

Eisai, MSD and the AG costed Grade ≥3 AEs that occurred in ≥5% of patients in either of the CLEAR trial treatment arms. Eisai, MSD and the AG used CLEAR trial AE rates for patients treated with lenvatinib plus pembrolizumab and sunitinib and rates used to inform NICE TAs for patients treated with sunitinib, pazopanib, tivozanib and cabozantinib. For patients treated with nivolumab plus ipilimumab, the AG used CheckMate 214 trial[99] AE data.

Eisai carried out a detailed process to estimate AE treatment costs; the approach used by MSD was much simpler and was largely based on assumptions. The AG was satisfied that the simpler approach used by MSD was appropriate and has used the MSD AE treatment costs in the MSD/AG model.

5.20.1 AG scenario analysis (AEs)

The AG carried out two scenario analyses: one in which AE costs were set to zero and one in which AE costs were doubled.

5.21 Subsequent treatments

Eisai and MSD relied on expert advice to forecast the specific subsequent treatments that patients would receive, and the proportions of patients receiving each of these specific treatments. Eisai estimates of subsequent treatment duration were based on data from the CLEAR trial; MSD relied on expert advice to estimate durations of treatment.

The AG considered that, for patients treated with lenvatinib plus pembrolizumab and sunitinib (pazopanib and tivozanib), modelled subsequent treatments should be based on the treatments received by patients in the CLEAR trial. The AG estimated subsequent treatments,

for each risk subgroup, separately using IA3 data presented by MSD (CS and response to clarification). Eisai also provided subsequent treatment data in their response to clarification (updated OS analysis); however, the MSD data were more detailed than the Eisai data and the AG was able to use the MSD data to estimate subsequent treatment costs using a micro-costing approach.

Based on clinical advice, the AG assumed that 60% of patients treated with cabozantinib would receive subsequent treatment with nivolumab and 40% of patients would receive a tyrosine kinase inhibitor (TKI), i.e., sunitinib, pazopanib or tivozanib. The AG assumed that the split between sunitinib, pazopanib and tivozanib was the same as the split for CLEAR trial patients randomised to treatment with lenvatinib plus pembrolizumab who were subsequently treated with a TKI. The duration of treatment with nivolumab was set equal to the average length of time that patients in the sunitinib arm of the CLEAR trial received nivolumab as a subsequent treatment and the duration of TKI treatment was set equal to the average length of time that patients in the sunitinib arm received a TKI as a subsequent therapy.

For patients treated with nivolumab plus ipilimumab, the AG assumed that subsequent treatments (and the duration of these treatments) were the same as those for CLEAR trial patients randomised to treatment with lenvatinib plus pembrolizumab.

The AG estimated the cost of two lines of subsequent treatment based on treatments received by at least five patients in each arm of the CLEAR trial. Treatments received by less than five patients or in the third-line setting were not considered as they were often used off-licence or were only available as part of a clinical trial. The total costs of subsequent treatments were reweighted to account for the cost of treatments received by fewer than five patients. Another limitation of this method was that any subsequent treatments received after the end of the trial period were not considered. The AG considers that MSD/AG subsequent treatment costs are likely to be underestimates.

5.21.1 AG sensitivity analyses (subsequent treatment costs)

The AG carried out sensitivity analyses that varied the costs of subsequent treatments by +/- 20%.

5.22 AG cost effectiveness results

As the treatment options for the intermediate/poor risk and favourable risk subgroups differ, the cost effectiveness results for these subgroups should be considered separately. The AG considers that the all-risk population results are not relevant to NHS patients; these results are presented in Appendix 17 (Section 9.17).

The AG cost effectiveness results for the intermediate/poor risk and favourable risk subgroups have been estimated using the list prices for the intervention, comparators and subsequent treatment drugs (Table 64 to Table 67). AG cost effectiveness results generated using confidential discounted prices are presented in a confidential appendix. Results from all AG probabilistic, sensitivity and scenario analyses are presented in Table 68 to Table 76.

A list of the AG scenarios can be found in Appendix 18 (Section 9.18). All of the parameters that were varied in the AG sensitivity and PSA analyses are listed in Appendix 19 (Section 9.19).

5.22.1 Intermediate/poor risk subgroup

For the intermediate/poor risk subgroup, the AG base case cost effectiveness results suggest that treatment with lenvatinib plus pembrolizumab generates more QALYs than cabozantinib or nivolumab plus ipilimumab but at a greater overall cost (list prices for all drugs). For the comparison of lenvatinib plus pembrolizumab versus cabozantinib, the ICER per QALY gained is £139,280 and for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab, the ICER per QALY gained is £218,482. Detailed results are presented in Table 64 and Table 65.

Table 64 AG pairwise deterministic results, intermediate/poor risk subgroup: LEM+PEM versus cabozantinib and versus nivolumab plus ipilimumab (list prices)

Drug	Total			Incremental: LEM+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEM+PEM	[redacted]	[redacted]	[redacted]	-	-	-	-
CABO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,249
NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,362

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; QALYs=quality adjusted life years

Table 65 AG fully incremental analysis, intermediate/poor risk subgroup (list prices)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
CABO	[redacted]	[redacted]	-	-	-
NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated by LEN+PEM
LEM+PEM	[redacted]	[redacted]	[redacted]	[redacted]	£166,249

AG=Assessment Group; ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

5.22.2 Favourable risk subgroup

For the favourable risk subgroup, the AG OS NMA results, and the CLEAR trial data suggest that treatment with sunitinib generates improved OS compared to treatment with lenvatinib plus pembrolizumab. The AG base case cost effectiveness results suggest that treatment with sunitinib generates more QALYs than lenvatinib plus pembrolizumab at a lower overall cost (list prices for all drugs), i.e., treatment with lenvatinib plus pembrolizumab is dominated by treatment with sunitinib. Detailed results are presented in Table 66 and Table 67.

Table 66 AG pairwise results, favourable risk subgroup: LEM+PEM versus sunitinib, versus pazopanib and versus tivozanib

Drug	Total			Incremental: LEM+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	[redacted]	[redacted]	-	-	-	-
SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

ICER=incremental cost effectiveness ratio; LYs=life years gained; QALYs=quality adjusted life year

Table 67 AG fully incremental analysis, favourable risk subgroup (list prices)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
SUNITINIB	[redacted]	[redacted]	-	-	-
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	PAZOPANIB is dominated by SUNITINIB
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	TIVOZANIB is dominated by SUNITINIB
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated by SUNITINIB

ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

5.23 AG probabilistic sensitivity analysis results

The AG undertook probabilistic sensitivity analyses (PSAs) using the parameter values and distributions detailed in Appendix 19 (Section 9.19). For both the intermediate/poor and favourable risk subgroups, as the MSD/AG model mean results (ICERs per QALY gained and incremental net monetary benefits (INMBs) converged by 1,000 iterations, the AG has presented cost effectiveness results generated using 1,000 iterations.

5.23.1 Intermediate/poor risk subgroup

For the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab, the AG PSA intermediate/poor risk subgroup pairwise incremental cost effectiveness results are shown in Table 68 and fully incremental results are shown

inTable 69. The corresponding scatter plot is shown in Figure 20 and the cost effectiveness acceptability curve (CEAC) is shown in Figure 21.

The mean probabilistic ICERs per QALY gained for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab are slightly higher than the deterministic cost effectiveness results. In all iterations, lenvatinib plus pembrolizumab was the most expensive treatment option and generated the most QALYs. At a willingness to pay (WTP) threshold of £50,000 per QALY gained, in 100% of iterations cabozantinib was the most cost effective treatment option. At a WTP threshold of £100,000 per QALY gained, in 0.8% of iterations lenvatinib plus pembrolizumab was the most cost effective treatment option.

Table 68 AG pairwise, intermediate/poor risk subgroup: LEM+PEM versus cabozantinib and versus nivolumab plus ipilimumab (list prices) (mean results from 1,000 PSA iterations)

Drug	Total			Incremental: LEM+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEM+PEM	[redacted]	[redacted]	[redacted]	-	-	-	-
CABO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,019
NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£134,253

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years

Table 69 AG fully incremental analysis, intermediate/poor risk subgroup (list prices) (mean results from 1,000 PSA iterations)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
CABO	[redacted]	[redacted]	-	-	-
NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated by LEN+PEM
LEM+PEM	[redacted]	[redacted]	[redacted]	[redacted]	£169,019

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years

Figure 20 AG cost and QALY scatter plot from 1,000 iterations: lenvatinib plus pembrolizumab, nivolumab plus ipilimumab and cabozantinib

Figure 21 AG cost effectiveness acceptability curve: lenvatinib plus pembrolizumab, cabozantinib and nivolumab plus ipilimumab

5.23.2 Favourable risk subgroup

For the comparison of lenvatinib plus pembrolizumab versus sunitinib, versus pazopanib and versus tivozanib, the AG PSA favourable risk subgroup pairwise incremental cost effectiveness results are shown in Table 70 and fully incremental results are shown in Table 71. The corresponding scatter plot is shown in Figure 22 and the CEAC is shown in Figure 23.

The mean probabilistic ICERs per QALY gained for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab are slightly higher than the deterministic cost effectiveness results. In all iterations, lenvatinib plus pembrolizumab was the most expensive treatment option and generated the most QALYs. At a willingness to pay (WTP) threshold of £50,000 per QALY gained, in 100% of iterations cabozantinib was the most cost effective treatment option. At a WTP threshold of £100,000 per QALY gained, in 0.8% of iterations lenvatinib plus pembrolizumab was the most cost effective treatment option.

The mean probabilistic results were almost identical to the deterministic cost effectiveness results; lenvatinib plus pembrolizumab was dominated by sunitinib, pazopanib and tivozanib, and sunitinib was the most cost effective treatment option. In all iterations, lenvatinib plus pembrolizumab was the most expensive treatment option and generated the fewest QALYs. As the QALYs generated for sunitinib, pazopanib and tivozanib are always the same in each iteration, the CEAC shows horizontal lines for these, i.e., the probability of any of these three treatments being cost effective does not vary with the WTP for a QALY threshold. In 85.9% of iterations, sunitinib was the cheapest treatment option and therefore was also the most cost effective option. In 14.1% of iterations, pazopanib was the cheapest treatment option and so the most cost-effective. Lenvatinib plus pembrolizumab or tivozanib were not the most cost effective options at any WTP threshold.

Table 70 AG pairwise results, favourable risk subgroup: lenvatinib plus pembrolizumab versus sunitinib, versus pazopanib and versus tivozanib (list prices) (mean results from 1,000 PSA iterations)

Drug	Total			Incremental: LEM+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	[redacted]	[redacted]	-	-	-	-
SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years

Table 71 AG fully incremental analysis, favourable risk subgroup (list prices)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
SUNITINIB	[redacted]	[redacted]	-	-	-
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	PAZOPANIB is dominated by SUNITINIB
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	TIVOZANIB is dominated by SUNITINIB
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated by SUNITINIB

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life years

[redacted]

Figure 22 AG cost and QALY scatter plot from 1,000 iterations: lenvatinib plus pembrolizumab sunitinib, pazopanib and tivozanib

[redacted]

Figure 23 AG cost effectiveness acceptability curve; lenvatinib plus pembrolizumab versus sunitinib, versus pazopanib and versus tivozanib

5.24 Sensitivity and scenario analyses

The AG performed one-way deterministic sensitivity analysis using the upper and lower bounds for all parameter values reported in Appendix 19 (Section 9.19).

5.24.1 AG one-way deterministic sensitivity analysis results

Intermediate/poor risk subgroup

The AG has presented tornado diagrams for the comparison of lenvatinib plus pembrolizumab versus cabozantinib (Figure 24) and versus nivolumab plus ipilimumab (Figure 25). INMBs with a value per QALY of £20,000 are shown as, in some cases, upper or lower bounds of input values generated negative ICERs per QALY gained which can be difficult to show (and interpret) in a tornado diagram. The tornado diagrams show that the INMBs were insensitive across the ranges of input values considered for most model parameters. Cost effectiveness results were most sensitive to the OS HRs for lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab.

Figure 24 AG tornado diagram: lenvatinib plus pembrolizumab versus cabozantinib

AE=adverse event; AG=Assessment Group; CT=computed tomography; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; OS=overall survival; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity

Figure 25 AG tornado diagram: lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab

AE=adverse event; AG=Assessment Group; CT=computed tomography; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; OS=overall survival; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity

Favourable risk subgroup

The AG has presented tornado diagrams for lenvatinib plus pembrolizumab versus sunitinib (Figure 26), versus pazopanib (Figure 27) and versus tivozanib (Figure 28). As treatment with lenvatinib plus pembrolizumab was dominated by sunitinib, pazopanib and tivozanib in the AG base case analysis, INMBs (with a WTP threshold of £20,000 per QALY) are shown; when treatments are dominated, cost effectiveness results can be difficult to show (and interpret) in a tornado diagram. The tornado diagrams show that the INMBs were insensitive across the range of input values considered for model parameters; the INMB values never change by more or less than 2%.

Figure 26 AG tornado diagram: lenvatinib plus pembrolizumab versus sunitinib

AE=adverse event; AG=Assessment Group; CT=computed tomography; EOL=end of life; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; OS=overall survival; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity

Figure 27 AG tornado diagram: lenvatinib plus pembrolizumab versus pazopanib

AE=adverse event; AG=Assessment Group; CT=computed tomography; EOL=end of life; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; OS=overall survival; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity

Figure 28 AG tornado diagram: lenvatinib plus pembrolizumab versus tivozanib

AE=adverse event; AG=Assessment Group; CT=computed tomography; EOL=end of life; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; OS=overall survival; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity

5.24.2 AG deterministic scenario analysis results (intermediate/poor risk subgroup)

Intermediate/poor risk subgroup

The AG has presented deterministic scenario results for the comparison of lenvatinib plus pembrolizumab versus cabozantinib (Table 72) and versus nivolumab plus ipilimumab (Table 73) for the intermediate/poor risk subgroup. The ICERs per QALY gained did not change significantly for most of the scenarios considered. This suggests that the results of the AG analyses were robust over most of the assumptions that were required to construct the MSD/AG model. The ICERs per QALY gained were sensitive to the magnitude of the discount rate but as there are no grounds to move away from using the annual base case value of 3.5% for costs and benefits, these results are not relevant. The AG considered that the following scenario results were particularly important when determining the cost effectiveness of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab:

- Uncertainty around the choice of PFS distribution or uncertainty around subsequent treatment costs did not significantly affect cost effectiveness results for lenvatinib plus pembrolizumab versus cabozantinib or versus nivolumab plus ipilimumab
- With the exception of using the MSD FP TTD approach to model TTD for cabozantinib, all the other AG alternative scenarios used to model TTD for lenvatinib plus pembrolizumab or cabozantinib, increased the size of the ICER per QALY gained for this comparison
- All the AG alternative scenarios used to model TTD for nivolumab plus ipilimumab or for lenvatinib plus pembrolizumab, decreased the ICERs per QALY gained for this comparison

- Using Eisai or MSD approaches to modelling OS for patients treated with cabozantinib lowers the ICER per QALY gained for lenvatinib plus pembrolizumab versus cabozantinib by 4.4% and 12.3% respectively; however, the resulting ICERs per QALY gained are still above £145,000. If the OS for patients treated with cabozantinib was the same as the OS for patients treated with lenvatinib plus pembrolizumab, then cabozantinib would dominate lenvatinib plus pembrolizumab.

Table 72 AG scenario analysis: lenvatinib versus cabozantinib (list prices)

AG scenarios Intermediate/poor risk subgroup	**Lenvatinib plus pembrolizumab**		**Cabozantinib**		**Incremental**		***ICER £/QALY***
	Cost	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,249
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£199,613
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£122,771
LEN+PEM PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,313
LEN+PEM PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,139
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,377
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,725
LEN+PEM PFS (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,665
LEN+PEM PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,330
CAB MSD FP PFS HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,248
LEN+PEM OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£143,746
Eisai CABO OS HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£158,945
MSD CABO FP OS HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£145,823
CABO OS=LEN+PEM OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
LEN+PEM TTD (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£175,417
LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£169,392
LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£175,541
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£155,332
Eisai CABO TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£186,377
Eisai CABO TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£172,583
Eisai CABO TTD (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£185,941
Eisai CABO TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£178,656
Eisai CABO TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£181,077
MSD CABO FP TTD HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£166,249
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£174,341

AG scenarios Intermediate/poor risk subgroup	Lenvatinib plus pembrolizumab		Cabozantinib		Incremental		*ICER £/QALY*
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Eisai health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,260
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£168,187
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£163,967
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165,702
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£167,141

AE=adverse events; AG=Assessment Group; FP=fractional polynomial; HR=hazard ratio; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 73 AG scenario analysis: lenvatinib versus nivolumab plus ipilimumab (list prices)

AG scenarios Intermediate/poor risk subgroup	**Lenvatinib plus pembrolizumab**		**Nivolumab plus ipilimumab**		**Incremental**		***ICER* £/QALY**
	Cost	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,362
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£161,647
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,200
LEN+PEM PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,926
LEN+PEM PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£132,574
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£134,380
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£129,201
LEN+PEM PFS (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£128,425
LEN+PEM PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£134,052
LEN+PEM OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£116,331
LEN+PEM TTD (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£85,146
LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£116,143
LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£84,529
MSD LEM+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£190,334
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£119,761
Eisai health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£136,597
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,673
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,817
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£132,004
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£134,954
NIV+IPI=Eisai PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominant
OS LEM+PEM=OS NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated

AE=adverse events; AG=Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

5.24.3 AG deterministic scenario analysis results (favourable risk subgroup)

The AG has presented deterministic scenario results for the comparison of lenvatinib plus pembrolizumab versus sunitinib (Table 74), versus pazopanib (Table 75) and versus tivozanib (Table 76) for the favourable risk subgroup. Lenvatinib plus pembrolizumab was dominated by sunitinib, pazopanib and tivozanib across all scenarios considered.

Table 74 AG scenario results: lenvatinib versus sunitinib (list prices)

AG scenario Favourable risk subgroup	**Lenvatinib plus pembrolizumab**		**Sunitinib**		**Incremental**		**ICER per QALY**
	Costs	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated by SUNITINIB
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SUNITINIB PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SUNITINIB PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SUNITINIB PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SUNITINIB PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AG OS NMA HR for SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OS LEN+PEM=OS SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG scenario Favourable risk subgroup	Lenvatinib plus pembrolizumab		Sunitinib		Incremental		ICER per QALY
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
MSD SUNITINIB TTD (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD SUNITINIB TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD SUNITINIB TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD SUNITINIB TTD (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD SUNITINIB TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD SUNITINIB TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation; OS=overall survival

Table 75 AG scenario results: lenvatinib versus pazopanib (list prices)

AG scenario Favourable risk subgroup	**Lenvatinib plus pembrolizumab**		**Pazopanib**		**Incremental**		**ICER per QALY**
	Costs	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated by PAZO
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PAZOPANIB PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PAZOPANIB PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PAZOPANIB PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PAZOPANIB PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AG OS NMA HR for PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OS LEN+PEM=OS PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD PAZOPANIB TTD (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD PAZOPANIB TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD PAZOPANIB TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD PAZOPANIB TTD (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD PAZOPANIB TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG scenario Favourable risk subgroup	Lenvatinib plus pembrolizumab		Pazopanib		Incremental		ICER per QALY
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
MSD PAZOPANIB TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation; OS=overall survival

Table 76 AG scenario results: lenvatinib versus tivozanib (list prices)

AG scenario Favourable risk subgroup	**Lenvatinib plus pembrolizumab**		**Tivozanib**		**Incremental**		**ICER per QALY**
	Costs	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated by TIVO
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LEN+PEM PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TIVOZANIB PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TIVOZANIB PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TIVOZANIB PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TIVOZANIB PFS (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AG OS NMA HR for TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
OS LEN+PEM=OS TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD TIVOZANIB TTD (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD TIVOZANIB TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD TIVOZANIB TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD TIVOZANIB TTD (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD TIVOZANIB TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG scenario Favourable risk subgroup	Lenvatinib plus pembrolizumab		Tivozanib		Incremental		ICER per QALY
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
MSD TIVOZANIB TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation; OS=overall survival

5.25 Discussion of the cost effectiveness analysis

The data (clinical effectiveness and cost effectiveness) used to populate the MSD/AG model are relevant to NHS clinical practice and can be used to inform NICE decision making.

The AG considered the cost effectiveness of lenvatinib plus pembrolizumab versus relevant comparators for the two distinct risk subgroups that comprise the all-risk population: patients with intermediate/poor risk disease and patients with favourable risk disease. For the largest risk subgroup (intermediate/poor risk disease), OS data from the CLEAR trial were used in the MSD/AG model (via the AG OS NMAs) to generate cost effectiveness results for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab.

An area of uncertainty that could not be resolved was around TTD for patients in the intermediate/poor risk subgroup who were treated with nivolumab plus ipilimumab. In the base case analysis, the AG assumed that nivolumab plus ipilimumab TTD data could be represented by lenvatinib TTD data (CLEAR trial). However, this assumption may not be valid as, compared to lenvatinib, both nivolumab and ipilimumab have different mechanisms of action, means of administration and dosing schedules. An alternative approach considered by the AG as a scenario analysis was to use the CLEAR trial MSD pembrolizumab TTD estimates (generalised gamma distribution) to represent TTD for patients treated with nivolumab plus ipilimumab. However, such an approach results in an implausibly long tail and generates higher costs for nivolumab plus ipilimumab than for lenvatinib plus pembrolizumab. Whilst the AG considers that the approach in the AG base case to model TTD for patients treated with nivolumab plus ipilimumab was reasonable (CLEAR trial lenvatinib TTD data) and was preferable to using CLEAR trial MSD pembrolizumab TTD, the AG cannot reject the possibility that nivolumab plus ipilimumab is more costly than lenvatinib plus pembrolizumab at list prices.

For the favourable risk subgroup, due to limited comparator RCT data, the AG assumed that the clinical effectiveness of pazopanib and tivozanib was equal to that of sunitinib. This assumption aligns with the view of previous NICE ACs.[25,26,32,33] Evidence from the CLEAR trial was incorporated into the MSD/AG model and generated cost effectiveness results that suggested that lenvatinib plus pembrolizumab was dominated by sunitinib, pazopanib and tivozanib. This finding was robust for all analysis of uncertainty undertaken by the AG.

6 DISCUSSION

6.1 Statement of principal findings

NICE has recommended different treatments for patients with untreated aRCC with different levels of disease risk (intermediate/poor risk and favourable risk subgroups). In the main body of the report, the AG has presented clinical effectiveness results for the three risk groups and has presented cost effectiveness results for patients in the intermediate/poor risk and favourable risk subgroups; cost effectiveness results for the all-risk population are presented in Appendix 17 (Section 9.17).

6.1.1 Direct clinical effectiveness results

The AG systematic review of clinical effectiveness evidence only identified one RCT of lenvatinib plus pembrolizumab versus sunitinib for patients with untreated aRCC, the CLEAR trial. Results from this trial demonstrated improved PFS and ORR for lenvatinib plus pembrolizumab in the intermediate/poor and favourable risk subgroups and all-risk population. CLEAR trial results from the updated OS analysis showed a statistically significant improvement for patients treated with lenvatinib plus pembrolizumab versus patients treated with sunitinib for the intermediate/poor risk subgroup and the all-risk population; there were too few events in the favourable risk subgroup for robust OS conclusions to be drawn. Generally, the AEs experienced by patients treated with lenvatinib plus pembrolizumab were consistent with the known safety profile of the two drugs. When compared to treatment with sunitinib, treatment with lenvatinib plus pembrolizumab appears to neither improve nor worsen HRQoL.

6.1.2 Indirect clinical effectiveness results

The AG carried out Bayesian HR NMAs for the three patient disease risk groups. However, due to limited data availability, it was not possible to carry out NMAs for all outcomes for all three patient risk groups. Further, as networks were sparse, it was only possible to generate meaningful results using FE NMAs.

AG PFS NMA results for the intermediate/poor risk subgroup, the favourable risk subgroup and the all-risk population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons due to within trial PH violations or uncertainty regarding the validity of the PH assumption.

AG OS NMA results for the intermediate/poor risk subgroup suggested that there was a numerical, but not a statistically significant, improvement in OS for patients treated with lenvatinib plus pembrolizumab compared with patients treated with cabozantinib or nivolumab

plus ipilimumab. Due to within trial PH violations or uncertainty regarding the validity of the PH assumption, the AG OS NMA results for the favourable risk subgroup and the all-risk population should not be used to infer any statistically significant difference (or lack of statistically significant difference) for any of the treatment comparisons.

The AG ORR NMA showed a statistically significantly improved ORR for lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab and a non-statistically significant numerical advantage for lenvatinib plus pembrolizumab versus cabozantinib in the intermediate/poor risk subgroup. Lenvatinib plus pembrolizumab also resulted in statistically significant improvements versus sunitinib and pazopanib in the all-risk population. Evidence was unavailable versus tivozanib in the all-risk population, or versus any relevant comparator in the all-risk population.

Results from the AG AE NMAs in the intermediate/poor risk subgroup showed non-statistically significant evidence that lenvatinib plus pembrolizumab resulted in an increase in Grade ≥3 AEs versus cabozantinib. In the all-risk population, there were statistically significantly more Grade ≥3 AEs for patients treated with lenvatinib plus pembrolizumab versus sunitinib and versus pazopanib. It was not possible for the AG to perform any HRQoL NMAs due to the heterogeneity of the HRQoL outcome scales used in the included trials and limited reported data (i.e., 95% CIs not reported, data not reported separately for risk subgroups).

6.1.3 Cost effectiveness results

For the intermediate/poor risk subgroup, AG base case cost effectiveness results (list prices) suggested that treatment with lenvatinib plus pembrolizumab generated more QALYs than cabozantinib and more QALYs than nivolumab plus ipilimumab, but at a greater overall cost than either of these two treatments. Using list prices, the ICERs per QALY gained for the comparison of lenvatinib plus pembrolizumab versus cabozantinib and versus nivolumab plus ipilimumab exceeded £100,000.

For the favourable risk subgroup, AG base case cost effectiveness results (list prices) suggested that treatment with sunitinib generated more QALYs than lenvatinib plus pembrolizumab at a lower overall cost, i.e., treatment with lenvatinib plus pembrolizumab was dominated by treatment with sunitinib (and, using the assumption of equivalent effectiveness, by pazopanib and tivozanib).

The AG base case cost effectiveness results for the intermediate/poor risk and favourable risk subgroups were robust over most of the assumptions used in the AG PSA, sensitivity and scenario analyses.

6.2 Strengths, limitations and uncertainties of the assessment

6.2.1 Strengths

Use of CLEAR trial data

The CLEAR trial is a well-designed trial and clinical advice to the AG is that efficacy and safety results are generalisable to NHS clinical practice for patients with untreated aRCC. This trial provided reliable evidence for the AG direct and indirect comparisons of lenvatinib plus pembrolizumab versus all relevant treatments listed in the final scope[27] issued by NICE.

Comparators

The AG included nivolumab plus ipilimumab as a comparator (intermediate/poor risk subgroup). Evidence for this comparison was missing from the Eisai[15] and MSD[51] submissions to NICE.

Cost effectiveness results

The MSD/AG model was populated with data provided by Eisai[15] and data provided by MSD[51] and generated base case ICERs per QALY gained that can be used to inform decision making. The AG carried out extensive one-way sensitivity analyses, scenario analyses and PSA. Results from these analyses demonstrate that AG base case cost effectiveness results are robust.

6.2.2 Weaknesses

Lack of direct evidence

Direct efficacy and safety evidence is only available for the comparison of lenvatinib plus pembrolizumab versus sunitinib from a single RCT. However, previous NICE ACs[25,26,32,33] have concluded that it may be appropriate to assume that sunitinib, pazopanib and tivozanib are similarly effective in clinical practice.

PH assumption

The PH assumption is violated for the data used in five of the six time to event (PFS and OS) NMAs, the exception being the intermediate/poor risk subgroup OS NMAs. This means that the HRs estimated from these NMAs are not applicable to all time points across the observed follow-up of the trials included in the NMAs. Further, the AG only has confidence in the FE NMA results. RE NMA results are presented in an appendix; these are considered unusable due to convergence issues which have occurred due the small number of included trials and sparse data.

6.2.3 Uncertainties

CLEAR trial subsequent treatments

In addition to a treatment-switching analysis to test whether adjusting for the effect of subsequent treatment affected OS results, Eisai[15] also conducted post-hoc analyses that examined OS for patients who did and did not receive subsequent treatment separately. The PH assumption was violated for patients who received subsequent treatments; the K-M data suggested an [redacted] and patients treated with sunitinib experienced an OS benefit. Clinical advice to the AG is that patients who do not receive subsequent treatments are a heterogeneous group and, therefore, the results from this post-hoc analysis are difficult to interpret.

AG NMA results

The main area of uncertainty affecting interpretation of AG HR NMA results was the effect of PH assumption violations; this was an issue for five of the six time to event (PFS and OS) NMAs.

There were limited data to inform some indirect comparisons. For the IMDC/MSKCC favourable risk subgroup there were no ORR data for any of the comparators and for the all-risk population there were no ORR data for tivozanib. Similarly, there were no AE outcomes available for nivolumab plus ipilimumab for the intermediate/poor risk subgroup, all comparators for the IMDC/MSKCC favourable risk subgroup, and tivozanib for the all-risk population.

A total of 13% of patients included in the SWITCH trials,[97,102] had non-clear cell aRCC. Results were not reported separately for patients with clear cell and non-clear cell histology. However, the AG considers that the inclusion of this proportion of patients with non-clear cell histology would not have a substantial impact on NMA results.

NICE ACs[25,26,32,33] have concluded that sunitinib, pazopanib and tivozanib can be considered to deliver similar efficacy outcomes. This means that CLEAR trial sunitinib results could be used as a proxy for the efficacy of pazopanib and tivozanib for the all-risk population and for the favourable risk subgroup. Thus, conclusions regarding the relative efficacy of lenvatinib plus pembrolizumab versus pazopanib and versus tivozanib may be generated from the CLEAR trial.

Since the OS PH assumptions for the data used to populate the AG OS NMAs were not violated for patients in the intermediate/poor risk subgroup, the AG OS NMA results are robust. However, the PFS PH assumptions for data used to populate the AG PFS NMAs were violated in some cases and, therefore, these results should not be used to infer any statistically significant difference (or lack of statistically significant difference) between treatments. However, a naïve comparison, shows that CLEAR trial median PFS for patients treated with lenvatinib plus pembrolizumab ([redacted] months) is longer than the PFS for patients treated with cabozantinib (8.6 months[96]) or nivolumab plus ipilimumab (11.6 months[99]). This is, potentially, the area of relative clinical effectiveness for patients with untreated aRCC, where there is most uncertainty.

Adverse events

While it was not possible for the AG to present AE evidence for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab, previously published reviews have compared the relative effectiveness of combination therapies to treat aRCC. The Mori et al 2021[54] meta-analysis results showed that lenvatinib plus pembrolizumab was less well tolerated (any AE, Grade ≥3 AEs and discontinuation due to AEs) than nivolumab plus cabozantinib or pembrolizumab plus axitinib. Three other NMAs[55-57] also reported that patients who received lenvatinib plus pembrolizumab were more likely to experience Grade ≥3 AEs and treatment discontinuations (due to AEs) when compared with other combination therapies, including nivolumab plus ipilimumab. As these published NMAs[55-57] were all conducted in the all-risk population, results are of limited relevance to NHS patients.

Cost effectiveness

AG OS NMA results for the intermediate/poor and favourable risk subgroups showed that there were no statistically significant differences between treatments. As AG cost effectiveness results are driven by differences in OS between treatments, if there is no OS gain for patients treated with lenvatinib plus pembrolizumab versus comparators, then the higher costs associated with lenvatinib plus pembrolizumab (list prices) means that it is unlikely to be a cost effective treatment.

An area of uncertainty that could not be resolved was around TTD for the intermediate/poor risk subgroup who were treated with nivolumab plus ipilimumab. The AG base case assumption that nivolumab plus ipilimumab TTD data would equal CLEAR trial lenvatinib TTD data may not be valid as both nivolumab and ipilimumab have different mechanisms of action, means of administration and dosing schedules compared to lenvatinib.

6.3 Other relevant factors

Favourable risk population

NICE[25,39] has recommended aRCC treatments for the all-risk population and for the intermediate/poor risk subgroup. If a patient does not have intermediate/poor risk disease then, by definition, the patient has favourable risk disease. The AG has, therefore, carried out clinical and cost effectiveness analyses for the favourable risk subgroup. Efficacy results from a recent population-based study[20] showed that median OS for the all-risk population was approximately half the length of that for the favourable risk subgroup (all risk population: 28.6 [95% CI: 25.9 to 31.0] months; favourable risk subgroup: 52.1 [95% CI: 43.4 to 61.2] months). These results suggest that it is informative to consider the favourable risk subgroup separately, alongside results for the intermediate/poor risk subgroup.

Whilst there were few events, favourable risk subgroup CLEAR trial results show no statistically significant OS benefit for lenvatinib plus pembrolizumab versus sunitinib; these results are consistent with previously published reviews[52,54,58] of combination therapies, including lenvatinib plus pembrolizumab.

It was beyond the scope of this MTA to compare lenvatinib plus pembrolizumab versus avelumab plus axitinib. Clinical advice to the AG is that treatment with avelumab plus axitinib is the preferred option for patients with favourable risk aRCC.

7 CONCLUSIONS

Good quality efficacy and safety evidence for the comparison of lenvatinib plus pembrolizumab versus sunitinib was available from the CLEAR trial. For most of the AG Bayesian HR NMA comparisons, it was difficult to reach conclusions due to within trial PH violations or uncertainty regarding the validity of the PH assumption. However, the data (clinical effectiveness and cost effectiveness) used to populate the MSD/AG model are relevant to NHS clinical practice and can be used to inform NICE decision making. The all-risk population comprises patients with intermediate/poor risk and patients with favourable risk disease. The AG cost effectiveness analyses have focused on the two subgroups. For all comparisons, the ICERs per QALY gained estimated by the AG were over £100,000.

7.1 Implications for service provision

Clinical advice to the AG is that, if NICE were to recommend lenvatinib plus pembrolizumab as a treatment option for patients with aRCC, there would be minimal impact on current NHS staffing and infrastructure.

7.2 Suggested research priorities

Clinical advice to the AG is that avelumab plus axitinib is the preferred first-line treatment option for patients with favourable risk disease who can tolerate this combination. As avelumab plus axitinib is currently only available to NHS patients via the CDF, avelumab plus axitinib was not a relevant comparator for this appraisal. If NICE were to recommend treatment with avelumab plus axitinib, clinical and cost effectiveness comparisons of this treatment combination versus lenvatinib plus pembrolizumab (if recommended), sunitinib, pazopanib and tivozanib would generate useful information for clinicians and patients.

Clinical advice to the AG is that the likelihood of future RCTs versus established treatments is low. Therefore, it is important that real world evidence is monitored to check that results seen in clinical practice reflect RCT results for patients with untreated aRCC.

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9 APPENDICES

9.1 Appendix 1: Systematic reviews including patients treated with lenvatinib plus pembrolizumab

Table 77 Analyses of combination therapy for aRCC which included patients treated with lenvatinib plus pembrolizumab

Author (Year)	Title	Population (n=total patients)	Stated purpose and Included studies	Main results / conclusions
Ciccarese et al (2021)[52]	Efficacy of VEGFR-TKIs plus immune checkpoint inhibitors in mRCC for patients with favourable IMDC prognosis.	1st line mRCC patients with favourable IMDC prognosis (n=839)	Meta-analysis evaluating whether the combinations of VEGFR-TKI+ICI compared to VEGFR-TKIs alone improve the outcome of mRCC patients with favourable IMDC prognosis. Included 4 RCTs of VEGFR-TKI+ICI therapies (pembrolizumab plus axitinib, nivolumab plus cabozantinib, avelumab plus axitinib, lenvatinib plus pembrolizumab) versus sunitinib.	Combination therapies improved PFS, but did not significantly prolong OS compared to sunitinib. Combination therapies resulted in a higher rate of treatment discontinuation compared to sunitinib.
Massari et al (2021)[53]	Immune-based combinations for the treatment of mRCC.	Treatment naïve mRCC patients (n=5175)	Meta-analysis of phase III clinical trials of immune-based combinations in mRCC patients. Included 6 RCTs of immune-based combination therapies (pembrolizumab plus axitinib, nivolumab plus cabozantinib, avelumab plus axitinib, pembrolizumab plus bevacizumab, nivolumab plus ipilimumab) versus sunitinib.	Compared with sunitinib, combination therapy resulted in statistically significant improvements in PFS, OS and ORR. Some combination therapies resulted in more all-Grade and Grade ≥3 AEs and others less all-Grade and Grade ≥3 AEs than treatment with sunitinib.
Mori et al (2021)[54]	Differences in oncological and toxicity outcomes between PD-L1 and PD-1 inhibitors in mRCC.	1st line mRCC patients (n=4025)	Systematic review, meta-analysis and NMA assessing the differences between anti-PD-1 and anti-PD-L1 therapies in RCTs of combination therapies. Included 5 RCTs total. 3 RCTs for PD-1 meta-analysis of combination therapies (pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab) versus sunitinib.	Anti-PD-1 type combination therapy (including lenvatinib plus pembrolizumab) had statistically significantly longer PFS, OS and ORR than sunitinib in the all-risk population and intermediate/poor risk subgroup. However, there was no statistically significant difference for OS in the favourable risk subgroup. There was no difference versus sunitinib for any grade AEs, but combination therapy had significantly worse grade ≥3 AEs. Lenvatinib plus pembrolizumab was less tolerated than other PD-1 combination therapies.

Author (Year)	Title	Population (n=total patients)	Stated purpose and Included studies	Main results / conclusions
Nocera et al (2021)[55]	Clinical outcomes and adverse events after first-line treatment in metastatic renal cell carcinoma: A systematic review and meta-analysis.	1st line mRCC patients (n=3320)	NMA of first-line trials comparing immune-based combination therapies. Only phase III RCTs with proven OS benefit relative to sunitinib were included, 4 in total. Interventions were: pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab, nivolumab plus ipilimumab	In NMA-derived ranking, against other combination therapies and sunitinib, lenvatinib plus pembrolizumab ranked first for PFS and ORR, and second for OS for providing maximal benefit. Lenvatinib plus pembrolizumab resulted in statistically significantly more grade ≥3 AEs than sunitinib and was ranked lower (i.e., considered to be least tolerated) than all other combination therapies.
Quhal et al (2021a)[56]	First-line immunotherapy-based combinations for mRCC.	1st line mRCC patients (n=5121)	NMA of the efficacy and safety of first-line ICI-based combination therapies. Included 6 RCTs of immune-based combination therapies (pembrolizumab plus axitinib, nivolumab plus cabozantinib, avelumab plus axitinib, lenvatinib plus pembrolizumab, atezolizumab plus bevacizumab, nivolumab plus ipilimumab).	Immune-based combination therapies had higher likelihood of providing better PFS, OS and ORR than sunitinib. Lenvatinib plus pembrolizumab resulted in statistically significantly improved PFS and ORR versus sunitinib. Compared with other immune-based combination therapies, lenvatinib plus pembrolizumab had highest likelihood of providing maximal PFS benefit and highest ORR. In the intermediate/poor risk subgroup, lenvatinib plus pembrolizumab had the highest likelihood of providing maximal PFS and OS and the highest probability of maximal PFS benefit in the favourable risk subgroup. The highest likelihood of grade ≥3 AEs and AE-related treatment discontinuation was associated with lenvatinib plus pembrolizumab.
Quhal et al (2021b)[57]	Adverse events of systemic immune-based combination therapies in the first-line treatment of patients with mRCC.	1st line mRCC patients (n=5121)	Comparison of the safety profiles of systemic immune checkpoint inhibitor-based combination therapies that were evaluated in the first-line setting of the management of patients with aRCC or mRCC. Included 6 RCTs of ICI-combination therapies (pembrolizumab plus axitinib, nivolumab plus cabozantinib, avelumab plus axitinib, lenvatinib plus pembrolizumab, atezolizumab plus bevacizumab, nivolumab plus ipilimumab).	Low treatment-related mortality was found from all combination therapies with no statistically significant differences versus sunitinib. Lenvatinib plus pembrolizumab had highest likelihood of grade ≥3 AEs, and treatment discontinuation due to AEs. Lenvatinib plus pembrolizumab had the highest likelihood of all-grade adrenal insufficiency and high-grade AST increase. All combinations had low likelihood of thrombocytopenia and neutropenia than sunitinib.

Author (Year)	Title	Population (n=total patients)	Stated purpose and Included studies	Main results / conclusions
Shpilsky et al (2021)[58]	First-line immunotherapy combinations in advanced renal cell carcinoma: a rapid review and meta-analysis.	1st line aRCC patients (n=5121)	Meta-analysis to combine the evidence of available first-line combination therapies compared to sunitinib monotherapy in advanced renal cell carcinoma. Included 6 RCTs of combination therapies (pembrolizumab plus axitinib, nivolumab plus cabozantinib, avelumab plus axitinib, lenvatinib plus pembrolizumab, atezolizumab plus bevacizumab, nivolumab plus ipilimumab).	Combination therapies resulted in statistically significantly improved PFS, OS compared to sunitinib in the all-risk population and intermediate/poor risk subgroup. ORR and AEs were only reported for the all-risk population. ORR was statistically significantly improved versus sunitinib. The incidence of grade ≥3 AEs was comparable between combination therapies and sunitinib. There were no statistically significant differences between combination therapies and sunitinib for PFS or OS in the favourable risk subgroup.

AE=adverse event; ALT=alanine transaminase; aRCC=advanced cell renal cell carcinoma; AST=aspartate aminotransferase; IMDC=International Metastatic Renal cell Carcinoma Database Consortium; mRCC=metastatic renal cell carcinoma; NMA=network meta-analysis; ORR=overall response rate; OS=overall survival; PD-1=programmed cell death-1; PD-L1=programmed cell death ligand-1; PFS=progression-free survival; P+Ax=pembrolizumab plus axitinib; P+L=pembrolizumab plus lenvatinib; sun=sunitinib; VEGFR-ICI+TKI=vascular endothelial growth factor receptor tyrosine kinase inhibitor

9.2 Appendix 2: AG search strategy for clinical and cost effectiveness

9.2.1 Clinical effectiveness searches

MEDLINE (via Ovid)

Ovid MEDLINE(R) ALL <1946 to October 07, 2021>

1	exp Carcinoma, Renal Cell/
2	exp Kidney Neoplasms/
3	(renal adj2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
4	(kidney adj1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
5	(clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
6	(non?clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
7	hypernephroma.tw,kw.
8	hypernephroid carcinoma*.tw,kw.
9	grawitz tumo?r$.tw,kw.
10	rcc.tw,kw.
11	or/1-10
12	(advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable).tw,kw. or Neoplasm Metastasis/
13	11 and 12
14	(mrcc or arcc).tw,kw.
15	13 or 14
16	randomized controlled trial.pt.
17	controlled clinical trial.pt.
18	(randomized or randomised).ab.
19	placebo.ab.
20	clinical trials as topic.sh.
21	randomly.ab.
22	trial.ti.
23	(randomised or randomized or RCT).ti.
24	or/16-23
25	exp animals/ not humans.sh.
26	24 not 25
27	15 and 26
28	limit 27 to english language

Note: Cochrane RCT sensitivity and precision maximising filter, adapted to search for (randomised or randomized or RCT) in title field. https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#_Ref19198290

The Cochrane Library (CENTRAL)

https://www.cochranelibrary.com/
Cochrane Central Register of Controlled Trials
Issue 10 of 12, October 2021

#1	MeSH descriptor: [Carcinoma, Renal Cell] explode all trees
#2	MeSH descriptor: [Kidney Neoplasms] explode all trees
#3	((renal NEAR/2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw
#4	((kidney NEAR/1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw
#5	((clear-cell NEAR/3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw
#6	(("non-clear cell" NEAR/3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw
#7	(hypernephroma):ti,ab,kw
#8	(hypernephroid carcinoma*):ti,ab,kw
#9	(grawitz tumo?r*):ti,ab,kw
#10	(rcc):ti,ab,kw
#11	{OR #1-#10}g
#12	(advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable):ti,ab,kw
#13	MeSH descriptor: [Neoplasm Metastasis] this term only
#14	#12 OR #13
#15	#11 AND #14
#16	(mrcc or arcc):ti,ab,kw
#17	#15 OR #16

Note: Cannot limit to English language
Searches terms with and without hyphen i.e. same results for clear-cell as for “clear cell”

Embase (via Ovid)

Embase <1974 to 2021 October 07>

1	exp renal cell carcinoma/
2	exp kidney tumor/ or exp kidney carcinoma/
3	(renal adj2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
4	(kidney adj1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
5	(clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
6	(non?clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
7	hypernephroma.tw,kw.
8	hypernephroid carcinoma*.tw,kw.
9	grawitz tumo?r$.tw,kw.
10	rcc.tw,kw.
11	or/1-10
12	(advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable).tw,kw.
13	metastasis/
14	12 or 13
15	11 and 14
16	(mrcc or arcc).tw,kw.

17	15 or 16
18	randomized controlled trial.sh.
19	controlled clinical trial.sh.
20	(randomized or randomised).ab.
21	placebo.ab.
22	"clinical trial (topic)"/
23	randomly.ab.
24	trial.ti.
25	(randomised or randomized or RCT).ti.
26	or/18-25
27	(random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
28	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
29	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.
30	(Systematic review not (trial or study)).ti.
31	(nonrandom$ not random$).ti,ab.
32	Random field$.ti,ab.
33	(random cluster adj3 sampl$).ti,ab.
34	(review.ab. and review.pt.) not trial.ti.
35	we searched.ab. and (review.ti. or review.pt.)
36	update review.ab.
37	(databases adj4 searched).ab.
38	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
39	Animal experiment/ not (human experiment/ or human/)
40	or/27-39
41	26 not 40
42	17 and 41
43	limit 42 to embase
44	limit 42 to (conference abstracts and yr="2019 -Current")
45	43 or 44
46	limit 45 to english language

Note: Adapted use of Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2018 revision) [NB there is no Cochrane RCT sensitivity and precision maximising filter for Embase]. Lines #18-25 are translated from the MEDLINE RCT filter above.
https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies#_Ref19198290

PubMed

https://pubmed.ncbi.nlm.nih.gov/

((((("Carcinoma, Renal Cell"[Mesh]) OR ("Kidney Neoplasms"[Mesh]) OR ("renal cancer*"[Text Word] OR "renal carcinoma*"[Text Word] OR "renal adenocarcinoma*"[Text Word] OR "renal tumor*"[Text Word] OR "renal tumour*"[Text Word] OR "renal malignanc*"[Text Word]) OR ("kidney cancer*"[Text Word] OR "kidney carcinoma*"[Text Word] OR "kidney adenocarcinoma*"[Text Word] OR "kidney tumor*"[Text Word] OR "kidney tumour*"[Text Word] OR "kidney malignanc*"[Text Word]) OR ("clear-cell cancer*"[Text Word] OR "clear-cell carcinoma*"[Text Word] OR "clear-cell adenocarcinoma*"[Text Word] OR "clear-cell tumor*"[Text Word] OR "clear-cell tumour*"[Text Word] OR "clear-cell malignanc*"[Text Word]) OR ("non-clear cell cancer*"[Text Word] OR "non-clear cell carcinoma*"[Text Word] OR "non-clear cell adenocarcinoma*"[Text Word] OR "non-clear cell tumor*"[Text Word] OR "non-clear cell tumour*"[Text Word] OR "non-clear cell malignanc*"[Text Word]) OR (hypernephroma[Text Word]) OR (hypernephroid carcinoma*[Text Word]) OR (grawitz tumor*[Text Word] OR grawitz tumour*[Text Word]) OR (rcc[Text Word])) AND ((advanced[Text Word] OR metastatic[Text Word] OR mRCC[Text Word] OR m-RCC[Text Word] OR aRCC[Text Word] OR a-RCC[Text Word] OR "first-line"[Text Word] OR "first line"[Text Word] OR metastasize[Text Word] OR metastasis[Text Word] OR metastases[Text Word] OR "stage iii"[Text Word] OR "stage 3"[Text Word] OR "stage 4"[Text Word] OR "stage iv"[Text Word] OR recurrent[Text Word] OR "non resectable"[Text Word] OR inoperable[Text Word] OR "non operable"[Text Word] OR unresectable[Text Word]) OR ("Neoplasm Metastasis"[Mesh]))) OR (mrcc[Text Word] OR arcc[Text Word])) AND ((((randomized controlled trial [pt] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "randomised" [Title/Abstract] OR "placebo"[Title/Abstract]) OR ("clinical trials as topic" [mesh: noexp]) OR (randomly [tiab] OR trial [ti] OR RCT [ti])) NOT (animals [mh] NOT humans [mh]))) Filters: English

Note: Cannot search in abstract only field in PubMed [RCT filter]

Clinicaltrials.gov

https://clinicaltrials.gov/

((advanced OR metastatic OR secondary OR EXPAND[Concept] "first-line" OR EXPAND[Concept] "first line" OR metastasis or mRCC or m-RCC OR aRCC OR a-RCC OR metastasize OR metastasis OR metastases OR EXPAND[Concept] "stage iii" OR EXPAND[Concept] "stage 3" OR EXPAND[Concept] "stage 4" OR EXPAND[Concept] "stage iv" OR recurrent OR EXPAND[Concept] "non resectable" OR EXPAND[Concept] "non-resectable" OR inoperable OR EXPAND[Concept] "non operable" OR EXPAND[Concept] "non-operable" OR unresectable) AND AREA[ConditionSearch] (EXPAND[Concept] "Renal cell" OR EXPAND[Concept] "renal clear cell" OR EXPAND[Concept] "renal clear-cell" OR EXPAND[Concept] "renal non-clear cell" OR EXPAND[Concept] "renal non clear cell" OR RCC OR EXPAND[Concept] "renal carcinoma" OR EXPAND[Concept] "renal cancer" OR EXPAND[Concept] "renal tumor" OR EXPAND[Concept] "renal tumour" OR EXPAND[Concept] "renal adenocarcinoma" OR EXPAND[Concept] "renal malignancy" OR EXPAND[Concept] "kidney cancer" OR EXPAND[Concept] "kidney carcinoma" OR EXPAND[Concept] "kidney adenocarcinoma" OR EXPAND[Concept] "kidney tumor" OR EXPAND[Concept] "kidney tumour" OR EXPAND[Concept] "kidney malignancy" OR EXPAND[Concept] "clear-cell cancer" OR EXPAND[Concept] "clear cell cancer" OR EXPAND[Concept] "clear-cell carcinoma" OR EXPAND[Concept] "clear cell carcinoma" OR EXPAND[Concept] "clear-cell adenocarcinoma" OR EXPAND[Concept] "clear cell adenocarcinoma" OR EXPAND[Concept] "clear-cell tumor" OR EXPAND[Concept] "clear cell tumor" OR EXPAND[Concept] "clear-cell tumour" OR EXPAND[Concept] "clear cell tumour" OR EXPAND[Concept] "clear-cell malignancy" OR EXPAND[Concept] "clear cell malignancy" OR EXPAND[Concept] "non-clear cell cancer" OR EXPAND[Concept] "non clear cell cancer" OR EXPAND[Concept] "non-clear cell carcinoma" OR EXPAND[Concept] "non clear cell carcinoma" OR EXPAND[Concept] "non-clear cell adenocarcinoma" OR EXPAND[Concept] "non clear cell adenocarcinoma" OR EXPAND[Concept] "non-clear cell tumor" OR EXPAND[Concept] "non clear cell tumor" OR EXPAND[Concept] "non-clear cell tumour" OR EXPAND[Concept] "non clear cell tumour" OR EXPAND[Concept] "non-clear cell malignancy" OR EXPAND[Concept] "non clear cell malignancy" OR hypernephroma OR EXPAND[Concept] "hypernephroid carcinoma" OR grawitz)) OR (aRCC OR mRCC or a-RCC OR m-RCC)

International Clinical Trials Registry Platform (ICTRP)

https://trialsearch.who.int/

Search 1:

TITLE: advanced OR metastatic OR metastasis OR metastasize OR secondary OR "first line" OR "first-line" recurrent OR non-resectable OR "non resectable" OR "stage 3" OR "stage 4" OR "stage iii" OR "stage iv" OR mRCC OR aRCC OR inoperable OR "non operable" OR unresectable

AND

CONDITION: "renal cell" OR "clear-cell" OR "non-clear cell" OR RCC OR "kidney cancer*" OR "renal cancer*" OR "renal carcinoma*" OR "renal adenocarcinoma" OR "renal tumor*" OR "renal tumour*" OR hypernephroma OR "hypernephroid carcinoma" OR grawitz

Search 2:

aRCC OR mRCC or a-RCC OR m-RCC

Note: Parentheses (brackets) cannot be used to determine the order in which terms are combined.
Searches automatically include synonyms generated using the UMLS metathesaurus.
Searches are restricted to 256 character spaces, truncated search strategies used.
With/without hyphen retrieves same numbers.

International Health Technology Assessment Database

https://database.inahta.org/

(("Neoplasm Metastasis"[mhe]) OR (advanced OR metastatic OR mRCC OR m-RCC OR aRCC OR a-RCC OR "first-line" OR "first line" OR metastasize OR metastasis OR metastases OR "stage iii" OR "stage 3" OR "stage 4" OR "stage iv" OR recurrent OR "non resectable" OR inoperable OR "non operable" OR unresectable)) AND (("renal cancer*" OR "renal carcinoma*" OR "renal adenocarcinoma*" OR "renal tumor*" OR "renal tumour*" OR "renal malignanc*" OR "kidney cancer*" OR "kidney carcinoma*" OR "kidney adenocarcinoma*" OR "kidney tumor*" OR "kidney tumour*" OR "kidney malignanc*" OR "clear cell cancer*" OR "clear cell carcinoma*" OR "clear cell adenocarcinoma*" OR "clear cell tumor*" OR "clear cell tumour*" OR "clear cell malignanc*" OR "non clear cell cancer*" OR "non clear cell carcinoma*" OR "non clear cell adenocarcinoma*" OR "non clear cell tumor*" OR "non clear cell tumour*" OR "hypernephroma" OR "hypernephroid carcinoma*" OR "grawitz tumor*" OR "grawitz tumour*" OR "rcc") OR ("Kidney Neoplasms"[mhe]) OR ("Carcinoma, Renal Cell"[mhe])) OR mRCC OR m-RCC or aRCC or a-RCC

9.2.2 Cost effectiveness searches

MEDLINE (via Ovid)

Ovid MEDLINE(R) ALL <1946 to October 07, 2021>

1	exp Carcinoma, Renal Cell/
2	exp Kidney Neoplasms/
3	(renal adj2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
4	(kidney adj1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
5	(clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
6	(non?clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
7	hypernephroma.tw,kw.
8	hypernephroid carcinoma*.tw,kw.
9	grawitz tumo?r$.tw,kw.
10	rcc.tw,kw.
11	or/1-10
12	(advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable).tw,kw. or Neoplasm Metastasis/
13	11 and 12
14	(mrcc or arcc).tw,kw.
15	13 or 14
16	Economics/
17	exp "Costs and Cost Analysis"/
18	Economics, Nursing/
19	Economics, Medical/
20	Economics, Pharmaceutical/
21	exp Economics, Hospital/
22	Economics, Dental/
23	exp "Fees and Charges"/
24	exp Budgets/
25	budget*.ti,ab,kf.
26	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
27	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.
28	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
29	(value adj2 (money or monetary)).ti,ab,kf.
30	exp models, economic/
31	economic model*.ab,kf.
32	markov chains/
33	markov.ti,ab,kf.
34	monte carlo method/
35	monte carlo.ti,ab,kf.
36	exp Decision Theory/
37	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.
38	or/16-37
39	15 and 38

40 limit 39 to yr="2006 -Current"

41 limit 40 to english language

Note: CADTH Economic evaluation/cost/model filter for MEDLINE Ovid used. https://www.cadth.ca/strings-attached-cadths-database-search-filters

The Cochrane Library (CENTRAL)

https://www.cochranelibrary.com/
Cochrane Central Register of Controlled Trials
Issue 10 of 12, October 2021

#1 MeSH descriptor: [Carcinoma, Renal Cell] explode all trees

#2 MeSH descriptor: [Kidney Neoplasms] explode all trees

#3 ((renal NEAR/2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw

#4 ((kidney NEAR/1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw

#5 ((clear-cell NEAR/3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw

#6 (("non-clear cell" NEAR/3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*))):ti,ab,kw

#7 (hypernephroma):ti,ab,kw

#8 (hypernephroid carcinoma*):ti,ab,kw

#9 (grawitz tumo?r*):ti,ab,kw

#10 (rcc):ti,ab,kw

#11 {OR #1-#10}

#12 (advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable):ti,ab,kw

#13 MeSH descriptor: [Neoplasm Metastasis] this term only

#14 #12 OR #13

#15 #11 AND #14

#16 (mrcc or arcc):ti,ab,kw

#17 #15 OR #16

#18 MeSH descriptor: [Economics] this term only

#19 MeSH descriptor: [Costs and Cost Analysis] explode all trees

#20 MeSH descriptor: [Economics, Nursing] this term only

#21 MeSH descriptor: [Economics, Medical] this term only

#22 MeSH descriptor: [Economics, Pharmaceutical] this term only

#23 MeSH descriptor: [Economics, Hospital] explode all trees

#24 MeSH descriptor: [Economics, Dental] this term only

#25 MeSH descriptor: [Fees and Charges] explode all trees

#26 MeSH descriptor: [Budgets] explode all trees

#27 (budget*):ti,ab,kw

#28 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed):ti,kw

#29 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed):ab

#30 (cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)):ab,kw

#31 ((value NEAR/2 (money or monetary))):ti,ab,kw

#32	MeSH descriptor: [Models, Economic] explode all trees
#33	(economic model*):ti,ab,kw
#34	MeSH descriptor: [Markov Chains] this term only
#35	(markov):ti,ab,kw
#36	MeSH descriptor: [Monte Carlo Method] this term only
#37	(monte carlo):ti,ab,kw
#38	MeSH descriptor: [Decision Theory] explode all trees
#39	((decision* NEAR/2 (tree* or analy* or model*))):ti,ab,kw
#40	62-#39
#41	#17 AND #40

Note: Cannot limit to English Language.

Embase (via Ovid)

Embase <1974 to 2021 October 07>

1	exp renal cell carcinoma/
2	exp kidney tumor/ or exp kidney carcinoma/
3	(renal adj2 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
4	(kidney adj1 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
5	(clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
6	(non?clear?cell adj3 (cancer* or carcinoma* or adenocarcinoma* or tumo?r* or malignanc*)).tw,kw.
7	hypernephroma.tw,kw.
8	hypernephroid carcinoma*.tw,kw.
9	grawitz tumo?r$.tw,kw.
10	rcc.tw,kw.
11	or/1-10
12	(advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable).tw,kw.
13	metastasis/
14	12 or 13
15	11 and 14
16	(mrcc or arcc).tw,kw.
17	15 or 16
18	Economics/
19	Cost/
20	exp Health Economics/
21	Budget/
22	budget*.ti,ab,kw.
23	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.
24	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.
25	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.
26	(value adj2 (money or monetary)).ti,ab,kw.
27	Statistical Model/
28	economic model*.ab,kw.

29 Probability/
30 markov.ti,ab,kw.
31 monte carlo method/
32 monte carlo.ti,ab,kw.
33 Decision Theory/
34 Decision Tree/
35 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw.
36 or/18-35
37 15 and 36
38 limit 37 to embase
39 limit 37 to (conference abstract status and yr="2019 -Current")
40 38 or 39
41 limit 40 to yr="2006 -Current"
42 limit 41 to english language

Note: CADTH Economic evaluation/cost/model filter for Embase Ovid used. https://www.cadth.ca/strings-attached-cadths-database-search-filters

PubMed

https://pubmed.ncbi.nlm.nih.gov/

((((("carcinoma, renal cell"[MeSH Terms] OR "Kidney Neoplasms"[MeSH Terms] OR ("renal cancer*"[Text Word] OR "renal carcinoma*"[Text Word] OR "renal adenocarcinoma*"[Text Word] OR "renal tumor*"[Text Word] OR "renal tumour*"[Text Word] OR "renal malignanc*"[Text Word]) OR ("kidney cancer*"[Text Word] OR "kidney carcinoma*"[Text Word] OR "kidney adenocarcinoma*"[Text Word] OR "kidney tumor*"[Text Word] OR "kidney tumour*"[Text Word] OR "kidney malignanc*"[Text Word]) OR ("clear cell cancer*"[Text Word] OR "clear cell carcinoma*"[Text Word] OR "clear cell adenocarcinoma*"[Text Word] OR "clear cell tumor*"[Text Word] OR "clear cell tumour*"[Text Word] OR "clear cell malignanc*"[Text Word]) OR ("non clear cell cancer*"[Text Word] OR "non clear cell carcinoma*"[Text Word] OR "non clear cell adenocarcinoma*"[Text Word] OR "non clear cell tumor*"[Text Word] OR "non clear cell tumour*"[Text Word]) OR "hypernephroma"[Text Word] OR "hypernephroid carcinoma*"[Text Word] OR ("grawitz tumor*"[Text Word] OR "grawitz tumour*"[Text Word]) OR "rcc"[Text Word]) AND ("advanced"[Text Word] OR "metastatic"[Text Word] OR "mRCC"[Text Word] OR "m-RCC"[Text Word] OR "aRCC"[Text Word] OR "a-RCC"[Text Word] OR "first-line"[Text Word] OR "first line"[Text Word] OR "metastasize"[Text Word] OR "metastasis"[Text Word] OR "metastases"[Text Word] OR "stage iii"[Text Word] OR "stage 3"[Text Word] OR "stage 4"[Text Word] OR "stage iv"[Text Word] OR "recurrent"[Text Word] OR "non resectable"[Text Word] OR "inoperable"[Text Word] OR "non operable"[Text Word] OR "unresectable"[Text Word] OR "Neoplasm Metastasis"[MeSH Terms])) AND ("Economics" OR "Costs and Cost Analysis"[mh] OR "Economics, Nursing"[mh] OR "Economics, Medical"[mh] OR "Economics, Pharmaceutical"[mh] OR "Economics, Hospital"[mh] OR "Economics, Dental"[mh] OR "Fees and Charges"[mh] OR "Budgets"[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR "models, economic"[mh] OR economic model*[tiab] OR "markov chains"[mh] OR markov[tiab] OR "monte carlo method"[mh] OR monte carlo[tiab] OR "Decision Theory"[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab])) AND ((english[Filter]) AND (2006:2021[pdat])))

NHS EED via Centre for Reviews and Dissemination

https://www.crd.york.ac.uk/CRDWeb/

1	MeSH DESCRIPTOR Carcinoma, Renal Cell EXPLODE ALL TREES
2	MeSH DESCRIPTOR Kidney Neoplasms EXPLODE ALL TREES
3	("renal cancer*")
4	("renal carcinoma*")
5	("renal adenocarcinoma*")
6	("renal tumor*")
7	("renal tumour*")
8	("renal malignanc*")
9	("kidney cancer*")
10	("kidney carcinoma*")
11	("kidney adenocarcinoma*")
12	("kidney tumor*")
13	("kidney tumour*")
14	("kidney malignanc*")
15	("clear-cell cancer*")
16	("clear-cell carcinoma*")
17	("clear-cell adenocarcinoma*")
18	("clear-cell tumor*")
19	("clear-cell tumour*")
20	("clear-cell malignanc*")
21	("non-clear cell cancer*")
22	("non-clear cell carcinoma*")
23	("non-clear cell adenocarcinoma*")
24	("non-clear cell tumor*")
25	("non-clear cell tumour*")
26	("non-clear cell malignanc*")
27	(hypernephroma)
28	(hypernephroid carcinoma*)
29	(grawitz tumor*)
30	(grawitz tumour*)
31	(rcc)
32	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33	(advanced)
34	(metastatic)
35	(mRCC)
36	(m-RCC)
37	(aRCC)
38	(a-RCC)
39	("first-line" or "first line")
40	(metastasize)
41	(metastasis)
42	(metastases)
43	("stage iii")
44	("stage 3")
45	("stage 4")
46	("stage iv")
47	(recurrent)
48	("non resectable")
49	(inoperable)
50	("non operable")

51 (unresectable)
52 MeSH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES
53 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
54 #32 AND #53
55 (mrcc)
56 (m-rcc)
57 (arcc)
58 (a-rcc)
59 #55 OR #56 OR #57 OR #58
60 #54 OR #59

EconLit (via EBSCOhost)

S1 TI ((renal N2 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR AB ((renal N2 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR SU ((renal N2 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)))
S2 TI ((kidney N1 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)) OR AB ((kidney N1 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)) OR SU ((kidney N1 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))
S3 TI ((clear-cell N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR AB ((clear-cell N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR SU ((clear-cell N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)))
S4 TI (("clear cell" N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR AB (("clear cell" N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR SU (("clear cell" N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)))
S5 TI ((non-clear-cell N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR AB ((non-clear-cell N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR SU ((non-clear-cell N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)))
S6 TI (("non clear cell" N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR AB (("non clear cell" N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*))) OR SU (("non clear cell" N3 (cancer* or carcinoma* or adenocarcinoma* or tumo#r* or malignanc*)))
S7 TI hypernephroma OR AB hypernephroma OR SU hypernephroma
S8 TI "hypernephroid carcinoma*" OR AB "hypernephroid carcinoma*" OR SU "hypernephroid carcinoma*"
S9 TI grawitz tumo#r* OR AB grawitz tumo#r* OR SU grawitz tumo#r*
S10 TI rcc OR AB rcc OR SU rcc
S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
S12 TI (advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable) OR AB (advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable) OR SU (advanced or metastatic or mRCC or m-RCC or aRCC or a-RCC or "first-line" or "first line" or metastasize or metastasis or metastases or "stage iii" or "stage 3" or "stage 4" or "stage iv" or recurrent or "non resectable" or inoperable or "non operable" or unresectable)
S13 S11 AND S12
S14 TI (mRCC OR m-RCC or aRCC or a-RCC) OR AB (mRCC OR m-RCC or aRCC or a-RCC) OR SU (mRCC OR m-RCC or aRCC or a-RCC)
S15 S13 OR S14
S16 S13 OR S14
Narrow by Language: - English, Published: 20060101-20211231

CEA Registry

https://cevr.tuftsmedicalcenter.org/databases/cea-registry
advanced renal cell
metastatic renal cell
advanced kidney
metastatic kidney
mRCC
aRCC
first-line renal cell
first-line kidney
first line renal cell
first line kidney
lenvatinib
sunitinib
pazopanib
tivozanib
cabozantinib
nivolumab

Note: Basic search only with free version of CEA Registry. No Boolean. No download function. Screened on website,

Clinicaltrials.gov

https://clinicaltrials.gov/

(((advanced OR metastatic OR secondary OR EXPAND[Concept] "first-line" OR EXPAND[Concept] "first line" OR metastasis or mRCC or m-RCC OR aRCC OR a-RCC OR metastasize OR metastasis OR metastases OR EXPAND[Concept] "stage iii" OR EXPAND[Concept] "stage 3" OR EXPAND[Concept] "stage 4" OR EXPAND[Concept] "stage iv" OR recurrent OR EXPAND[Concept] "non resectable" OR EXPAND[Concept] "non-resectable" OR inoperable OR EXPAND[Concept] "non operable" OR EXPAND[Concept] "non-operable" OR unresectable) AND AREA[ConditionSearch] (EXPAND[Concept] "Renal cell" OR EXPAND[Concept] "renal clear cell" OR EXPAND[Concept] "renal clear-cell" OR EXPAND[Concept] "renal non-clear cell" OR EXPAND[Concept] "renal non clear cell" OR RCC OR EXPAND[Concept] "renal carcinoma" OR EXPAND[Concept] "renal cancer" OR EXPAND[Concept] "renal tumor" OR EXPAND[Concept] "renal tumour" OR EXPAND[Concept] "renal adenocarcinoma" OR EXPAND[Concept] "renal malignancy" OR EXPAND[Concept] "kidney cancer" OR EXPAND[Concept] "kidney carcinoma" OR EXPAND[Concept] "kidney adenocarcinoma" OR EXPAND[Concept] "kidney tumor" OR EXPAND[Concept] "kidney tumour" OR EXPAND[Concept] "kidney malignancy" OR EXPAND[Concept] "clear-cell cancer" OR EXPAND[Concept] "clear cell cancer" OR EXPAND[Concept] "clear-cell carcinoma" OR EXPAND[Concept] "clear cell carcinoma" OR EXPAND[Concept] "clear-cell adenocarcinoma" OR EXPAND[Concept] "clear cell adenocarcinoma" OR EXPAND[Concept] "clear-cell tumor" OR EXPAND[Concept] "clear cell tumor" OR EXPAND[Concept] "clear-cell tumour" OR EXPAND[Concept] "clear cell tumour" OR EXPAND[Concept] "clear-cell malignancy" OR EXPAND[Concept] "clear cell malignancy" OR EXPAND[Concept] "non-clear cell cancer" OR EXPAND[Concept] "non clear cell cancer" OR EXPAND[Concept] "non-clear cell carcinoma" OR EXPAND[Concept] "non clear cell carcinoma" OR EXPAND[Concept] "non-clear cell adenocarcinoma" OR EXPAND[Concept] "non clear cell adenocarcinoma" OR EXPAND[Concept] "non-clear cell tumor" OR EXPAND[Concept] "non clear cell tumor" OR EXPAND[Concept] "non-clear cell tumour" OR EXPAND[Concept] "non clear cell tumour" OR EXPAND[Concept] "non-clear cell malignancy" OR EXPAND[Concept] "non clear cell malignancy" OR hypernephroma OR EXPAND[Concept] "hypernephroid carcinoma" OR grawitz)) OR (aRCC OR mRCC or a-RCC OR m-RCC)) AND (economic OR economics OR cost OR costs OR costly OR costing OR budget OR price OR prices OR pricing OR pharmacoeconomics OR pharmaco-economics OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed OR EXPAND[Concept] "value for money" OR EXPAND[Concept] "monetary value" OR EXPAND[Concept] "economic model" OR EXPAND[Concept] "economic models" OR markov OR monte carlo OR EXPAND[Concept] "Decision Theory" OR EXPAND[Concept] "decision tree" OR EXPAND[Concept] "decision analysis" OR EXPAND[Concept] "decision model")

International Clinical Trials Registry Platform (ICTRP)

https://trialsearch.who.int/

Search 1:

TITLE: (economic OR economics OR cost OR costs OR costly OR costing OR budget OR price OR prices OR pricing OR pharmacoeconomics OR pharmaco-economics OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed OR "value for money" OR "monetary value" OR "economic model" OR " economic models" OR markov OR monte carlo OR "Decision Theory" OR decision tree OR decision analysis OR decision model)

AND

CONDITION: "renal cell" OR "clear-cell" OR "clear cell" OR RCC OR "kidney cancer*" OR "renal cancer*" OR "renal carcinoma*" OR "renal adenocarcinoma" OR "renal tumor*" OR "renal tumour*" OR hypernephroma OR "hypernephroid carcinoma" OR grawitz

Search 2:

TITLE: (economic OR economics OR cost OR costs OR costly OR costing OR budget OR price OR prices OR pricing OR pharmacoeconomics OR pharmaco-economics OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed OR "value for money" OR "monetary value" OR "economic model" OR " economic models" OR markov OR monte carlo OR "Decision Theory" OR decision tree OR decision analysis OR decision model)

AND

CONDITION: (aRCC OR mRCC or a-RCC OR m-RCC)

Note: Limited to 2006 onwards
Parentheses (brackets) cannot be used to determine the order in which terms are combined.
Searches automatically include synonyms generated using the UMLS metathesaurus.
Searches are restricted to 256 character spaces per line – truncated strategies used

International Health Technology Assessment Database

https://database.inahta.org/

(("Neoplasm Metastasis"[mhe]) OR (advanced OR metastatic OR mRCC OR m-RCC OR aRCC OR a-RCC OR "first-line" OR "first line" OR metastasize OR metastasis OR metastases OR "stage iii" OR "stage 3" OR "stage 4" OR "stage iv" OR recurrent OR "non resectable" OR inoperable OR "non operable" OR unresectable)) AND (("renal cancer*" OR "renal carcinoma*" OR "renal adenocarcinoma*" OR "renal tumor*" OR "renal tumour*" OR "renal malignanc*" OR "kidney cancer*" OR "kidney carcinoma*" OR "kidney adenocarcinoma*" OR "kidney tumor*" OR "kidney tumour*" OR "kidney malignanc*" OR "clear cell cancer*" OR "clear cell carcinoma*" OR "clear cell adenocarcinoma*" OR "clear cell tumor*" OR "clear cell tumour*" OR "clear cell malignanc*" OR "non clear cell cancer*" OR "non clear cell carcinoma*" OR "non clear cell adenocarcinoma*" OR "non clear cell tumor*" OR "non clear cell tumour*" OR "hypernephroma" OR "hypernephroid carcinoma*" OR "grawitz tumor*" OR "grawitz tumour*" OR "rcc") OR ("Kidney Neoplasms"[mhe]) OR ("Carcinoma, Renal Cell"[mhe])) OR mRCC OR m-RCC or aRCC or a-RCC

9.2.3 Summary of search results

Table 78 Summary of search results

Database	Date	Clinical No date (+ English language)	Economics 2006- (+ English language)
MEDLINE	11/10/21	2565	449
Embase	11/10/21	3163	1625
PubMed	11/10/21	2628	387
Cochrane (CENTRAL)[1]	11/10/21	2937	109
Clinicaltrials.gov[1,2]	11/10/21	1770	54
International Clinical Trials Registry Platform (ICTRP)	11/10/21	1383	9
NHS Economic Evaluation Database (EED)	11/10/21	-	44
EconLit	11/10/21	-	26
International Health Technology Assessment Database	11/10/21	58	43
Total in Endnote (excluding EU-CTR, CEA, confs)		14504	2746
Duplicates removed in Endnote		6168	843
Total uploaded to Covidence		8336	1903
Duplicates in removed in Covidence		50	4
Total to screen in Covidence		8286	1899

[1] Cannot limit to English language
[2] Cannot limit by date

9.3 Appendix 3: AG assessment of statistical approaches

9.3.1 Statistical approach used for the analysis of the CLEAR trial data

Information about the statistical approach used by the company to analyse the CLEAR trial data has been extracted from the Eisai CS,[15] the Clinical Study Report (CSR) of the IA3 data cut-off,[71] the HRQoL outcomes study report (version 1, dated 13 February 2021)[73] and the HRQoL outcomes statistical analysis plan (HRQoL SAP version 2.1, dated 5 October 2020),[69] the trial protocol (Amendment 7, dated 6 August 2020)[74] and the trial statistical analysis plan (TSAP version 3, dated 14 August 2020)[75] which was available as online supplementary documents to the published paper of the CLEAR trial.[67] A summary of the AG checks of the pre-planned statistical approach for the CLEAR trial is provided in Table 79.

Table 79 AG assessment of statistical approaches used in the CLEAR trial

Item	AG assessment	Statistical approach	AG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Analysis populations of the CLEAR trial are the ITT population (FAS), PP analysis set and the safety analysis set (Eisai CS,[15] Section 4.4)	The AG is satisfied that the CLEAR trial analysis populations are clearly defined and pre-specified (TSAP, Section 5.2.1)
Was an appropriate trial design and sample size calculation pre-specified?	Yes	The CLEAR trial sample size and power calculations are pre-specified (TSAP, Section 4) Five interim analyses (IA1 to IA5) were pre-planned with a Lan-DeMets O'Brien-Fleming alpha spending function used to determine the threshold for statistical significance for each analysis (TSAP, Section 6). Multiplicity adjustments for testing the superiority of both lenvatinib plus pembrolizumab and lenvatinib plus everolimus compared to sunitinib are also pre-specified (TSAP, Section 5.3.3). Results of pre-planned IA3 data cut-off (28th August 2020) are presented in the Eisai CS[15] (Section 4.6). The IA3 data cut-off is the final planned analysis of PFS and served as the primary analysis of OS as the superiority of lenvatinib plus pembrolizumab over sunitinib was demonstrated.[72] Updated OS analyses requested by the EMA (data cut-off date 31st March 2021) are also presented (Eisai CS,[15] Section 4.6.2.2)	The AG is satisfied that the CLEAR trial pre-specified sample size calculation and statistical power calculations are appropriate and were correctly implemented.
Were all protocol amendments made prior to analysis?	Yes	A summary of the 'Revision History' is provided in the latest version of the protocol (Amendment 7, 6th August 2020). Most amendments relate to administrative changes or minor clarifications of wording. Amendments 4 and 6 include modifications to the sample size and power calculations, interim analyses and multiplicity adjustments following IA1 and IA2	The AG is satisfied that all protocol amendments were made prior to the IA3 data cut-off and were appropriate.
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The CLEAR trial primary efficacy outcome is BICR-assessed PFS using FDA censoring rules. Key secondary efficacy outcomes are BICR-assessed PFS using EMA censoring rules, OS and BICR-assessed ORR. Definitions and statistical analysis approaches for primary and secondary efficacy outcomes are outlined in the Eisai CS[15] (Appendix L3, Table 99) and clinical effectiveness results are presented for the ITT population (Eisai CS,[15] Section 4.6 and Appendix M3, M4 and M6). A complete list of primary, secondary and exploratory endpoints and statistical analysis approaches is pre-specified (TSAP, Section 5.1 and Section 5.4).	The AG is satisfied that efficacy outcomes were clearly defined, pre-specified, analysed appropriately, and that relevant primary and secondary efficacy outcomes are presented.
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs presented in the Eisai CS[15] (Appendix M3) and in the HRQoL study report were assessed in the HRQoL analysis set (i.e. all patients who had any HRQoL data and received at least one dose of study treatment). PROs measured were changes from baseline FKSI-DRS, EORTC QLQ-C30 and EQ-5D-3L scores, analysed using an MMRM approach and time to deterioration analysed using K-M methods and Cox PH models.	The AG is satisfied that the PRO outcome definitions and analysis approaches were pre-specified (HRQoL SAP Sections 2 to 3) and are appropriate.

Item	AG assessment	Statistical approach	AG comments
Was the analysis approach for AEs appropriate and pre-specified?	Partly	AEs were assessed and graded using the NCI CTCAE version 4.03 classification system (Protocol, Section 9.5.1.4) within the safety analysis population (all randomised patients who received at least one dose of study medication [TSAP, Section 5.2.1]). AEs are presented as numbers and percentages of patients experiencing events. An overview of AEs, SAEs, AEs leading to study drug discontinuation, dose modification or death, TEAEs by NCI CTCAE grade and AESIs occurring in the CLEAR trial are presented in the Eisai CS[15] (Section 4.8 and Appendix F). RDs and 95% CIs are presented comparing lenvatinib plus pembrolizumab and sunitinib for some of the AE summaries in the Eisai CS[15] (Section 4.8), computed using the Miettinen and Nurminen method.[133] Additional summary tables of safety data in the CLEAR trial are provided in the CSR (Section 12.2 and Section 12.3)	The AG is satisfied that the analysis approach for AEs was pre-specified (TSAP, Section 5.6.2) and is appropriate. The AG notes that the comparative analyses of AEs were not pre-specified in the TSAP and is uncertain why these comparisons are not computed for all AE summaries
Were modelling assumptions (e.g., proportional hazards) assessed?	Yes	The PH assumption for BICR-assessed PFS and OS were assessed by plotting the log cumulative hazard versus log(time), by using the Grambsch-Therneau test[105] of Schoenfeld's residuals (Eisai CS[15] [Section 5.3.1 and 5.3.2] and Eisai response to the AG clarification letter, questions A1 and A2). Based on these assessments, Eisai consider that over the observed period, the assumption of PH was not violated for BICR-assessed PFS but was violated for the updated analyses of OS (unadjusted for treatment crossover).	The AG agrees with the Eisai assessments of the PH assumption.
Was a suitable approach employed for handling missing data?	Yes	Missing data were handled with censoring rules for time-to-event outcomes (TSAP, Section 5.4.1 and Table 4) or general rules for handling other missing data (TSAP, Section 5.3.5)	The AG is satisfied that all pre-specified methods for handling missing data are appropriate
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses were pre-specified for BICR-assessed PFS, OS and BICR-assessed ORR in the ITT population (TSAP, Section 5.3.4) and presented in the Eisai CS[15] (Appendix E). Sensitivity analyses were pre-specified for BICR-assessed PFS in the ITT population (TSAP, Section 5.4.1) and BICR-assessed PFS results in the PP analysis set are presented as a sensitivity analysis (Eisai CS,[15] Appendix M1 and M2)	The AG is satisfied that all relevant, pre-specified subgroup analyses and sensitivity analyses are presented.

AE=adverse event; AESI=adverse event of special interest; AG=Assessment Group; BICR=Blinded Independent Central Review; CI=confidence interval; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life-Core 30; EMA=European Medicines Agency; EQ-5D-3L=European quality of life five-dimension three level; FAS=Full Analysis Set; FDA=US Federal Drug Agency; FKSI-DRS=Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms; HR=hazard ratio; HRQoL=health-related quality of life; IA=interim analysis; ITT=intention to treat; K-M=Kaplan Meier; MMRM=mixed model for repeated measures; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PP=per protocol; PRO=patient reported outcome; SAE=serious adverse event; RD=risk difference; SAP=statistical analysis plan; TEAE=treatment emergent adverse event; TSAP=trial statistical analysis plan

Source: Extracted from the Eisai CS,[15] the CSR of the IA3 data cut-off,[71] the most recent version of the trial protocol and the TSAP,[67] Eisai response to the AG clarification letter, and includes AG comment

9.3.2 Statistical approach used for treatment switching analyses of OS in the CLEAR trial

CLEAR trial OS data were confounded due to patients in both the lenvatinib plus pembrolizumab arm and the sunitinib arm receiving subsequent systemic anti-cancer medication during OS follow-up. Therefore, Eisai performed treatment switching analyses. A summary and AG critique of the Eisai approach to the treatment switching analyses used to assess OS in the CLEAR trial is provided in Table 80.

Table 80 AG summary and critique of statistical approaches used for treatment switching analyses of OS in the CLEAR trial

Item	AG assessment	Statistical approach	AG comments
Were treatment switchers clearly defined?	Yes	Treatment switching analyses were conducted to adjust for receiving any subsequent anti-cancer therapy in the CLEAR trial; [redacted] of 355 patients in the lenvatinib plus pembrolizumab arm and [redacted] of 357 patients in the sunitinib arm had received any subsequent systemic anti-cancer medication up to the data cut-off date (31st March 2021) of the updated OS analyses (Eisai CS,[15] Table 15).	The AG considers that the company has clearly defined which patients were included in the treatment switching analyses.
Was an appropriate method used?	Yes	Eisai used two different adjustment methods, as described in DSU TSD 16:[85] the two-stage estimation method and the IPCW method. Eisai preferred the two-stage estimation method over the IPCW method due to the "capability of the two-stage approach to generate two counterfactual scenarios where (1) no patients receive subsequent treatment and (2) all patients receive subsequent treatment and combine both of these estimates to generate additional scenarios with varying proportions of patients receiving subsequent treatment to more closely reflect real-world practice." (Eisai CS,[15] Section 4.6.3.2). In the first stage of the two-stage estimation method, Eisai used log-normal, log-logistic and Weibull models to estimate the acceleration factor (i.e. the effect of subsequent anti-cancer medication on OS in the lenvatinib plus pembrolizumab and sunitinib arms). The company selected the log-normal model as the best fitting model according to AIC and BIC statistics, but presented adjusted OS results for all three accelerated failure time models (Eisai CS,[15] Table 16). Eisai implemented the two-stage method with and without re-censoring, and adjusting for treatment arm and (1) stratification factors of the CLEAR trial (geographic region and MSKCC prognostic groups) or (2) selected baseline covariates (IMDC prognostic risk subgroup, number of metastatic organs/sites involved, and prior nephrectomy). Eisai presented adjusted OS results with and without re-censoring and for both sets of adjustment factors (Eisai CS,[15] Table 16).	The AG agrees that the two-stage method is appropriate and that the company has implemented the two-stage method correctly (Eisai CS,[15] Section 4.6.3.2). The AG also considers that methods to select an accelerated failure time model in the first stage and adjustment factors considered within the two-stage estimation are appropriate. The AG also considers that it was appropriate for the company to present adjusted OS HRs from all models considered. Given the limited OS data available from the CLEAR trial, the AG considers that the two-stage method adjusted OS HRs without re-censoring are the most appropriate for decision making. However, the AG notes that two-stage adjusted OS HRs without re-censoring may be at risk of bias due to informative censoring if any prognostic factors in the CLEAR trial are related to the censoring mechanism

Item	AG assessment	Statistical approach	AG comments
Were modelling assumptions assessed and shown to be valid?	Yes	Assessment of the 'no unmeasured confounders' for the two-stage method and the IPCW method were presented in an additional report of the OS treatment switching analyses (Section 5.2.2).[72] The two-stage method requires the identification of a 'secondary baseline,' defined by the company as the date of study treatment discontinuation for the CLEAR trial,[72] and requires the assumption that all patients are in a similar clinical condition (e.g. disease stage) at the time of secondary baseline. Patients discontinued study treatments due to disease progression, adverse events and patient choice / withdrawal of consent (CSR, Table 2). The two-stage method also requires the strong assumption that there is no time-dependent confounding between the time of secondary baseline and the time of treatment switch (i.e. the date that a subsequent anti-cancer therapy was started). The median (range) duration of treatment in the CLEAR trial is 17.00 ([redacted]) months in the lenvatinib plus pembrolizumab arm and 7.84 ([redacted]) months in the sunitinib arm (Eisai CS,[15] Table 17) and the median (range) time from randomisation to first subsequent anti-cancer therapy in the CLEAR trial is [redacted] months in the lenvatinib plus pembrolizumab arm and [redacted] months in the sunitinib arm (Eisai CS,[15] Table 16). The assumptions that patients are in a similar condition at the time of secondary baseline and no time-dependent confounding were not assessed by the company within the CS or the additional report of the OS treatment switching analyses.[72]	The AG agrees with the company that assumption of no unmeasured confounders may not be met fully but the impact of any violation of this assumption is likely to be small. The AG considers that patients who have discontinued treatment due to disease progression cannot be considered to be in a similar clinical condition to patients who have discontinued treatment due to adverse events or due to patient choice. However, the impact of the violation of this assumption on the adjusted OS HRs is unknown. Due to the similarity in the durations of time on treatment and time from randomisation to first subsequent anti-cancer therapy in the CLEAR trial, the AG considers that it is unlikely that any time-dependent confounding could have occurred.
Were results presented appropriately?	Yes	Numbers of OS events and adjusted OS HRs with 95% CIs are presented for lenvatinib plus pembrolizumab versus sunitinib for the CLEAR trial ITT population for all treatment switching analyses conducted: no treatment-switching adjustment (i.e. unadjusted), and two-stage estimation method with log-normal, log-logistic and Weibull acceleration factors, with and without re-censoring and with adjustment for stratification factors only or with adjustment for selected baseline covariates (Eisai CS,[15] Table 16). 95% CIs of adjusted median OS and HRs were estimated using bootstrapping to account for uncertainty introduced into the OS estimates following treatment switching adjustments. Results of the IPCW adjustment method are presented in an additional report of the OS treatment switching analyses[72] (Section 5.4)	The AG considers that all relevant results are presented appropriately.

AG=Assessment Group; AIC=Akaike information criterion; BIC=Bayesian information criterion; CI=confidence interval; DSU=Decision Support Unit; HR=hazard ratio; IMDC=International Metastatic RCC Database Consortium; IPCW=inverse probability of censoring weights; ITT=intention to treat; MSKCC=Memorial Sloan Kettering Cancer Center; OS=overall survival; RCC=renal cell carcinoma; TSD=technical support document

Source: Extracted from the Eisai CS;[15] Section 4.6.3.2, Table 16, the CSR of the IA3 data cut-off,[71] additional report of the OS treatment switching analyses,[72] DSU TSD 16,[85] and includes AG comment

9.4 Appendix 4: Subgroup results from the CLEAR trial by risk subgroup for PFS

Table 81 PFS results from the CLEAR trial, MSKCC favourable risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Favourable risk		FAS	
	Lenvatinib + pembrolizumab (N=96)	Sunitinib (N=97)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC – IA3 data cut-off				
Number of events (%)	39 (40.6)	60 (61.9)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	0.36 (0.23 to 0.54)		0.39 (0.32 to 0.49)	
p value	p<0.0001		p<0.0001	
PFS per EMA by BIRC – IA3 data cut-off				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value				

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 82 PFS results from the CLEAR trial, IMDC favourable risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Favourable risk		FAS	
	Lenvatinib + pembrolizumab (N=110)	Sunitinib (N=124)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC – IA3 data cut-off				
Number of events (%)	43 (45.1)	67 (54.0)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	0.41 (0.28 to 0.62)		0.39 (0.32 to 0.49)	
p value	p<0.0001		p<0.0001	
PFS per EMA by BIRC – IA3 data cut-off				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value				

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=not estimable; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 83 PFS results from the CLEAR trial, MSKCC intermediate risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Intermediate risk		FAS	
	Lenvatinib + pembrolizumab (N=227)	Sunitinib (N=228)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by				
Number of events (%)	101 (44.5)	126 (55.3)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	0.44 (0.34 to 0.58)		0.39 (0.32 to 0.49)	
p value	p<0.0001		p<0.0001	
PFS per EMA by BIRC				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value				

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; PFS=progression-free survival

Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 84 PFS results from the CLEAR trial, IMDC intermediate risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Intermediate risk		FAS	
	Lenvatinib + pembrolizumab (N=210)	Sunitinib (N=192)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC				
Number of events (%)	97 (46.1)	110 (57.3)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	0.39 (0.29 to 0.52)		0.39 (0.32 to 0.49)	
p value	p<0.0001		p<0.0001	
PFS per EMA by BIRC				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value				

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; PFS=progression-free survival

Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 85 PFS results from the CLEAR trial, MSKCC poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Poor risk		FAS	
	Lenvatinib + pembrolizumab (N=32)	Sunitinib (N=32)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC				
Number of events (%)	20 (62.5)	19 (59.4)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	0.18 (0.08 to 0.42)		0.39 (0.32 to 0.49)	
p value	p<0.0001		p<0.0001	
PFS per EMA by BIRC				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value				

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 86 PFS results from the CLEAR trial, IMDC poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Poor risk		FAS	
	Lenvatinib + pembrolizumab (N=33)	Sunitinib (N=37)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC				
Number of events (%)	18 (54.5)	26 (70.3)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	0.28 (0.13 to 0.60)		0.39 (0.32 to 0.49)	
p value	p=0.0005		p<0.0001	
PFS per EMA by BIRC				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value				

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=not estimable; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)
Note: p value for PFS for the poor risk subgroup reported in the text to be "p<0.0005" (PFS by FDA) and "p<0.0002" (PFS by EMA) but from Appendix E1.1, and E1.2, Figures 81 and 89, p=0.0005 (log rank test, PFS by FDA) and p=0.0002 (log rank test, PFS by EMA)

Table 87 PFS results from the CLEAR trial, MSKCC intermediate/poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Intermediate/poor risk		FAS	
	Lenvatinib + pembrolizumab (N=259)	Sunitinib (N=224)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC				
Number of events (%)	121 (46.7)	145 (64.7)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	[redacted]		0.39 (0.32 to 0.49)	
p value			p<0.0001	
PFS per EMA by BIRC				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value			[redacted]	

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)
Note: N and number of events calculated by summing N and number of events from individual risk subgroups in tables above (Table 83 to Table 86)

Table 88 PFS results from the CLEAR trial, IMDC intermediate/poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off

Characteristic / outcome	Intermediate/poor risk		FAS	
	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
PFS per FDA by BIRC				
Number of events (%)	115 (47.3)	136 (59.4)	160 (45.1)	205 (57.4)
Median PFS in months (95% CI)	[redacted]	[redacted]	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)
HR (95% CI)	[redacted]		0.39 (0.32 to 0.49)	
p value			p<0.0001	
PFS per EMA by BIRC				
Number of events (%)	Not reported	Not reported	[redacted]	[redacted]
Median PFS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value			[redacted]	

BIRC=Blinded Independent Review Committee; CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E1.1, and E1.2 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)
Note: N and number of events calculated by summing N and number of events from individual risk subgroups in (Table 83, Table 84, Table 85 and Table 86)

9.5 Appendix 5: Subgroup results from the CLEAR trial by risk subgroup for OS

Table 89 OS results from the CLEAR trial, MSKCC favourable risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Favourable risk		FAS	
	Lenvatinib + pembrolizumab (N=96)	Sunitinib (N=97)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	11 (11.5)	13 (13.4)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	0.86 (0.38 to 1.92)		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E2, and E3 and CSR[71] (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 90 OS results from the CLEAR trial, IMDC favourable risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Favourable risk		FAS	
	Lenvatinib + pembrolizumab (N=110)	Sunitinib (N=124)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	14 (12.7)	15 (12.1)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	1.15 (0.55 to 2.40)		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix D2.4.2 (Table 19), Appendix E2, and E3 and CSR[71] (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 91 OS results from the CLEAR trial, MSKCC intermediate risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Intermediate risk		FAS	
	Lenvatinib + pembrolizumab (N=227)	Sunitinib (N=228)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	57 (25.1)	73 (32.0)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	0.66 (0.47 to 0.94)		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E2, and E3 and CSR[71] (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 92 OS results from the CLEAR trial, IMDC intermediate risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Intermediate risk		FAS	
	Lenvatinib + pembrolizumab (N=210)	Sunitinib (N=192)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	56 (26.7)	60 (31.3)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	0.72 (0.50 to 1.05)		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E2, and E3 and CSR[71] (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 93 OS results from the CLEAR trial, MSKCC poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Poor risk		FAS	
	Lenvatinib + pembrolizumab (N=32)	Sunitinib (N=32)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	12 (37.5)	15 (49.9)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	0.50 (0.23 to 1.08)		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E2, and E3 and CSR[71] (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 94 OS results from the CLEAR trial, IMDC poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Poor risk		FAS	
	Lenvatinib + pembrolizumab (N=33)	Sunitinib (N=37)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	10 (30.3)	25 (67.6)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	0.30 (0.14 to 0.64)		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix E2, and E3 and CSR[71] (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 95 OS results from the CLEAR trial, MSKCC intermediate/poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Intermediate/poor risk		FAS	
	Lenvatinib + pembrolizumab (N=259)	Sunitinib (N=224)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	69 (26.7)	88 (39.3)	[redacted]	[redacted]
Median OS in months (95% CI)	Not reported	Not reported	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	[redacted]		0.66 (0.49 to 0.88)	
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
p value	Not reported		Not reported	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; MSKCC=Memorial Sloan-Kettering Cancer Center; NE=not estimable; OS=overall survival; PFS=progression-free survival
Note: N and number of events calculated by summing N and number of events from individual risk subgroups in Table 91, Table 92, Table 93 and Table 94
Source: Eisai CS,[15] Appendix E2, and E3 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

Table 96 OS results from the CLEAR trial, IMDC intermediate/poor risk subgroup and FAS (all-risk) population for comparison, IA3 data cut-off and updated OS analysis

Characteristic / outcome	Intermediate/poor risk		FAS	
	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
OS – IA3 data cut-off				
Number of deaths (%)	66 (27.2)	85 (37.1)	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NE (33.6 to NE)	NE (NE to NE)
HR (95% CI)	[redacted]			
p value	[redacted]		p=0049	
OS – updated OS analysis				
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	Not reported	Not reported	NE (NE to NE)	NE (NE to NE)
HR (95% CI)	[redacted]		0.66 (0.49 to 0.88)	
p value	Not reported		p=0049	

CI=confidence interval; EMA=European Medicines Agency; FAS=Full Analysis Set; FDA=US Food and Drug Administration; HR=hazard ratio; IA3=third interim analysis; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NE=not estimable; OS=overall survival; PFS=progression-free survival
Source: Eisai CS,[15] Appendix D2.4.2, Table 19, E2, and E3 (subgroup data) and Motzer et al 2021a,[67] Eisai CS[15] and MSD CS[51] (FAS data)

9.6 Appendix 6: Subgroup results from the CLEAR trial by risk subgroup for ORR

Table 97 BIRC assessed objective response in the CLEAR trial by MSKCC and IMDC risk subgroup, IA3 data cut-off

Subgroup	ORR LEN+PEM n/N (%)	ORR sunitinib n/N (%)	OR LEN+PEM vs sunitinib (95% CI)	RD (%) LEN+PEM vs sunitinib (95% CI)	p-value
MSKCC risk subgroup					
Favourable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate/ Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IMDC risk subgroup					
Favourable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate/ Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BICR=Blinded Independent Review Committee; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IA3=third interim analysis; MSKCC=Memorial Sloan Kettering Cancer Center; OR=odds ratio; ORR=objective response rate; RD=risk difference.
Source: Eisai CS,[15] Appendix E4.1

9.7 Appendix 7: AG assessment of the statistical approach to the companies' NMAs

Summaries and AG critiques of the Eisai and MSD NMA statistical approaches are provided in Table 98 and Table 99 respectively.

Table 98 AG summary and critique of the NMA statistical approaches used by Eisai

Item	AG assessment	Statistical approach	AG comments
Were NMAs conducted for all relevant outcomes?	Yes	Eisai presented NMAs for PFS (according to FDA and EMA censoring rules), OS, ORR, CR, all-cause Grade≥3 AEs and treatment discontinuation due to AEs for the intermediate/poor risk subgroup and separately by IMDC or MSKCC risk subgroups where data were available and the all-risk population (Eisai CS,[15] Section 4.7; Eisai CS,[15] Appendix D 3.1 to D 3.7)	Indirect evidence is presented for all relevant outcomes for all relevant patient populations and subgroups
Were the networks of comparators appropriate?	Partly	The Eisai search process identified 36 trials that met the SLR inclusion criteria. Following a feasibility assessment, Eisai excluded 27 trials (Eisai CS,[15] Appendix D.2.1.2) and included nine trials[23,67,96-98,100-103] in at least one of their NMAs. Eisai NMAs of PFS included (Eisai CS,[15] Appendix D.3.2): • lenvatinib plus pembrolizumab, sunitinib and cabozantinib (intermediate/poor risk subgroup) • lenvatinib plus pembrolizumab, sunitinib, pazopanib (favourable risk subgroup) • lenvatinib plus pembrolizumab, sunitinib, pazopanib, tivozanib, sorafenib and interferon-alpha (all-risk population) Eisai NMAs of OS included (Eisai CS,[15] Appendix D.3.1): • lenvatinib plus pembrolizumab, sunitinib and cabozantinib (intermediate/poor risk subgroup) • lenvatinib plus pembrolizumab, sunitinib, pazopanib (favourable risk subgroup) • lenvatinib plus pembrolizumab, sunitinib, pazopanib and interferon-alpha (all -risk population) Eisai NMAs of ORR, CR, all-cause Grade≥3 AEs and treatment discontinuation due to AEs included (Eisai CS,[15] Appendix D.3.3 to Appendix D.3.7): • lenvatinib plus pembrolizumab, sunitinib and cabozantinib (intermediate/poor risk subgroup) • lenvatinib plus pembrolizumab, sunitinib, pazopanib, sorafenib and interferon-alpha (all-risk population)	No comparative evidence is presented in the Eisai CS[15] for lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab in the intermediate/poor risk subgroup. Therefore, the AG has performed NMAs of PFS, OS and ORR to include all relevant comparators by IMDC risk subgroup (Section 4.4). The AG acknowledges that as it is not possible to connect tivozanib to the network of comparators for the all-risk population for OS, ORR or Grade≥3 AEs, no indirect comparisons of lenvatinib plus pembrolizumab versus tivozanib can be made for OS, ORR or Grade≥3 AEs

Item	AG assessment	Statistical approach	AG comments
Were NMA methods appropriate?	Yes	The methods used in the Eisai NMAs are described in the Eisai CS[15] (Appendix D.2.2 and D.2.3 and Eisai response to the AG clarification letter, question A3). Eisai performed NMAs in a Bayesian framework using both FE and RE models. For PFS and OS, the company conducted NMAs estimating constant HRs, as well as 1st order and 2nd order FP NMAs (with 1st and 2nd order parameter values ranging from -3 to 3) according to the methods of Jansen,[134] to estimate time-varying HRs due to PH assumption violation within the included trials. Model fit was assessed according to the DIC statistic and clinical plausibility of estimates. Although Eisai considered that due to heterogeneity of the evidence base, RE models would be more clinically plausible, as a small number of trials were included in the NMAs with little or no data present to estimate heterogeneity variance (Appendix D.2.2), FE models were presented and selected as the base case for all NMAs	The AG considers that the Bayesian HR NMAs for all outcomes as described in Appendix D.2.2 and that the FP NMAs for PFS and OS using the methods described by Jansen[134] have been correctly implemented The AG agrees with Eisai that due to the heterogeneity in the evidence base, RE models are more clinically plausible than FE models (Section 4.3.7) but acknowledges the instability of results of RE NMAs, due to the small number of included trials and sparse data. However, it should be noted when interpreting FE NMA results that FE NMAs do not take account of observed heterogeneity between the trials
Was inconsistency appropriately assessed in the NMAs?	Yes	Eisai assessed inconsistency 'locally' within the closed loops including sunitinib, sorafenib, pazopanib, tivozanib, interferon-alpha and sorafenib in the all-risk population networks of PFS, ORR, CR, all-cause Grade≥3 AEs and treatment discontinuation due to AEs using methods described by Bucher[135] to compare direct and indirect evidence. Statistically significant inconsistency between the studies providing direct and indirect comparisons between sunitinib and sorafenib was observed for PFS and treatment discontinuation due to AEs. Inconsistency could not be statistically assessed within the OS NMAs or the NMAs within IMDC or MSKCC risk subgroups due to lack of closed loops within the networks	The local assessments of inconsistency performed by Eisai are appropriate. The AG has performed a 'global' assessment of inconsistency in the AG PFS NMA in the all-risk population by applying an unrelated mean effects NMA model[114] and by comparing model fit statistics of inconsistency models with consistency models (see Section 4.3.9). The AG acknowledges that the consistency of indirect estimates of OS and indirect estimates for all outcomes within the IMDC and MSKCC risk subgroups is unknown
Was the PH assumption appropriately assessed within the NMAs of PFS and OS?	Yes	Eisai assessed the PH assumption for PFS and OS in the included trials by plotting the log cumulative hazard versus log(time) and by using the Grambsch-Therneau test[105] of PH (Eisai CS,[15] Section 5.3.1 and 5.3.2 and Eisai response to the AG clarification letter, questions A1 and A2). Based on these assessments, Eisai considers that over the observed periods of the trials, the assumption of PH was violated for at least one of the trials for PFS and for OS. Due to these PH violations, in addition to PFS and OS NMAs estimating constant HRs, Eisai also used FP models to estimate time-varying HRs in their PFS and OS NMAs	The AG agrees with the Eisai assessments of PH violation and agrees that estimating time-varying HRs for the PFS and OS NMAs is appropriate. The AG considers that due to the limitations of FP NMAs for decision making (Eisai CS[15] Appendix D.2.3 and Section 4.3.8 of this AG report), it is appropriate to also present NMAs estimating constant HRs for PFS and OS

Item	AG assessment	Statistical approach	AG comments
Was the presentation of NMA results appropriate?	Yes	Eisai presented FE NMA results for lenvatinib plus pembrolizumab versus each comparator included in the network for the intermediate/poor risk subgroup and by IMDC/MSKCC risk subgroups and all-risk population(Eisai CS,[15] Section 4.7; Appendix D 3.1 to D 3.7). Constant HRs and time-varying HRs (with 95% CrIs) are presented for PFS and OS NMAs (Eisai CS,[15] Appendix D.3.1 to D.3.3 and Appendix D.4.1 and D4.2). ORs (with 95% CrIs) are presented for ORR, CR, all-cause Grade≥3 AEs and treatment discontinuation due to AEs NMAs. The probability that lenvatinib plus pembrolizumab is better than the comparator is also presented for NMAs of all outcomes (Eisai CS,[15] Appendix D.3.1 to D.3.7). Eisai also present subgroup, scenario and sensitivity analyses where data are available to examine NMA results for IMDC or MSKCC risk subgroups and to examine the robustness of NMA results to assumptions and to the exclusion of trials from the NMAs (Eisai CS,[15] Appendix D.2.2.2.3 and Appendix D.3.1 to D.3.7)	The presentation of Eisai NMA results for all outcomes is appropriate. In addition to results for lenvatinib plus pembrolizumab versus each comparator, the AG presents FE NMA results for all pairs of comparators included within each network (Section 4.4).

AE=adverse event; AG=Assessment Group; CR=complete response; CrI=credible interval; CS=company submission; DIC=deviance information criterion; EMA=European Medicines Agency; FDA=Food and Drug Administration; FE=fixed-effects; FP=fractional polynomial; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; RE=random-effects; SLR=systematic literature review

Source: Extracted from Section B.4.7 and Appendix D to the Eisai CS[15] the Eisai response to the AG clarification letter, and includes AG comment

Table 99 AG summary and critique of NMA statistical approaches used by MSD

Item	AG assessment	Statistical approach	AG comments
Were NMAs conducted for all relevant outcomes?	Yes	MSD presented NMAs for PFS and OS (according to FDA censoring rules) for the intermediate/poor risk subgroup and all-risk population (Section 2.9.3, Appendix M)	Indirect evidence is presented for the key efficacy outcomes for the relevant populations listed within the final scope.[27] No indirect evidence is presented for response outcomes or safety outcomes, or separately for IMDC or MSKCC risk subgroups
Were the networks of comparators appropriate?	Yes	Following a feasibility assessment of trials identified in the SLR (Appendix D.1.1), MSD included six trials [67,96,97,100,101,103] in at least one of their NMAs. MSD NMAs of PFS included (Section 2.9.3; Figure 13; Appendix M): • lenvatinib plus pembrolizumab, sunitinib and cabozantinib (intermediate/poor risk subgroup) • lenvatinib plus pembrolizumab, sunitinib, pazopanib, tivozanib and sorafenib (all-risk population) MSD NMAs of OS included (Section 2.9.3; Figure 12; Appendix M): • lenvatinib plus pembrolizumab, sunitinib and cabozantinib (intermediate/poor risk subgroup) • lenvatinib plus pembrolizumab, sunitinib and pazopanib (all-risk population)	No comparative evidence is presented in the MSD CS[51] for lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab in the intermediate/poor risk subgroup. Therefore, the AG has performed NMAs of PFS, OS and ORR to include all relevant comparators by IMDC risk subgroup (Section 4.4). The AG acknowledges that as it is not possible to connect tivozanib to the network of comparators for the all-risk population for OS, no indirect comparisons of lenvatinib plus pembrolizumab versus tivozanib can be made for OS.
Were NMA methods appropriate?	Yes	The methods used for the MSD NMAs are described in the MSD CS[51],[51] (Appendix D.1.1 and MSD response to the AG clarification letter, question A2). MSD performed NMAs in a Bayesian framework using both FE and RE models. For PFS and OS, the company conducted NMAs estimating constant HRs, as well as 1st order and 2nd order FP NMAs (with 1st and 2nd order parameter values of -1, 0 and 1) according to the methods of Jansen,[134] to estimate time-varying HRs due to PH assumption violation within the included trials. Model fit was assessed according to the DIC statistic and clinical plausibility of estimates. Although MSD considered that RE models would be more clinically plausible due to heterogeneity of the evidence base, as a small number of trials were included in the NMAs with most treatment comparisons informed by one trial, only FE models were presented (Section 2.9; Appendix D.1.1; Appendix M)	The AG considers that the Bayesian HR NMAs for all outcomes as described in Appendix D.1.1 and that the FP NMAs for PFS and OS using the methods described by Jansen[134] have been correctly implemented. The AG agrees with MSD that RE models are more clinically plausible than FE models due to the heterogeneity in the evidence base (Section 4.3.7) but acknowledges the instability of the results of RE NMAs due to the small number of included trials and sparse data. However, it should be noted when interpreting FE NMA results that FE NMAs do not take account of observed heterogeneity between the trials.
Was inconsistency appropriately assessed in the NMAs?	Not assessed	MSD did not undertake any assessments of inconsistency in the NMAs.	The AG has performed a 'global' assessment of inconsistency for PFS by applying an unrelated mean effects NMA model[114] and by comparing model fit statistics of inconsistency models with consistency models (Section 4.3.9)

Item	AG assessment	Statistical approach	AG comments
			Due to lack of closed loops within the network for OS, inconsistency cannot be formally assessed. Therefore, the consistency of indirect estimates of OS is unknown.
Was the PH assumption appropriately assessed within the NMAs of PFS and OS?	Partly	MSD assessed the PH assumption for PFS and OS in the CLEAR trial by plotting the log cumulative hazard versus log(time), by plotting Schoenfeld residuals versus time and by using the Grambsch-Therneau test[105] of PH (MSD CS[51],[51]: Section 3.3 and MSD response to the AG clarification letter, question A1). MSD did not present assessments of the PH assumption for PFS and OS in the other trials included in the NMAs. In order to relax the PH assumption for the NMAs, in addition to PFS and OS NMAs estimating constant HRs, MSD also used FP models to estimate time-varying HRs in their PFS and OS NMAs	The AG agrees that estimating time-varying HRs for the PFS and OS NMAs is appropriate to relax the PH assumption. The AG considers that due to the limitations of FP NMAs for decision making (Eisai CS[15] Appendix D.2.3 and Section 4.3.8 of this AG report), it is appropriate to also present NMAs estimating constant HRs for PFS and OS.
Was the presentation of NMA results appropriate?	Yes	MSD presented FE NMA results for all pairs of comparators included in each network for the intermediate/poor risk subgroup and by IMDC or MSKCC risk subgroups and all-risk population. Constant HRs and time-varying HRs (with 95% CrIs) are presented for PFS and OS NMAs (Section 2.9; Appendix M)	The presentation of MSD PFS and OS NMA results is appropriate.

AG=Assessment Group; CrI=credible interval; CS=company submission; DIC=deviance information criterion; FDA=Food and Drug Administration; FE=fixed-effects; FP=fractional polynomial; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; RE=random-effects; SLR=systematic literature review
Source: Extracted from Section B.2.9 and Appendix M to the MSD CS[51] and MSD response to the AG clarification letter and includes AG comment

9.8 Appendix 8: Network diagrams for AG NMAs

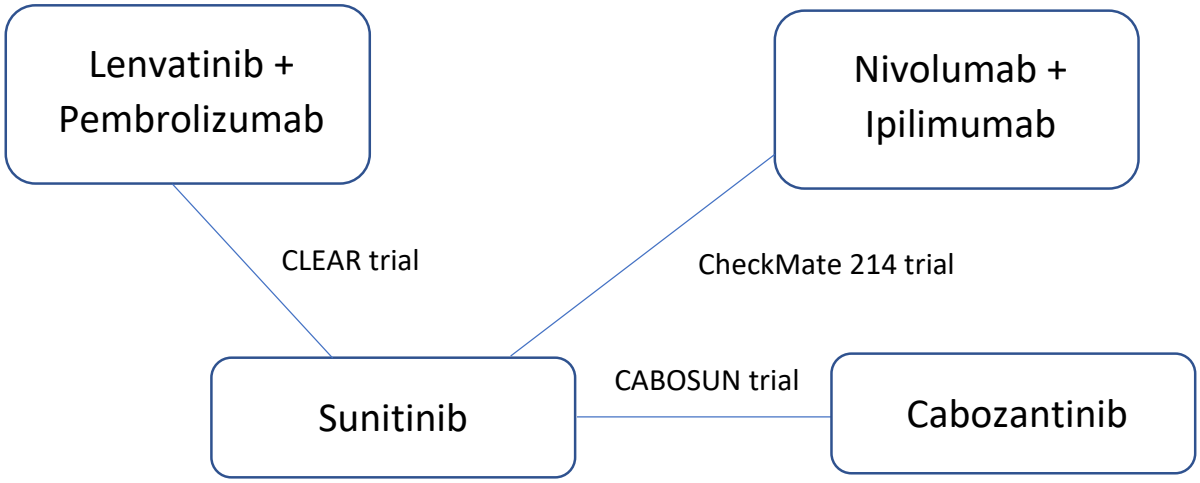

Figure 29 Network diagram for the AG NMAs for the intermediate/poor risk subgroup (PFS, OS and ORR)

AG=Assessment Group; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

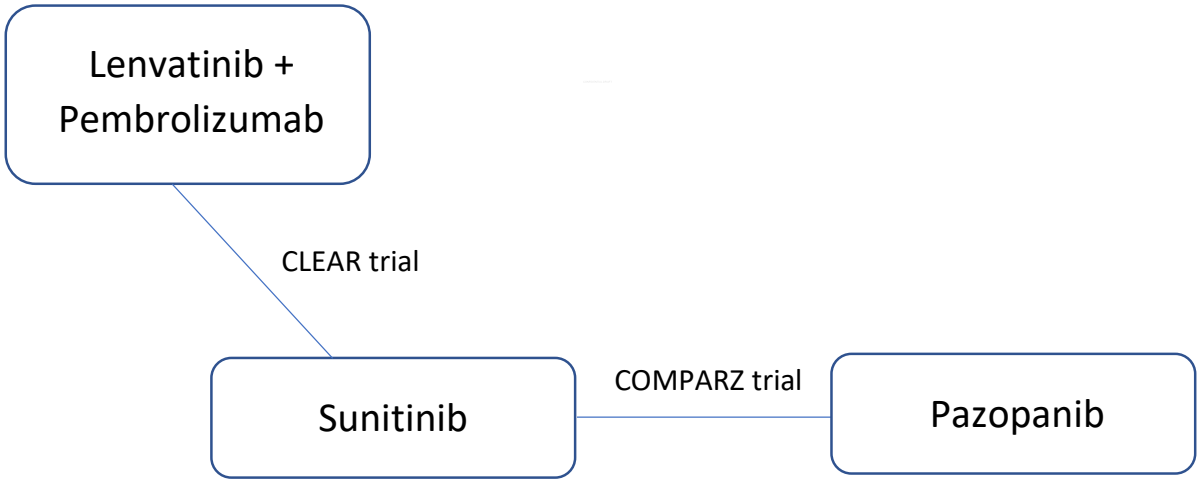

Figure 30 Network diagram for the AG NMAs for the all-risk population (OS and ORR) and for the favourable risk subgroup (PFS, OS, Grade ≥3 AEs)

AE=adverse events; AG=Assessment Group; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

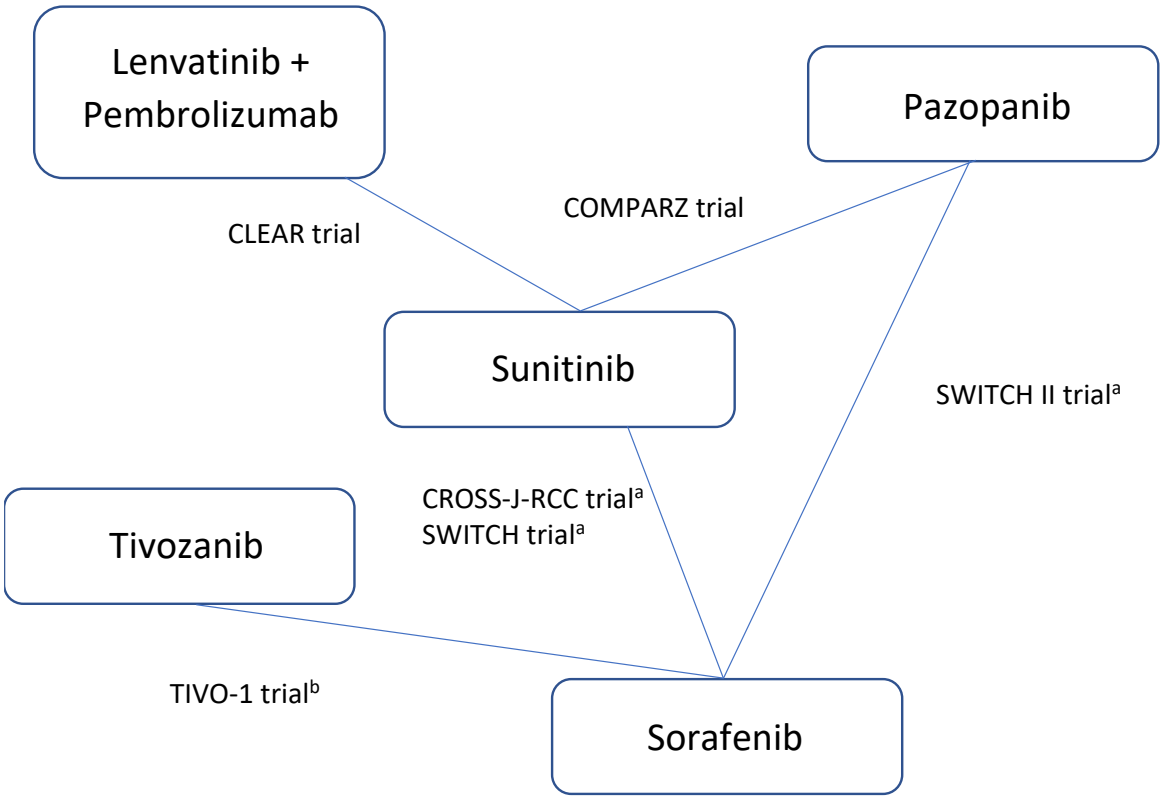

Figure 31 Network diagram for the AG PFS NMA for the all-risk population

[a] The CROSS-J-RCC,[103] SWITCH[97] and SWITCH II[102] had a sequential design (patients received first-line therapy with the treatment they were randomised to, and patients who discontinued first-line therapy due to disease progression or toxicity received the other trial treatment second line). PFS data for first-line treatment used in the NMAs
[b] The TIVO-1 trial recruited patients with untreated mRCC and patients who had received prior systematic therapy for mRCC. PFS data for the untreated subgroup is used in the NMAs
AG=Assessment Group; NMA=network meta-analysis; mRCC=metastatic renal cell carcinoma; PFS=progression-free survival

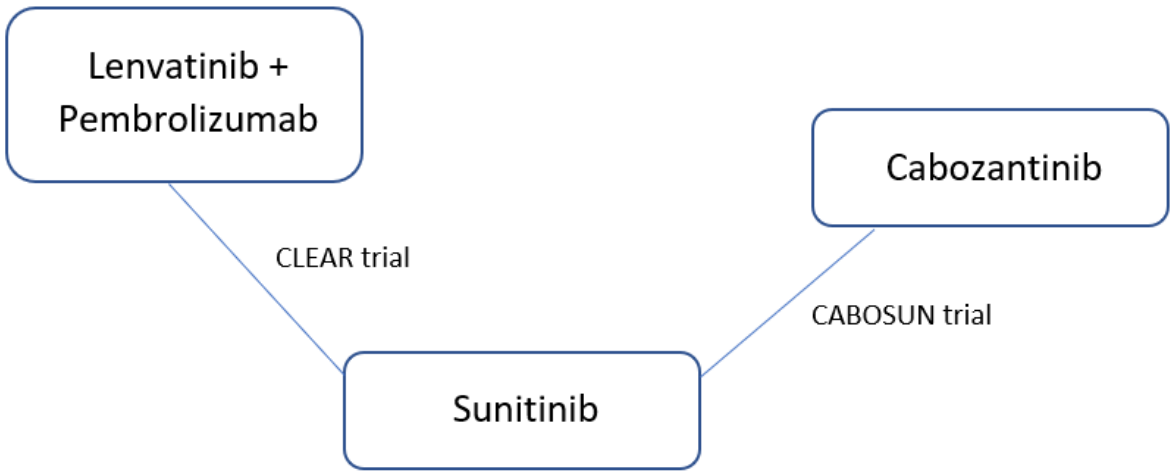

Figure 32 Network diagram for the AG NMAs for the intermediate/poor risk subgroup (Grade ≥3 AEs)

AE=adverse events; AG=Assessment Group; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

9.9 Appendix 9: Outcome data included in AG NMAs

Table 100 PFS outcome data from the trials included in the AG NMAs

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	Median PFS months (95% CI)[a]	HR (95% CI)[a]
Intermediate/poor risk subgroup						
CLEAR	Lenvatinib + pembrolizumab	• IMDC risk subgroups • Final analysis of PFS • BIRC assessed	[redacted]	243	[redacted]	[redacted]
	Sunitinib		[redacted]	229	[redacted]	
	Lenvatinib + pembrolizumab	• MSKCC risk subgroups • Final analysis of PFS • BIRC assessed	[redacted]	259	[redacted]	[redacted]
	Sunitinib		[redacted]	260	[redacted]	
CABOSUN[96]	Cabozantinib	• IMDC risk subgroups • Updated analysis of PFS • BIRC assessed	25 (IQR: 21.9 to 30.9)	79	8.6 (6.8 to 14.0)	0.48 (0.31 to 0.74
	Sunitinib		25 (IQR: 21.9 to 30.9)	78	5.3 (3.0 to 8.2)	
CheckMate 214[99]	Nivolumab + ipilimumab	• IMDC risk subgroups • Updated analysis of PFS • BIRC assessed	39.3 (NR to NR)	425	11.6 (8.4 to 15.5)	0.75 (0.62 to 0.90
	Sunitinib		39.3 (NR to NR)	422	8.3 (7.0 to 10.8)	

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	Median PFS months (95% CI)[a]	HR (95% CI)[a]
Favourable risk subgroup						
CLEAR	Lenvatinib + pembrolizumab	• IMDC risk subgroup • Final analysis of PFS • BIRC assessed	[redacted]	110	[redacted]	[redacted]
	Sunitinib		[redacted]	124	[redacted]	[redacted]
	Lenvatinib + pembrolizumab	• MSKCC risk subgroup • Final analysis of PFS • BIRC assessed	[redacted]	96	[redacted]	[redacted]
	Sunitinib		[redacted]	97	[redacted]	[redacted]
COMPARZ[100]	Pazopanib	• IMDC risk subgroup • BIRC assessed	NR	151	NR	1.02 (0.62 to 1.42)[e]
	Sunitinib		NR	152	NR	
	Pazopanib	• MSKCC risk subgroup • BIRC assessed	NR	151	NR	1.01 (0.63 to 1.39)[e]
	Sunitinib		NR	152	NR	
CROSS-J-RCC[103 b]	Sunitinib	• MSKCC risk subgroup • Interim analysis of first-line PFS • Investigator assessed	NR	12	NR	0.25 (0.08 to 0.73)[f]
	Sorafenib		NR	14	NR	
SWITCH[97 b]	Sorafenib	• MSKCC risk subgroup • First-line PFS • Investigator assessed	NR	71	NR	1.30 (0.87 to 1.94)[f]
	Sunitinib		NR	82	NR	
SWITCH II[102 b]	Sorafenib	• Not reported for first line therapy[b]	NR	NR	NR	NR
	Pazopanib		NR	NR	NR	
TIVO-1[101]	Tivozanib	• Not reported for untreated subgroup[a]	NR	NR	NR	NR
	Sorafenib		NR	NR	NR	

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	Median PFS months (95% CI)[a]	HR (95% CI)[a]
All-risk population						
CLEAR	Lenvatinib + pembrolizumab	• Final analysis of PFS • BIRC assessed	[redacted]	355	FDA: 23.9 (20.8 to 27.7) EMA: 22.1 (18.4 to 25.9)	FDA: 0.39 (0.32 to 0.49) EMA: 0.41 (0.33 to 0.50)
	Sunitinib		[redacted]	357	FDA: 9.2 (6.0 to 11.0) EMA: 9.2 (7.0 to 11.0)	
COMPARZ[100]	Pazopanib	• BIRC assessed	NR	557	8.4 (8.3 to 10.9)	1.05 (0.90 to 1.22)
	Sunitinib		NR	553	9.5 (8.3 to 11.1)	
CROSS-J-RCC[103] [b]	Sunitinib	• Interim analysis of first-line PFS • Investigator assessed	NR	57	8.7 (5.5 to 21.1)	0.67 (0.42 to 1.08)
	Sorafenib		NR	63	7.0 (6.1 to 12.2)	
SWITCH[97] [b]	Sorafenib	• First-line PFS • Investigator assessed	Mean: 10.3	182	5.9 (90% CI 5.5 to 7.9)	1.19 (0.93 to 1.45)[d]
	Sunitinib		Mean: 10.3	183	8.5 (90% CI 7.1 to 11.2)	
SWITCH II[102] [b]	Sorafenib	• First-line PFS • Assessment method: NR	NR	189	5.6 (4.7 to 6.3)	0.69 (0.54 to 0.87)
	Pazopanib		NR	188	9.3 (7.4 to 10.6)	
TIVO-1[101]	Tivozanib	• Untreated subgroup[c] • BIRC assessed	NR	181	12.7 (9.1 to 15.0)	0.76 (0.58 to 0.99)
	Sorafenib		NR	181	9.1 (7.3 to 10.8)	

[a] PFS was assessed in the CLEAR trial using two different censoring rules advocated by the FDA and by the EMA
[b] The CROSS-J-RCC,[103] SWITCH[97] and SWITCH II[102] trials had a sequential design (patients received first-line therapy with the treatment they were randomised to, and patients who discontinued first-line therapy due to disease progression or toxicity received the other trial treatment second line). PFS data for first-line treatment is extracted.
[c] The TIVO-1 trial recruited patients with untreated mRCC and patients who had received prior systematic therapy for mRCC. PFS data for the untreated subgroup is extracted from the TIVO-1 trial publication.[101]
[d] 90% CI reported in the publication of the SWITCH trial,[97] 95% CI calculated by the AG
[e] Extracted from K-M curves
[f] Data not included in the AG PFS NMAs for the favourable risk subgroup as Sorafenib is not a relevant comparator and data cannot be used to connect relevant comparators (i.e. Tivozanib) to the networks for PFS
AG=Assessment Group; BIRC=blinded independent review committee; CI=confidence interval; CS=company submission; EMA=European Medicines Agency; FDA=Food and Drug Administration; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IQR=interquartile range; K-M=Kaplan-Meier; mRCC=metastatic renal cell carcinoma; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NE=not estimable; NMA=network meta-analysis; NR=not reported; PFS=progression-free survival
Source: Extracted from Eisai CS,[15] Appendix D.2.4, Table 14 and Table 20 and from the publications of the trials included in the NMAs[67,96,97,99-103]

Table 101 OS outcome data from the trials included in the AG NMAs

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	Median OS months (95% CI)	HR (95% CI)
Intermediate/poor risk subgroup						
CLEAR	Lenvatinib + pembrolizumab	• IMDC risk subgroups • Updated OS analysis	[redacted]	243	[redacted]	[redacted]
	Sunitinib		[redacted]	229	[redacted]	
	Lenvatinib + pembrolizumab	• MSKCC risk subgroups • Updated OS analysis	[redacted]	259	[redacted]	[redacted]
	Sunitinib		[redacted]	260	[redacted]	
CABOSUN[96]	Cabozantinib	• IMDC risk subgroups • Updated OS analysis	35.4 (IQR:31.4 to 40.4)	79	26.6 (14.6 to NE)	0.80 (0.53 to 1.21)
	Sunitinib		35.4 (IQR:31.4 to 40.4)	78	21.2 (16.3 to 27.4)	
CheckMate 214[99]	Nivolumab + ipilimumab	• IMDC risk subgroups • Updated OS analysis	43.6 (NR to NR)	425	47.0 (35.6 to NE)	0.66 (0.55 to 0.80)
	Sunitinib		32.3 (NR to NR)	422	26.6 (22.1 to 33.5)	
Favourable risk subgroup						
CLEAR	Lenvatinib + pembrolizumab	• IMDC risk subgroups • Updated OS analysis	[redacted]	110	[redacted]	[redacted]
	Sunitinib		[redacted]	124	[redacted]	
	Lenvatinib + pembrolizumab	• MSKCC risk subgroups • Updated OS analysis	[redacted]	96	[redacted]	[redacted]
	Sunitinib		[redacted]	97	[redacted]	
COMPARZ[100]	Pazopanib	• MSKCC risk subgroups • Final OS analysis[a]	NR	151	42.5 (37.9 to NR)	0.88 (0.63 to 1.21)
	Sunitinib		NR	152	43.6 (37.1 to 47.4)	
TIVO-1[101]	Tivozanib	• Not reported for untreated subgroup[b]	NR	NR	NR	NR
	Sorafenib		NR	NR	NR	

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	Median OS months (95% CI)	HR (95% CI)
All-risk population						
CLEAR	Lenvatinib + pembrolizumab	• Updated OS analysis	[redacted]	355	[redacted]	[redacted]
	Sunitinib		[redacted]	357	[redacted]	
COMPARZ[100]	Pazopanib	• Final analysis of OS[a]	NR	557	28.3 (26.0 to 35.5)	0.92 (0.79 to 1.06)
	Sunitinib		NR	553	29.1 (25.4 to 33.1)	
TIVO-1[101]	Tivozanib	• Untreated subgroup[b]	NR	181	NR	1.23 (0.67 to 1.55)[c]
	Sorafenib		NR	181	NR	

[a] Final OS analysis reported by Motzer et al 2014[104]
[b] The TIVO-1 trial[101] recruited patients with untreated mRCC and patients who had received prior systematic therapy for mRCC. OS data for the untreated subgroup is extracted from TA512.[32]
[c] Data not included in the AG OS NMAs for the all-risk population as Tivozanib cannot be connected to the networks for OS
AG=Assessment Group; CI=confidence interval; CS=company submission; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IQR=interquartile range; mRCC=metastatic renal cell carcinoma; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NE=not estimable; NR=not reported; NMA=network meta-analysis; OS=overall survival
Source: Extracted from Eisai CS,[15] Appendix D.2.4, Table 13 and Table 19 and from the publications of the trials included in the NMAs[67,96,97,99-103]

Table 102 ORR outcome data from the trials included in the AG NMAs

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	ORR (n)	ORR (%)
Intermediate/poor risk subgroup						
CLEAR	Lenvatinib + pembrolizumab	• IMDC risk subgroups • Time of final PFS analysis • BIRC assessed	[redacted]	243	[redacted]	[redacted]
	Sunitinib		[redacted]	229	[redacted]	[redacted]
	Lenvatinib + pembrolizumab	• MSKCC risk subgroups • Time of final PFS analysis • BIRC assessed	[redacted]	259	[redacted]	[redacted]
	Sunitinib		[redacted]	260	[redacted]	[redacted]
CABOSUN[96]	Cabozantinib	• IMDC risk subgroups • Updated PFS analysis • BIRC assessed	25 (IQR: 21.9 to 30.9)	79	16	20
	Sunitinib		25 (IQR: 21.9 to 30.9)	78	7	9
CheckMate 214[99]	Nivolumab + ipilimumab	• IMDC risk subgroups • Updated PFS analysis • BIRC assessed	39.3 (NR to NR)	425	179	42.1
	Sunitinib		39.3 (NR to NR)	422	111	26.3

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	ORR (n)	ORR (%)
All-risk population						
CLEAR	Lenvatinib + pembrolizumab	• Time of final PFS analysis • BIRC assessed	[redacted]	355	252	71
	Sunitinib		[redacted]	357	129	36.1
COMPARZ[100]	Pazopanib	• BIRC assessed	NR	557	3	31
	Sunitinib		NR	553	137	25
CROSS-J-RCC[103] [a]	Sunitinib	• Interim analysis of first-line ORR • Investigator assessed	NR	57	14[b]	29.8[b]
	Sorafenib		NR	63	10[b]	21.2[b]
SWITCH[97] [a]	Sorafenib	• First-line ORR • Investigator assessed	Mean: 10.3	177	55[b]	31[b]
	Sunitinib		Mean: 10.3	176	51[b]	29[b]
SWITCH II[102] [a]	Sorafenib	• First-line ORR • Assessment method: NR	NR	189	54[b]	28.6[b]
	Pazopanib		NR	188	87[b]	46.3[b]
TIVO-1[101]	Tivozanib	• Not reported for untreated subgroup	NR	NR	NR	NR
	Sorafenib		NR	NR	NR	NR

[a] The CROSS-J-RCC,[103] SWITCH[97] and SWITCH II[102] trials had a sequential design (patients received first-line therapy with the treatment they were randomised to, and patients who discontinued first-line therapy due to disease progression or toxicity received the other trial treatment second line). ORR data for first-line treatment is extracted.
[b] Data not included in the AG ORR NMAs for the all-risk population as Sorafenib is not a relevant comparator and data cannot be used to connect relevant comparators (i.e., tivozanib) to the networks for ORR
AG=Assessment Group; BIRC=blinded independent review committee; CI=confidence interval; CS=company submission; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IQR=interquartile range; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; NR=not reported; ORR=objective response rate; PFS=progression-free survival
Source: Extracted from Eisai CS,[15] Appendix D.2.4, Table 14 and Table 20 and from the publications of the trials included in the NMAs[67,96,97,99-103]

Table 103 Grade ≥3 AE outcome data from the trials included in the AG NMAs

Trial	Intervention	Analysis methods	Median follow-up months (95% CI)	N	Grade ≥3 AE (n)	Grade ≥3 AE (%)
Intermediate/poor risk subgroup						
CLEAR	Lenvatinib + pembrolizumab	Grade ≥3 TEAE, NCI CTCAE v4.03 (IMDC)	[redacted]	241	[redacted]	[redacted]
	Sunitinib		[redacted]	220	[redacted]	[redacted]
	Lenvatinib + pembrolizumab	Grade ≥3 TEAE, NCI CTCAE v4.03 (MSKCC)	[redacted]	256	[redacted]	[redacted]
	Sunitinib		[redacted]	247	[redacted]	[redacted]
CABOSUN[96]	Cabozantinib	All cause AEs, NCI CTCAE v4 (IMDC)	25 (IQR: 21.9 to 30.9)	78	53	68
	Sunitinib		25 (IQR: 21.9 to 30.9)	72	47	65
CheckMate 214[99]	Nivolumab + ipilimumab	NR	NR	NR	NR	NR
	Sunitinib		NR	NR	NR	NR
	Intervention		Median follow-up months (95% CI)	N	Grade ≥3 AE (n)	Grade ≥3 AE (%)
All-risk population						
CLEAR	Lenvatinib + pembrolizumab	Grade ≥3 TEAE, NCI CTCAE v4.03	[redacted]	[redacted]	[redacted]	[redacted]
	Sunitinib		[redacted]	[redacted]	[redacted]	[redacted]
COMPARZ[100]	Pazopanib	Grade 3+ TEAEs, NCI CTCAE v3	NR	554	423	76
	Sunitinib		NR	548	419	77
CROSS-J-RCC[103] [a]	Sunitinib	Interim analysis, 1st line treatment, Grade ≥3 all-cause AEs, NCI CTCAE v3	NR	57	48[b]	84.2[b]
	Sorafenib		NR	63	50[b]	79.4[b]
SWITCH[97] [a]	Sorafenib	Grade 3/4 TEAEs, NCI CTCAE v3	Mean: 10.3 months	177	117[b]	66[b]
	Sunitinib		Mean: 10.3 months	176	118[b]	67[b]
SWITCH II[102] [a]	Sorafenib	Grade 3/4 TEAEs, NCI CTCAE v4.03	NR	183	108[b]	59[b]
	Pazopanib		NR	183	117[b]	64[b]
TIVO-1[101]	Tivozanib	NR	NR	NR	NR	NR
	Sorafenib		NR	NR	NR	NR

[a] The CROSS-J-RCC,[103] SWITCH[97] and SWITCH II[102] trials had a sequential design (patients received first-line therapy with the treatment they were randomised to, and patients who discontinued first-line therapy due to disease progression or toxicity received the other trial treatment second line). Grade ≥3 AE data for first-line treatment is extracted.
[b] Data not included in the AG Grade ≥3 AE NMAs for the all-risk population as Sorafenib is not a relevant comparator and data cannot be used to connect relevant comparators (i.e. Tivozanib) to the

networks for Grade ≥3 AEs
AE=adverse event; AG=Assessment Group; CI=confidence interval; CS=company submission; CTCAE=common terminology criteria for adverse events; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IQR=interquartile range; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NCI=National Cancer Institute; NMA=network meta-analysis; NR=not reported; TEAE=treatment emergent adverse event
Source: Extracted from Eisai CS,[15] Appendix D.2.4, Table 17 and Table 23 and from the publications of the trials included in the NMAs[67,96,97,99-103]

9.10 Appendix 10: AG quality assessment of the trials included in the NMAs

The AG assessed quality of the RCTs in accordance with suggested criteria published in the CRD's Guidance for undertaking reviews in healthcare.[59] The results of the AG's quality assessment of the eight RCTs[67,96,97,99-103] included in the AG NMAs are presented in Table 104.

Table 104 AG quality assessments of trials included in the NMAs

Quality assessment item[59]	CABOSUN[96]	CheckMate 214[99]	CLEAR	COMPARZ[100]	CROSS-J-RCC[103]	TIVO-1[101]	SWITCH[97]	SWITCH II[102]
Was the method used to assign participants to treatment arms really random?	✓	✓	✓	✓	✓	✓[a]	✓	unclear
Was the allocation of treatment concealed?	✓	✓	✓	✓	✓	✓[a]	✓	unclear
Was the number of participants randomised stated?	✓	✓	✓	✓	✓	✓	✓	✓
Were details of baseline comparability presented?	✓	✓	✓	✓	✓	✓	✓	✓
Was baseline comparability achieved?	✓	✓	✓	✓	✓	✓	✓	✓
Were the study eligibility criteria specified?	✓	✓	✓	✓	✓	✓	✓	✓
Were any co-interventions identified that may influence the outcomes for each group?	✗	✗	✗	✗	✗	✗	✗	✗
Were the outcome assessors blinded to treatment allocation?	✓	✓	✓	✓	✗	✓[a]	✗	✗
Were the individuals administering the intervention blinded to treatment allocation?	✗	✗	✗	✗	✗	✗	✗	✗
Were the participants receiving the intervention blinded to treatment allocation?	✗	✗	✗	✗	✗	✗	✗	✗
Was the success of the blinding procedure assessed?	NA	NA	NA	NA	NA	NA	NA	NA
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	✓	✓	✓	✓	✓	✓	✓	✓
Were the reasons for patient withdrawals stated?	✓	✓	✓	✓	✓	✓	✓	✓
Was an intention to treat analysis included?	✓	✓	✓	✓	✓	✓	✓	✓
Is there any evidence that more outcomes were measured than were reported?	✗	✗	✗	✗	✗	✗	✗	✗

[a] Information taken from TA512[32]
AG=Assessment Group; NA=not applicable; NMA=network meta-analysis
Source: AG quality assessments based on information extracted the publications of the trials considered for inclusion in the NMAs[23,67,96-103] and from TA512[32]

9.11 Appendix 11: Trial design and patient characteristics in the trials included in the AG NMAs

Table 105 Summary of trial design and patient demographic characteristics in the trials included in the AG NMAs

Trial	Trial design and location	Population	Treatments	N	Median age (range) years	Male: n (%)
CABOSUN[96]	Phase II, open label, USA	Untreated advanced or metastatic clear cell RCC; Intermediate or poor risk disease by IMDC criteria	Cabozantinib	79	63 (IQR: 56 to 69)	66 (84%)
			Sunitinib	78	64 (IQR: 57 to 71)	57 (73%)
CheckMate 214[99]	Phase III, open label, International	Untreated advanced clear cell RCC	Nivolumab + ipilimumab	425[a]	62 (26 to 85)	314 (74%)
			Sunitinib	422[a]	61 (21 to 85)	301 (71%)
CLEAR	Phase III, open label, International	Untreated advanced clear cell RCC	Lenvatinib + pembrolizumab	355	64 (34 to 88)	255 (72%)
			Sunitinib	357	61 (29 to 82)	275 (77%)
COMPARZ[100]	Phase III, open label, International	Untreated advanced or metastatic clear cell RCC	Pazopanib	557	61 (18 to 88)	398 (71%)
			Sunitinib	553	62 (23 to 86)	415 (75%)
CROSS-J-RCC[103]	Phase III sequential design, open label, Japan	Untreated metastatic clear cell RCC; Favourable or intermediate risk disease by MSKCC criteria	Sunitinib	57	67 (41 to 79)	46 (81%)
			Sorafenib	63	66 (44 to 79)	53 (84%)
SWITCH[97]	Phase III sequential design, open label, Europe	Untreated advanced or metastatic RCC; 87% with clear cell histology; Favourable or intermediate risk disease by MSKCC criteria	Sunitinib	182	65 (40 to 83)	135 (74%)
			Sorafenib	183	64 (39 to 84)	139 (76%)
SWITCH II[102]	Phase III sequential design, open label, Europe	Untreated advanced or metastatic RCC; 87% with clear cell histology; Favourable or intermediate risk disease by MSKCC criteria	Pazopanib	188	68 (26 to 86)	137 (73%)
			Sorafenib	189	68 (31 to 84)	136 (72%)
TIVO-1[101]	Phase II, open label, International	Metastatic clear cell RCC; untreated patients (70%) and patients who had received previous systematic therapy (30%)	Tivozanib	181[b]	NR	NR
			Sorafenib	181[b]	NR	NR

[a] IMDC intermediate/poor risk population data only extracted from the CheckMate 214 trial[99]
[b] Age and sex not reported separately for the untreated subgroup in the TIVO-1 trial[101]
AG=Assessment Group; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IQR=interquartile range; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; NR=not reported; RCC=renal cell carcinoma
Source: Extracted from the publications of the trials included in the NMAs[67,96,97,99-103]

Table 106 Summary of IMDC and MSKCC risk subgroups in the trials included in the AG NMAs

Trial	Treatments	N	IMDC risk subgroups: n (% of N)					MSKCC risk subgroups: n (% of N)				
			Favourable	Intermediate	Poor	Intermediate /Poor	Not evaluated	Favourable	Intermediate	Poor	Intermediate /Poor	Unknown
CABOSUN[96]	Cabozantinib	79	NA	64 (81%)	15 (19%)	79 (100%)	NA	NR	NR	NR	NR	NR
	Sunitinib	78	NA	63 (81%)	15 (19%)	78 (100%)	NA	NR	NR	NR	NR	NR
CheckMate 214[99]	Nivolumab + ipilimumab	425[a]	NA[a]	334 (74%)	91 (21%)	425 (100%)	NA	NR	NR	NR	NR	NR
	Sunitinib	422[a]	NA[a]	333 (79%)	89 (21%)	422 (100%)	NA	NR	NR	NR	NR	NR
CLEAR	Lenvatinib + pembrolizumab	355	110 (31%)	210 (59%)	33 (9%)	243 (68%)	2 (1%)	96 (27%)	227 (64%)	32 (9%)	259 (73%)	NA
	Sunitinib	357	124 (35%)	192 (54%)	37 (10%)	229 (64%)	4 (1%)	97 (27%)	228 (64%)	32 (9%)	260 (73%)	NA
COMPARZ[100]	Pazopanib	557	NR	NR	NR	NR	NR	151 (27%)	322 (58%)	67 (12%)	389 (70%)	17 (3%)
	Sunitinib	553	NR	NR	NR	NR	NR	152 (27%)	328 (59%)	52 (9%)	380 (68%)	21 (4%)
CROSS-J-RCC[103]	Sunitinib	57	NR	NR	NR	NR	NR	12 (21%)	45 (79%)	NA	NA	NA
	Sorafenib	63	NR	NR	NR	NR	NR	14 (22%)	49 (78%)	NA	NA	NA
SWITCH[97]	Sunitinib	182	NR	NR	NR	NR	NR	71 (39%)	108 (59%)	1 (1%)	109 (60%)	2 (1%)
	Sorafenib	183	NR	NR	NR	NR	NR	82 (45%)	94 (51%)	1 (1%)	95 (52%)	6 (3%)
SWITCH II[102]	Pazopanib	188	NR	NR	NR	NR	NR	91 (48%)	89 (47%)	5 (3%)	94 (50%)	3 (2%)
	Sorafenib	189	NR	NR	NR	NR	NR	95 (50%)	90 (48%)	4 (2%)	94 (50%)	0 (0%)
TIVO-1[101]	Tivozanib	181[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Sorafenib	181[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

[a] IMDC intermediate/poor risk population data only extracted from the CheckMate 214 trial[99]
[b] The TIVO-1 trial[101] recruited patients with untreated mRCC and patients who had received prior systematic therapy for mRCC. Risk subgroup data not reported separately for the untreated subgroup.
AG=Assessment Group; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; mRCC=metastatic renal cell carcinoma; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NA=not applicable; NMA=network meta-analysis; NR=not reported
Source: Extracted from the publications of the trials included in the NMAs[67,96,97,99-103]

9.12 Appendix 12: Proportional hazards assessments for trials included in the AG NMAs

The AG assessed the validity of the PH assumption for RCTs included in the AG NMAs using figures (i.e., Schoenfeld residuals plots or log cumulative hazard plots) and statistical tests (i.e., Grambsch-Therneau test[105]) presented in the Eisai CS[15] (Section 5.3.1 and 5.3.2), the Eisai response to question A1 and A2 of the AG clarification letter, and in the MSD response to additional clarification questions. The AG also digitized K-M data presented in the publication of the 42-month follow-up of the CheckMate 214 trial[99] (this RCT was not included in the Eisai or MSD NMAs), and assessed the PH assumption for OS and PFS in the intermediate/poor risk subgroup by plotting Schoenfeld residuals and performing a Grambsch-Therneau test.[105]

Results of the tests of Schoenfeld residuals conducted by Eisai and the AG are presented in Table 107. Plots of Schoenfeld residuals against time for the intermediate/poor risk subgroup in the CheckMate 214 trial[99] for PFS and OS are presented in Figure 33 and Figure 34.

Table 107 Assessments of proportion hazards assumption for studies included in the AG NMAs (all-risk population, intermediate/poor risk and favourable risk subgroups)

Trial[a]	p-values of Schoenfeld Residuals test					
	IMDC intermediate/poor risk subgroup		Favourable risk subgroup		All-risk population	
	PFS	OS	PFS	OS	PFS	OS
CLEAR[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CABOSUN	[redacted]	[redacted]	NA	NA	NA	NA
CheckMate 214	0.0002	0.4055	NA	NA	NA	NA
COMPARZ	NA	NA	NR	NR	[redacted]	[redacted]
CROSS-J-RCC	NA	NA	NR	NR	[redacted]	[redacted]
SWITCH	NA	NA	NR	NR	[redacted]	[redacted]
SWITCH II	NA	NA	NR	NR	[redacted]	[redacted]
TIVO-1	NA	NA	NR	NR	[redacted]	[redacted]

[a] PH assessment conducted by the AG for the CheckMate 214 trial.[99] PH assessments for the other trials included in the NMAs conducted by Eisai and presented in Eisai response to the AG clarification letter, questions A1 and A2, Table 1 and Table 2.
[b] PH assessment conducted on PFS according to the FDA censoring rule for the CLEAR trial
AG=Assessment Group; FDA=FDA=food and drug administration; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; K-M=Kaplan Meier; NA=not applicable; NMA=network meta-analysis; NR=not reported; OS=overall survival; PFS=progression-free survival; PH=proportional hazards
Source: Extracted from Eisai response to the AG clarification letter, question A1 and A2, Table 1 and Table 2; MSD response to additional clarification questions; AG testing of digitised K-M data extracted from the CheckMate 214 trial publication[99]

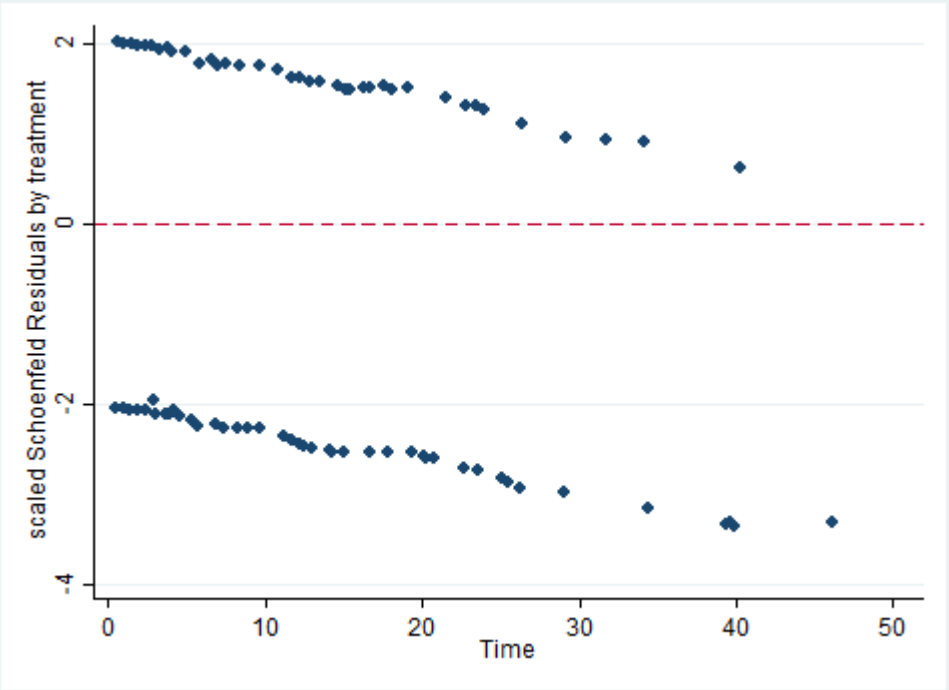

Figure 33 Schoenfeld residuals plot for PFS (CheckMate 214 trial, intermediate/poor risk subgroup)

PFS=progression-free survival

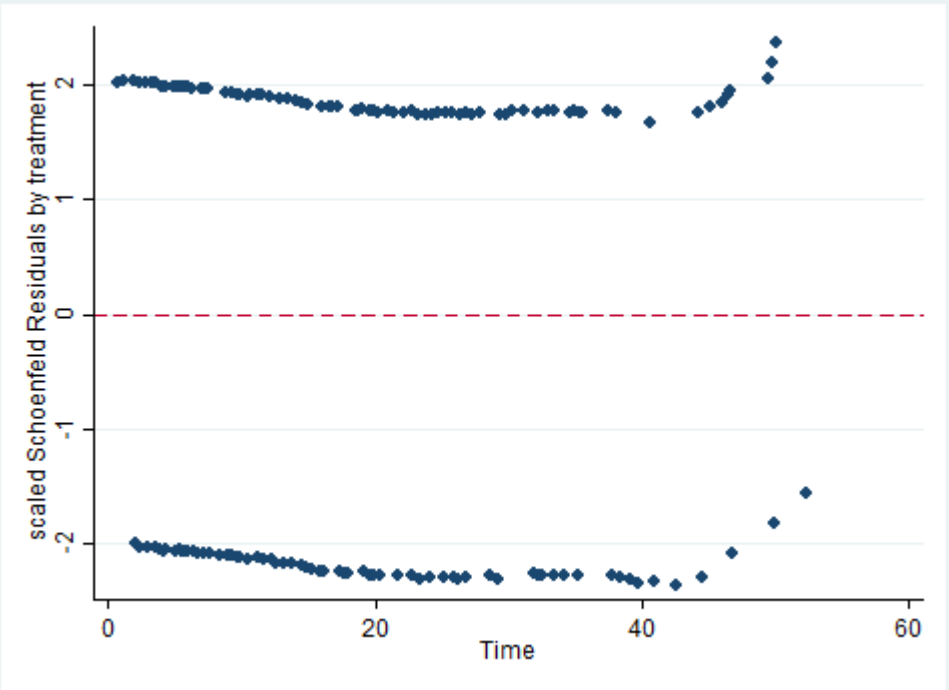

Figure 34 Schoenfeld residuals plot for OS (CheckMate 214 trial, intermediate/poor risk subgroup)

OS=overall survival

9.13 Appendix 13: Example statistical code for AG NMAs

Fixed and random-effects NMAs of contrast-based time-to-event data (PFS and OS)

```
###     Install and run multinma to conduct Bayesian network meta-analysis        ###

if (!require("multinma")) install.package("multinma")

library("multinma")
options(mc.cores = parallel::detectCores())

###     Load datasets ###

os_1 <- read.csv("OS all-risk.csv")
os_2 <- read.csv("OS intermediate poor IMDC.csv")
os_3 <- read.csv("OS favourable IMDC.csv")
os_4 <- read.csv("OS favourable MSKCC.csv")

###     Setting up networks and network plots         ###

os_1_network <-       set_agd_contrast(os_1,
                      study = studyc,
                      trt = trtc_1,
                      y = loghr,
                      se = seloghr,
                      sample_size = n,
                                    trt_ref = "Sunitinib")
plot(os_1_network, weight_edges = TRUE, weight_nodes = TRUE)

os_2_network <-       set_agd_contrast(os_2,
                      study = studyc,
                      trt = trtc_1,
                      y = loghr,
                      se = seloghr,
                      sample_size = n,
                                    trt_ref = "Sunitinib")
plot(os_2_network, weight_edges = TRUE, weight_nodes = TRUE)

os_3_network <-       set_agd_contrast(os_3,
                      study = studyc,
                      trt = trtc_1,
                      y = loghr,
                      se = seloghr,
                      sample_size = n,
                                    trt_ref = "Sunitinib")
plot(os_3_network, weight_edges = TRUE, weight_nodes = TRUE)

os_4_network <-       set_agd_contrast(os_4,
                      study = studyc,
                      trt = trtc_1,
                      y = loghr,
                      se = seloghr,
                      sample_size = n,
                                    trt_ref = "Sunitinib")
plot(os_4_network, weight_edges = TRUE, weight_nodes = TRUE)
```

```
###     Fixed-effect NMA                ###

FE_os_1         <-      nma(os_1_network,
                trt_effects = "fixed",
                        consistency = "consistency",
                        link="log",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10))

FE_os_2         <-      nma(os_2_network,
                trt_effects = "fixed",
                        consistency = "consistency",
                        link="log",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10))

FE_os_3         <-      nma(os_3_network,
                trt_effects = "fixed",
                        consistency = "consistency",
                        link="log",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10))

FE_os_4         <-      nma(os_4_network,
                trt_effects = "fixed",
                        consistency = "consistency",
                        link="log",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10))

###     Random-effects NMA ###

RE_os_1         <-      nma(os_1_network,
                trt_effects = "random",
                        consistency = "consistency",
                        link="log",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                        adapt_delta = 0.99,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10),
```

```
                    prior_het = half_normal(scale = 5))

RE_os_2     <-      nma(os_2_network,
                trt_effects = "random",
                    consistency = "consistency",
                    link="log",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    adapt_delta = 0.99,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10),
                    prior_het = half_normal(scale = 5))

RE_os_3     <-      nma(os_3_network,
                trt_effects = "random",
                    consistency = "consistency",
                    link="log",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    adapt_delta = 0.99,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10),
                    prior_het = half_normal(scale = 5))

RE_os_4     <-      nma(os_4_network,
                trt_effects = "random",
                    consistency = "consistency",
                    link="log",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    adapt_delta = 0.99,
                prior_intercept = normal(scale = 10),
                prior_trt = normal(scale = 10),
                    prior_het = half_normal(scale = 5))

### Generate all pairwise contrasts between treatments    ###

###     All-risk ###

FE_all_os1 <- relative_effects(FE_os_1, all_contrasts = TRUE)
RE_all_os1 <- relative_effects(RE_os_1, all_contrasts = TRUE)

###     Intermediate poor IMDC      ###

FE_all_os2 <- relative_effects(FE_os_2, all_contrasts = TRUE)
RE_all_os2 <- relative_effects(RE_os_2, all_contrasts = TRUE)

###     NMA favourable IMDC         ###

FE_all_os3 <- relative_effects(FE_os_3, all_contrasts = TRUE)
RE_all_os3 <- relative_effects(RE_os_3, all_contrasts = TRUE)
```

```
###     OS NMA favourable MSKCC ###

FE_all_os4 <- relative_effects(FE_os_4, all_contrasts = TRUE)
RE_all_os4 <- relative_effects(RE_os_4, all_contrasts = TRUE)

###     Inconsistency models - all-risk only   ###

FE_pfs_1_inc  <-      nma(pfs_1_network,
                          trt_effects = "fixed",
                          consistency = "ume",
                          link = "log",
                          chains = 3,
                          iter = 2e5,
                          warmup = 1e5,
                          control = list(max_treedepth = 15),
                          prior_intercept = normal(scale = 10),
                          prior_trt = normal(scale = 10))

FE_pfs_1_sens_inc    <-      nma(pfs_sens1_network,
                          trt_effects = "fixed",
                          consistency = "ume",
                          link = "log",
                          chains = 3,
                          iter = 2e5,
                          warmup = 1e5,
                          control = list(max_treedepth = 15),
                          prior_intercept = normal(scale = 10),
                          prior_trt = normal(scale = 10))

###     Model fit statistics      ####

dic_FE_pfs1 <- dic(FE_pfs_1)
dic_FE_pfs1_inc <- dic(FE_pfs_1_inc)

dic_FE_pfs_sens1 <- dic(FE_pfs_sens1)
dic_FE_pfs_sens1_inc <- dic(FE_pfs_1_sens_inc)
Fixed and random effects NMAs of arm-based binary data (ORR)

###     Install and run multinma to conduct Bayesian network meta-analysis        ###

if (!require("multinma")) install.package("multinma")

library("multinma")
options(mc.cores = parallel::detectCores())

###     Load datasets          ###

orr_1 <- read.csv("ORR all-risk.csv")
orr_2 <- read.csv("ORR intermediate poor IMDC.csv")

###     Setting up networks and network plots        ###

orr_1_network <-      set_agd_arm(orr_1,
                  study = study.c,
                  trt = trtc,
```

```
                r=r1,
                n=n1,
                trt_ref = "Sunitinib")
plot(orr_1_network, weight_edges = TRUE, weight_nodes = TRUE)

orr_2_network <-    set_agd_arm(orr_2,
                study = study.c,
                trt = trtc,
                r=r1,
                n=n1,
                trt_ref = "Sunitinib")
plot(orr_2_network, weight_edges = TRUE, weight_nodes = TRUE)

###   Fixed effects NMA             ###

FE_orr_1      <-    nma(orr_1_network,
              trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
              prior_intercept = normal(scale = 10),
              prior_trt = normal(scale = 10))

FE_orr_2      <-    nma(orr_2_network,
              trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
              prior_intercept = normal(scale = 10),
              prior_trt = normal(scale = 10))

###   Random effects NMA ###

RE_orr_1      <-    nma(orr_1_network,
              trt_effects = "random",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    adapt_delta = 0.99,
              prior_intercept = normal(scale = 10),
              prior_trt = normal(scale = 10),
                    prior_het = half_normal(scale = 5))

RE_orr_2      <-    nma(orr_2_network,
              trt_effects = "random",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
```

```
                warmup = 1e5,
                adapt_delta = 0.99,
          prior_intercept = normal(scale = 10),
          prior_trt = normal(scale = 10),
                prior_het = half_normal(scale = 5))

### Generate all pairwise contrasts between treatments     ###

###     All-risk ###

FE_all_orr1 <- relative_effects(FE_orr_1, all_contrasts = TRUE)
RE_all_orr1 <- relative_effects(RE_orr_1, all_contrasts = TRUE)

##      Intermediate poor IMDC        ###

FE_all_orr2 <- relative_effects(FE_orr_2, all_contrasts = TRUE)
RE_all_orr2 <- relative_effects(RE_orr_2, all_contrasts = TRUE)
```

9.14 Appendix 14: Additional results tables

Table 108 Results from AG PFS random effects NMAs by risk group (FDA censoring rule)

Treatment	Comparator	Random effects HR (95% CrI)[a]
Intermediate/poor risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.40 (0 to 773)
Lenvatinib + pembrolizumab	Cabozantinib	0.76 (0 to 25591)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.53 (0 to 21807)
Cabozantinib	Sunitinib	0.53 (0 to 953)
Nivolumab + ipilimumab	Sunitinib	0.76 (0 to 1339)
Nivolumab + ipilimumab	Cabozantinib	1.46 (0 to 48050)
IMDC/MSKCC favourable risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.45 (0 to 1249)
Lenvatinib + pembrolizumab	Pazopanib	0.44 (0 to 34201)
Pazopanib	Sunitinib	1.02 (0 to 2592)
All-risk population		
Lenvatinib + pembrolizumab	Sunitinib	0.39 (0.04 to 3.49)
Lenvatinib + pembrolizumab	Pazopanib	0.30 (0.02 to 4.85)
Lenvatinib + pembrolizumab	Tivozanib	0.45 (0.02 to 12.43)
Lenvatinib + pembrolizumab	Sorafenib	0.34 (0.02 to 4.57)
Pazopanib	Sunitinib	1.31 (0.24 to 7.17)
Tivozanib	Sunitinib	0.88 (0.07 to 11.59)
Sorafenib	Sunitinib	1.15 (0.29 to 4.71)
Pazopanib	Tivozanib	1.49 (0.09 to 23.1)
Pazopanib	Sorafenib	1.14 (0.20 to 6.05)
Tivozanib	Sorafenib	0.76 (0.09 to 7.03)

[a] HR<1 favours the treatment over the comparator

AG=Assessment Group; CrI=credible interval; FDA=food and drug administration; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKKC=Memorial Sloan–Kettering Cancer Center; NMA=network meta-analysis; PFS=progression-free survival

Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 100) of this AG report

Table 109 Results from AG OS random effects NMAs by risk group

Treatment	Comparator	Random effects HR (95% CrI)[a]
Intermediate/poor risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.66 (0 to 1200)
Lenvatinib + pembrolizumab	Cabozantinib	0.80 (0 to 32209)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.95 (0 to 36680)
Cabozantinib	Sunitinib	0.83 (0 to 1525)
Nivolumab + ipilimumab	Sunitinib	0.69 (0 to 1274)
Nivolumab + ipilimumab	Cabozantinib	0.84 (0 to 30031)
IMDC/MSKCC favourable risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	1.19 (0 to 2981)
Lenvatinib + pembrolizumab	Pazopanib	1.30 (0 to 74608)
Pazopanib	Sunitinib	0.92 (0 to 2465)
All-risk population		
Lenvatinib + pembrolizumab	Sunitinib	0.74 (0 to 1959)
Lenvatinib + pembrolizumab	Pazopanib	0.81 (0 to 57526)
Pazopanib	Sunitinib	0.91 (0 to 2345)

[a]HR<1 favours the treatment over the comparator
AG=Assessment Group; CrI=credible interval; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKKC=Memorial Sloan–Kettering Cancer Center; NMA=network meta-analysis; OS=overall survival
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 101) of this AG report

Table 110 Results from AG ORR NMAs by risk group (fixed and random effects)

Treatment	Comparator	OR (95% CrI)[a]	
		Fixed effects	Random effects
Intermediate/poor risk subgroup			
Lenvatinib + pembrolizumab	Sunitinib	6.55 (4.39 to 9.87)	5.37 (0 to 7259)
Lenvatinib + pembrolizumab	Cabozantinib	2.46 (0.84 to 6.82)	2.25 (0 to 72403)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	3.19 (1.95 to 5.26)	2.83 (0 to 86682)
Cabozantinib	Sunitinib	2.66 (1.05 to 7.32)	2.36 (0 to 3533)
Nivolumab + ipilimumab	Sunitinib	2.03 (1.52 to 2.75)	1.90 (0 to 3072)
Nivolumab + ipilimumab	Cabozantinib	0.76 (0.27 to 2.03)	0.80 (0 to 30638)
All-risk population			
Lenvatinib + pembrolizumab	Sunitinib	4.35 (3.16 to 5.99)	3.56 (0 to 7044)
Lenvatinib + pembrolizumab	Pazopanib	3.22 (2.14 to 4.85)	2.77 (0 to 130614)
Pazopanib	Sunitinib	1.35 (1.03 to 1.75)	1.30 (0 to 3072)

[a]OR>1 favours the treatment over the comparator
AG=Assessment Group; CrI=credible interval; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 102) of this AG report

Table 111 Results from AG NMAs for MSKCC favourable risk subgroup: PFS and OS, fixed and random effects

Treatment	Comparator	HR (95% CrI)[a]	
		Fixed effects	Random effects
PFS by FDA censoring rule			
Lenvatinib + pembrolizumab	Sunitinib	0.36 (0.23 to 0.57)	0.41 (0 to 1261)
Lenvatinib + pembrolizumab	Pazopanib	0.36 (0.18 to 0.68)	0.40 (0 to 30946)
Pazopanib	Sunitinib	1.01 (0.63 to 1.62)	1.01 (0 to 2592)
PFS by EMA censoring rule			
Lenvatinib + pembrolizumab	Sunitinib	0.36 (0.24 to 0.54)	0.41 (0 to 1176)
Lenvatinib + pembrolizumab	Pazopanib	0.36 (0.19 to 0.66)	0.41 (0 to 34544)
Pazopanib	Sunitinib	1.01 (0.63 to 1.62)	1.00 (0 to 2441)
OS			
Lenvatinib + pembrolizumab	Sunitinib	1.00 (0.51 to 1.95)	1.03 (0 to 2490)
Lenvatinib + pembrolizumab	Pazopanib	1.14 (0.54 to 2.41)	1.16 (0 to 72403)
Pazopanib	Sunitinib	0.88 (0.63 to 1.23)	0.88 (0 to 2345)

[a] HR<1 favours the treatment over the comparator
AG=Assessment Group; CrI=credible interval; EMA=European Medicines Agency, FDA=Food and Drug Administration; HR=hazard ratio; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 100) and Table 101) and of this AG report

Table 112 Results from AG PFS fixed and random effects NMAs by risk group (EMA censoring rule)

Treatment	Comparator	HR (95% CrI)[a]	
		Fixed effects	Random effects
Intermediate/poor risk subgroup			
Lenvatinib + pembrolizumab	Sunitinib	0.45 (0.36 to 0.56)	0.49 (0 to 953)
Lenvatinib + pembrolizumab	Cabozantinib	0.93 (0.57 to 1.52)	0.92 (0 to 33190)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.60 (0.45 to 0.80)	0.63 (0 to 24343)
Cabozantinib	Sunitinib	0.48 (0.31 to 0.74)	0.53 (0 to 973)
Nivolumab + ipilimumab	Sunitinib	0.75 (0.62 to 0.90)	0.77 (0 to 1313)
Nivolumab + ipilimumab	Cabozantinib	1.57 (0.97 to 2.51)	1.46 (0 to 45707)
IMDC/MSKCC favourable risk subgroup			
Lenvatinib + pembrolizumab	Sunitinib	0.42 (0.28 to 0.63)	0.47 (0 to 1495)
Lenvatinib + pembrolizumab	Pazopanib	0.41 (0.22 to 0.78)	0.46 (0 to 36316)
Pazopanib	Sunitinib	1.02 (0.62 to 1.68)	1.03 (0 to 2592)
All-risk population			
Lenvatinib + pembrolizumab	Sunitinib	0.41 (0.33 to 0.51)	0.42 (0.04 to 4.48)
Lenvatinib + pembrolizumab	Pazopanib	0.35 (0.27 to 0.46)	0.32 (0.02 to 5.99)
Lenvatinib + pembrolizumab	Tivozanib	0.53 (0.36 to 0.78)	0.48 (0.01 to 18.17)
Lenvatinib + pembrolizumab	Sorafenib	0.40 (0.30 to 0.53)	0.36 (0.02 to 6.05)
Pazopanib	Sunitinib	1.16 (1.01 to 1.34)	1.31 (0.23 to 8.00)
Tivozanib	Sunitinib	0.78 (0.57 to 1.07)	0.88 (0.06 to 13.2)
Sorafenib	Sunitinib	1.03 (0.86 to 1.22)	1.15 (0.26 to 5.1)
Pazopanib	Tivozanib	1.49 (1.07 to 2.05)	1.51 (0.08 to 27.94)
Pazopanib	Sorafenib	1.13 (0.94 to 1.35)	1.15 (0.19 to 6.96)
Tivozanib	Sorafenib	0.76 (0.58 to 1.00)	0.76 (0.08 to 7.61)

[a] HR<1 favours the treatment over the comparator

AG=Assessment Group; CrI=credible interval; EMA=European Medicines Agency; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC=Memorial Sloan–Kettering Cancer Center risk score; NMA=network meta-analysis; PFS=progression-free survival

Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 100) of this AG report

Table 113 Results from AG Grade ≥3 AE[a] NMAs by risk subgroup

Treatment	Comparator	OR (95% CrI)[b]	
		Fixed effects	Random effects
IMDC intermediate/poor risk subgroup[c]			
Lenvatinib + pembrolizumab	Sunitinib	2.03 (1.30 to 3.19)	1.88 (0 to 4188)
Lenvatinib + pembrolizumab	Cabozantinib	1.80 (0.79 to 4.10)	1.68 (0 to 100710)
Cabozantinib	Sunitinib	1.13 (0.57 to 2.25)	1.12 (0 to 2670)
All-risk population			
Lenvatinib + pembrolizumab	Sunitinib	1.84 (1.28 to 2.66)	1.70 (0 to 4230)
Lenvatinib + pembrolizumab	Cabozantinib	1.86 (1.17 to 2.94)	1.70 (0 to 115844)
Cabozantinib	Sunitinib	0.99 (0.76 to 1.31)	0.99 (0 to 2566)

[a] Treatment emergent AE data extracted from the CLEAR trial and COMPARZ trial,[100] all-cause AEs extracted from the CABOSUN trial[96]
[b] HR<1 favours the treatment over the comparator
[c] No data available for favourable risk subgroup
AE=adverse event; AG=Assessment Group; CrI=credible interval; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; OR=odds ratio
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 103) of this AG report

9.15 Appendix 15: AG assessment of inconsistency in the NMAs

For PFS in the all-risk population, the only NMA with a closed loop present within the network, the AG assessed inconsistency by applying an unrelated mean effects model[114] and by comparing model fit statistics and results of this inconsistency model with the results of the AG PFS NMAs presented in Table 30 and Appendix 14 (Section 9.14; Table 112) which assume consistency.

Inconsistency models such as the unrelated mean effects model[114] are more complex than NMA models which assume consistency. Therefore, due to the small number of trials included in the network and instability of random-effects NMA results (Appendix 14; Section 9.14), fixed-effect inconsistency models only were applied.

Model fit statistics of fixed-effect AG PFS NMA models assuming consistency and inconsistency are presented in Table 114.

Table 114 Model fit statistics for AG fixed-effects PFS NMA consistency and inconsistency models (all-risk population)

Model	Posterior mean residual deviance	Number of data points	pD	DIC
Consistency model using FDA censoring rule	13.4	6	4	17.4
Inconsistency model* using FDA censoring rule	5.7	6	5	10.7
Consistency model using EMA censoring rule	13.4	6	4	17.4
Inconsistency model[a] using EMA censoring rule	5.7	6	5	10.7

* Unrelated mean effects model[114] applied to assess inconsistency
AG=Assessment Group; DIC=deviance information criterion; EMA=European Medicines Agency; FDA=food and drug administration; NMA=network meta-analysis; pD=effective number of model parameters; PFS=progression-free survival
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 100) of this AG report

Model fit statistics demonstrate that inconsistency models seem to provide a better fit (lower posterior mean residual deviance and DIC statistic) but a higher level of complexity (in terms of effective number of model parameters). However, despite the better model fit of the inconsistency models, AG fixed-effects PFS NMA results from the unrelated mean effects model were very similar (Table 115) to the results of the AG fixed-effects PFS NMA results assuming consistency (Table 30 and Appendix 14 [Section 9.14; Table 112]) and conclusions are unchanged.

Therefore, any inconsistency present between direct and indirect evidence for PFS in the all-risk population does not seem to have had an important impact on the PFS NMA results.

Table 115 Results from AG fixed effects PFS NMAs using an inconsistency model (all-risk population)

Treatment	Comparator	Fixed effects HR (95% CrI)[a]	
		FDA censoring rule	EMA censoring rule
Lenvatinib + pembrolizumab	Sunitinib	0.39 (0.32 to 0.48)	0.41 (0.33 to 0.51)
Lenvatinib + pembrolizumab	Pazopanib	0.34 (0.26 to 0.43)	0.35 (0.27 to 0.46)
Lenvatinib + pembrolizumab	Tivozanib	0.50 (0.34 to 0.73)	0.53 (0.36 to 0.78)
Lenvatinib + pembrolizumab	Sorafenib	0.38 (0.29 to 0.50)	0.40 (0.30 to 0.53)
Pazopanib	Sunitinib	1.05 (0.90 to 1.22)	1.05 (0.90 to 1.22)
Tivozanib	Sunitinib	0.78 (0.57 to 1.07)	0.78 (0.57 to 1.07)
Sorafenib	Sunitinib	1.25 (1.01 to 1.55)	1.25 (1.00 to 1.55)
Pazopanib	Tivozanib	1.49 (1.07 to 2.05)	1.49 (1.07 to 2.05)
Pazopanib	Sorafenib	1.45 (1.14 to 1.86)	1.45 (1.14 to 1.86)
Tivozanib	Sorafenib	0.76 (0.58 to 1.00)	0.76 (0.58 to 1.00)

[a]HR<1 favours the treatment over the comparator
AG=Assessment Group; CrI=credible interval; EMA=European Medicines Agency; FDA=food and drug administration; HR=hazard ratio; NMA=network meta-analysis; progression-free survival
Source: AG analysis using statistical code Appendix 13 (Section 9.13) applied to the data in Appendix 9 (Section 9.9, Table 100) of this AG report

Due to the lack of closed loops within the OS and ORR NMAs, and within all NMAs conducted in the intermediate/poor risk and favourable risk subgroups, inconsistency cannot be statistically assessed within these networks. Therefore, the consistency of indirect estimates of OS is unknown.

9.16 Appendix 16: AG quality assessment of included study

Table 116 CHEERS quality assessment checklist for the included study

	Li et al 2021[115]
Title	Yes, p1
Abstract	Yes, p1
Background and objectives	Yes, p2
Target population and subgroup	Yes, p2 (Methods: Analytics Overview)
Setting and location	Yes, p2 (Under Introduction)
Study perspective	Yes, p2 (Under Introduction)
Comparators	Yes, p2 (Method: Analytic Overview)
Time horizon	Yes, p2 (Method: Analytic Overview)
Discount rate	Yes, p2 (Method: Analytic Overview)
Choice of health outcomes	Yes, p3 (Transition probability and Costs and Utilities)
Measurement of effectiveness	Yes, p2 & p3 (Transition Probability)
Measurement and valuation of preference-based outcomes	Yes, p3 (Costs and Utilities)
Estimating resources and costs	Individual resource use was reported for drug costs in the supplementary material but not for AEs
Currency, price date, and conversion	Costs were adjusted to 2021 US$, p2
Choice of model	Yes, p2
Assumptions	Yes, p2 & p3
Analytical methods	Yes, p2 & p3
Study parameters	Yes, p4 & p5
Incremental costs and outcomes	Yes, p6
Characterising uncertainty	Yes, one-way sensitivity, probabilistic sensitivity and scenario analyses were undertaken (p7 & supplementary material)
Characterising heterogeneity	NA
Study findings, limitations, generalisability, and current knowledge	Yes, p7 & p8
Source of funding	Yes, p8
Conflicts of interest	Yes, p10

AD=adverse events; NA=not applicable; NR=not reported; p=page
Source: CHEERS checklist[116] and includes AG comment

9.17 Appendix 17: Assessment of cost effectiveness (all-risk population)

Unless described in this section, all parameters used in the all-risk population model are the same as were used in the intermediate/poor risk and favourable risk subgroup models (see main body of the report).

9.17.1 Intervention and comparator treatments

The intervention is lenvatinib plus pembrolizumab. The comparators listed in the final scope[27] issued by NICE are sunitinib, pazopanib and tivozanib.

9.17.2 Populating the MSD/AG model: progression-free survival

Eisai and MSD fitted distributions to CLEAR trial BIRC PFS data (FDA censoring rules). The PFS distributions chosen by Eisai, MSD and the AG for the all-risk population are shown in

Table 117. The PFS distributions chosen by the AG for lenvatinib plus pembrolizumab and sunitinib/pazopanib/tivozanib are shown graphically for the all-risk population in Figure 35.

Table 117 Modelling progression-free survival (all-risk population)

Treatment	Eisai	MSD	AG
Lenvatinib plus pembrolizumab	Log-normal	Exponential	Gamma
Sunitinib	Log-normal	Gamma	Log-normal
Pazopanib/tivozanib	Equal to sunitinib	Equal to sunitinib	Equal to sunitinib

AG=Assessment Group
Source: Eisai CS,[15] Section 5.3.2; MSD CS,[51] Section B 3.3

Figure 35 base case PFS distributions, all-risk population

Source: AG model

Lenvatinib plus pembrolizumab

All the MSD AIC statistics for the distributions fitted to CLEAR trial lenvatinib plus pembrolizumab data lie within five AIC points of each other (Table 118). Eisai chose to model lenvatinib and pembrolizumab PFS using a log-normal distribution and MSD chose to model lenvatinib and pembrolizumab PFS using an exponential distribution. The AG considered that the gamma distribution, which has the lowest AIC statistic (highest ranking), and on visual inspection, seemed to offer long-term projections that were clinically plausible, was an appropriate option in the base case (Figure 36).

Table 118 MSD CLEAR trial PFS data goodness-of-fit statistics, all-risk population, IA3 data cut-off

Distribution	Lenvatinib plus pembrolizumab	
	AIC [rank]	BIC [rank]
Exponential	[redacted] [4]	[redacted] [1]
Gamma	[redacted] [1]	[redacted] [2]
Generalised gamma	[redacted] [5]	[redacted] [7]
Gompertz	[redacted] [6]	[redacted] [5]
Log-logistic	[redacted] [3]	[redacted] [4]
Log-normal	[redacted] [7]	[redacted] [6]
Weibull	[redacted] [2]	[redacted] [3]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion
Source: Adapted from MSD model

Figure 36 AG PFS distributions for lenvatinib plus pembrolizumab, all-risk population

Sunitinib (pazopanib and tivozanib)

Eisai chose to model sunitinib (pazopanib and tivozanib) PFS using a log-normal distribution. MSD chose to model sunitinib (pazopanib and tivozanib) PFS using a gamma distribution. Although the gamma distribution only ranked 4/7 using AIC statistics (Table 119), MSD considered the gamma distribution generated the most plausible long-term survival estimates.

The AG considered the distribution with the lowest AIC statistic (generalised gamma distribution) generated PFS estimates that were too optimistic ([redacted]% of patients are still alive and progression-free at 40 years). The AG considered that the log-normal distribution (ranked 2/7 using AIC statistics) produced long-term PFS projections that were clinically plausible and therefore considered that this was an appropriate option to use in the base case.

Table 119 MSD CLEAR trial PFS data goodness-of-fit statistics, all-risk population, IA3 data cut

Distribution	Sunitinib [rank]	
	AIC	BIC
Exponential	[redacted] [6]	[redacted] [5]
Gamma	[redacted] [4]	[redacted] [4]
Generalised gamma	[redacted] [1]	[redacted] [1]
Gompertz	[redacted] [7]	[redacted] [7]
Log-logistic	[redacted] [3]	[redacted] [3]
Log-normal	[redacted] [2]	[redacted] [2]
Weibull	[redacted] [5]	[redacted] [6]

AG=Assessment Group; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion
Source: Adapted from MSD model

Figure 37 AG PFS distributions for sunitinib (pazopanib and tivozanib, all-risk population

9.17.3 AG scenario analyses: all-risk population (PFS)

The AG explored the effect on cost effectiveness results of using the distributions that were within five points of the AIC statistic for the chosen distribution to model PFS for lenvatinib plus pembrolizumab. The distributions for sunitinib, pazopanib and tivozanib were unchanged.

The AG explored the effect on cost effectiveness results of using the MSD preferred gamma distribution to model PFS for sunitinib, pazopanib and tivozanib. The distribution for lenvatinib plus pembrolizumab was unchanged.

9.17.4 Populating the MSD/AG model: overall survival

The distributions chosen by Eisai, MSD and the AG for OS in the all-risk population are shown in Table 120.

Table 120 Modelling OS (all-risk population)

Treatment	Eisai	MSD	AG
Lenvatinib plus pembrolizumab	Exponential	Exponential	K-M+exponential
Sunitinib	Exponential	Gamma	K-M+exponential
Pazopanib/tivozanib	Equal to sunitinib	Equal to sunitinib	Equal to sunitinib

AG=Assessment Group; K-M=Kaplan-Meier
Source: Eisai CS,[15] Section 5.3.1; MSD CS,[51] Section B 3.3

Figure 38 AG base case OS distributions, all-risk population

Lenvatinib plus pembrolizumab

Both companies chose the exponential distribution (ranked 6/7 using AIC and BIC statistics) to estimate OS for patients receiving lenvatinib plus pembrolizumab. This distribution was not within five points of the distribution with the lowest AIC statistic. The companies' choice was based on good visual fit to the CLEAR trial OS K-M data and because the higher ranking distributions appeared to generate implausible long-term OS estimates. Although the AG was satisfied that the companies followed DSU guidance,[130] the AG did not consider that any of the distributions considered by Eisai or MSD provided a good visual fit to the available CLEAR trial OS K-M data available.

The AG examined the CLEAR trial OS K-M data received during the NICE MTA clarification process and observed that the lenvatinib plus pembrolizumab OS hazard was constant beyond 80 weeks. The AG therefore considered that the companies' choice of an exponential distribution was appropriate, but that K-M data should be used up to the point that censoring and small numbers of events rendered the data too uncertain (the AG considered that this occurred at 120 weeks). The AG observed that between 80 and 120 weeks the OS hazard was constant. The AG appended the exponential distribution (based on the hazard between 80 and 120 weeks) to the CLEAR trial OS K-M data from 120 weeks onwards.

Table 121 MSD CLEAR trial OS goodness-of-fit statistics, all-risk population, updated OS analysis

Distribution	**Lenvatinib plus pembrolizumab**	
	AIC [rank]	**BIC [rank]**
Exponential	[redacted] [6]	[redacted] [6]
Gamma	[redacted] [4]	[redacted] [3]
Generalised gamma	[redacted] [2]	[redacted] [5]
Gompertz	[redacted] [1]	[redacted] [1]
Log-logistic	[redacted] [5]	[redacted] [4]
Log-normal	[redacted] [7]	[redacted] [7]
Weibull	[redacted] [3]	[redacted] [2]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; OS=overall survival
Source: Adapted from MSD model

Figure 39 AG OS distributions for lenvatinib plus pembrolizumab, all-risk population

Sunitinib (pazopanib and tivozanib)

To model OS for patients treated with sunitinib, Eisai chose the exponential distribution as it did not cross the lenvatinib plus pembrolizumab OS distribution. MSD chose the gamma distribution as they considered distributions with higher ranking AIC statistics (Table 122) generated implausible long-term OS projections. Although the AG was satisfied that the companies followed DSU guidance,[130] the AG did not consider that any of the distributions considered by Eisai or MSD provided a good visual fit to the available CLEAR trial OS K-M data available.

The AG examined the CLEAR trial OS K-M data received during the NICE MTA clarification process and observed that the sunitinib OS hazard was constant beyond 50 weeks. The AG therefore considered that the MSD choice of an exponential distribution was appropriate, but that K-M data should be used up to the point that censoring and small numbers of events rendered the data too uncertain (the AG considered that this occurred at 120 weeks). The AG observed that between 50 and 120 weeks the OS hazard was constant. The AG appended the exponential distribution (based on the hazard between 50 and 120 weeks) to the CLEAR trial OS K-M data from 120 weeks onwards.

Table 122 MSD CLEAR trial OS data goodness-of-fit statistics, all-risk population, updated OS analysis

Distribution	Sunitinib	
	AIC [rank]	BIC [rank]
Exponential	[redacted] [5]	[redacted] [3]
Gamma	[redacted] [6]	[redacted] [6]
Generalised gamma	[redacted] [1]	[redacted] [1]
Gompertz	[redacted] [4]	[redacted] [5]
Log-logistic	[redacted] [3]	[redacted] [4]
Log-normal	[redacted] [2]	[redacted] [2]
Weibull	[redacted] [7]	[redacted] [7]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; OS=overall survival
Source: Adapted from MSD model

Figure 40 OS distributions for sunitinib (pazopanib and tivozantinib), all-risk population

9.17.5 AG scenario analyses: all-risk population (OS)

The AG carried out the following scenario analyses using company base approaches to modelling:

- use the exponential distribution (Eisai and MSD preferred distribution) instead of the AG K-M+exponential distribution to model OS for lenvatinib plus pembrolizumab
- use the exponential distribution (Eisai preferred distribution) instead of the AG K-M+exponential distribution to model OS for sunitinib
- use the gamma distribution (MSD preferred distribution) instead of the AG K-M+exponential distribution to model OS for sunitinib

9.17.6 Populating the model: time to treatment discontinuation

The AG considered that TTD for patients receiving lenvatinib and sunitinib should be modelled by fitting a distribution to CLEAR trial TTD K-M data and, for patients receiving pembrolizumab, the CLEAR trial TTD K-M data should be used directly. The parametric distributions chosen by Eisai, MSD and the AG to model TTD for all treatments are shown in Table 123. The TTD distributions chosen by the AG are shown graphically for the all-risk population in Figure 41.

Table 123 Modelling time to treatment discontinuation (all-risk population)

Treatment	Eisai	MSD	AG
Lenvatinib	Generalised gamma	Generalised gamma	Generalised gamma (Eisai)
Pembrolizumab	Weibull	K-M data (CLEAR trial data are complete)	
Sunitinib	Generalised gamma	Log-logistic	
Pembrolizumab/tivozanib	Equal to sunitinib	Equal to sunitinib	Equal to sunitinib

AG=Assessment Group; K-M=Kaplan-Meier
Source: Eisai CS,[15] Section 5.3.2; MSD CS,[51] Section B 3.3

Figure 41 AG base case TTD distributions, all-risk population

Lenvatinib

Eisai and MSD provided CLEAR trial lenvatinib TTD K-M data during the NICE MTA clarification process (Figure 42). However, the two datasets differed slightly - there was a clear gap between the two datasets by 24 months. The AG concluded that as the safety data from the CLEAR trial suggested a lower level of treatment discontinuation for lenvatinib than for pembrolizumab (25.6% versus 28.7%[67]), the Eisai TTD K-M lenvatinib data were likely to be the most accurate as they followed a trajectory that was consistently above the TTD K-M pembrolizumab data until 24 months, i.e., until the time when the pembrolizumab stopping rule was activated. In contrast, the MSD TTD lenvatinib K-M data crossed the pembrolizumab TTD K-M data at 20 months.

Both companies chose to use generalised gamma distributions to model TTD for patients treated with lenvatinib (in the MSD CS[51] this was the highest ranking distribution using AIC statistics) (Table 124). The AG considered that the Eisai generalised gamma distribution provided a good visual fit to the TTD K-M data and did not cross the pembrolizumab TTD K-M data until 24 months. The AG therefore chose to use the Eisai generalised gamma distribution to model lenvatinib K-M TTD data.

Table 124 MSD CLEAR trial TTD data goodness-of-fit statistics, all-risk population, IA3 data cut

Distribution	**Lenvatinib**	
	AIC [rank]	**BIC [rank]**
Exponential	[redacted] [3]	[redacted] [1]
Gamma	[redacted] [5]	[redacted] [5]
Generalised gamma	[redacted] [1]	[redacted] [4]
Gompertz	[redacted] [2]	[redacted] [2]
Log-logistic	[redacted] [6]	[redacted] [6]
Log-normal	[redacted] [7]	[redacted] [7]
Weibull	[redacted] [4]	[redacted] [3]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; OS=overall survival
Source: MSD model

Figure 42 TTD distributions for lenvatinib, all-risk population

Pembrolizumab

MSD modelled pembrolizumab TTD by directly using the K-M data from the CLEAR trial and applied a 2-year stopping rule in line with the CLEAR trial protocol. Eisai modelled pembrolizumab TTD by fitting a Weibull distribution to the CLEAR trial K-M data; it is clear from the Eisai model outputs that a stopping rule for pembrolizumab at 2 years had been applied. The CLEAR trial pembrolizumab TTD K-M data are almost complete ( ) and so the AG used the TTD K-M data directly to estimate the cost of treatment with pembrolizumab for patients in the all-risk population. The AG did not include an enforced stopping rule at 2 years but used the K-M data directly, which means that some patients remained on pembrolizumab for a short period of time beyond 2 years.

Sunitinib

Eisai used the generalised gamma distribution to model sunitinib TTD. The company considered this distribution to have good statistical and visual fit to the tail of the sunitinib TTD K-M data. The AG and MSD used the log-logistic distribution as this has the lowest AIC (Table 125) and was a good visual fit to the sunitinib TTD K-M data.

Table 125 MSD TTD data goodness-of-fit statistics (all-risk population)

Distribution	Sunitinib	
	AIC [rank]	BIC [rank]
Exponential	[redacted] [5]	[redacted] [5]
Gamma	[redacted] [7]	[redacted] [7]
Generalised gamma	[redacted] [2]	[redacted] [3]
Gompertz	[redacted] [4]	[redacted] [4]
Log-logistic	[redacted] [1]	[redacted] [1]
Log-normal	[redacted] [3]	[redacted] [2]
Weibull	[redacted] [6]	[redacted] [6]

Abbreviations: AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion
Source: MSD model

Figure 43 TTD distributions for sunitinib, all-risk population

9.17.7 AG scenario analyses: all-risk population (TTD)

The AG explored the effect on cost effectiveness results of using the distributions that were within five points of the AIC statistic for the distribution used to model TTD for patients treated with lenvatinib. The distributions for sunitinib, pazopanib and tivozanib were unchanged.

The AG explored the effect on cost effectiveness results of using the distributions that were within five points of the AIC statistic for the distribution used to model TTD for patients treated with sunitinib. The distribution for lenvatinib plus pembrolizumab was unchanged.

9.17.8 Utility values

The AG considers that the MSD time to death approach provided the best reflection of the HRQoL of long-term survivors and used this approach in the MSD/AG model (Table 126).

Table 126 MSD time to death utility values (excluding AE disutilities)

Risk subgroup	Time to death (days)					
	360+	270-359	180-269	90-179	30-89	0-29
All-risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: MSD response to additional clarification questions, Table 1

9.17.9 AG scenario analyses (utility values)

The AG has carried out two scenario analyses. One scenario analysis used the Eisai treatment dependent health state utility values and the other used the MSD treatment independent health state utility values (Table 127).

Table 127 Eisai and MSD health state utility values

Company	Health state	Treatment	All-risk population
			Mean
Pre-progression			
Eisai	Progression-free	LEN+PEM	[redacted]
		Sunitinib	[redacted]
		Pazopanib	
		Tivozanib	
MSD	Pre-progression (on-treatment)		[redacted]
	Pre-progression (off-treatment)		[redacted]
Post-progression			
Eisai	Post-progression (all treatments)		[redacted]
MSD	Progressed (on-treatment)		[redacted]
	Progressed (off-treatment)		[redacted]

NA=not applicable
Source: Eisai CS,[15] Table 33 and MSD response to additional clarification questions, Table 2

9.17.10 AG scenario analysis (AEs)

The AG has carried out two scenario analyses: one in which AE costs were set to zero and one in which AE costs were doubled.

9.17.11 AG sensitivity analyses (subsequent treatment costs)

The AG carried out sensitivity analyses that varied the costs of subsequent treatments by +/- 20%.

9.17.12 AG cost effectiveness results

The all-risk population cost effectiveness results are presented here for completeness. The AG cost effectiveness results were estimated using the list prices for the intervention, comparators and subsequent treatments (Table 128 to Table 129). AG cost effectiveness results generated using confidential discounted prices are presented in a confidential appendix. Results from all AG probabilistic, sensitivity and scenario analyses are presented in Table 130 to Table 134.

9.17.13 Deterministic results

Table 128 AG pairwise deterministic base case results, all-risk population: LEM+PEM versus sunitinib, versus pazopanib and versus tivozanib

Drug	Total			Incremental: LEM+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	[redacted]	[redacted]	-	-	-	-
SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,205,044
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,167,492
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,048,514

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; QALYs=quality adjusted life years

Table 129 AG fully incremental analysis, all-risk population (list prices)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
SUNITINIB	[redacted]	[redacted]	-	-	-
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	PAZOPANIB is dominated by SUNITINIB
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	TIVOZANIB is dominated by SUNITINIB
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	£4,205,044

AG=Assessment Group; ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

9.17.14 Probabilistic sensitivity analysis results

Table 130 AG pairwise probabilistic results, all-risk population: LEM+PEM versus sunitinib, versus pazopanib and versus tivozanib (list prices) (mean results from 1,000 PSA iterations)

Drug	Total			Incremental: LEM+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	[redacted]	[redacted]	-	-	-	-
SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,198,700
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,156,477
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,041,152

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life year

Table 131 AG fully incremental analysis, all-risk population (list prices) (mean results from 1,000 PSA iterations)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
SUNITINIB	[redacted]	[redacted]	-	-	-
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	PAZOPANIB is dominated by SUNITINIB
TIVOZANIB	[redacted]	[redacted]	[redacted]	[redacted]	TIVOZANIB is dominated by SUNITINIB
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	£4,198,700

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; PSA=probabilistic sensitivity analysis; QALYs=quality adjusted life year

Figure 44 AG probabilistic cost effectiveness plane: lenvatinib plus pembrolizumab, sunitinib, pazopanib and tivozanib

Figure 45 Cost effectiveness acceptability curve: lenvatinib plus pembrolizumab, nivolumab plus ipilimumab and cabozantinib

9.17.15 AG One-way deterministic sensitivity analysis results

Figure 46 AG tornado diagram: lenvatinib plus pembrolizumab versus sunitinib

AE=adverse event; AG=Assessment Group; CT=computed tomography; INMB=incremental net monetary benefit; IV=intravenous; PD=progressed disease; PF=progression free; RDI=relative dose intensity

Figure 47 AG tornado diagram: lenvatinib plus pembrolizumab versus pazopanib

AE=adverse event; AG=Assessment Group; CT=computed tomography; INMB=incremental net monetary benefit; IV=intravenous; PD=progressed disease; PF=progression free; RDI=relative dose intensity

Figure 48 AG tornado diagram: lenvatinib plus pembrolizumab versus tivozanib

AE=adverse event; AG=Assessment Group; CT=computed tomography; INMB=incremental net monetary benefit; IV=intravenous; PD=progressed disease; PF=progression free; RDI=relative dose intensity

9.17.16 AG deterministic scenario analysis results (all-risk population)

Table 132 AG scenario analyses: lenvatinib plus pembrolizumab versus sunitinib (list prices)

AG scenarios ***All-risk population***	**Lenvatinib plus pembrolizumab**		**Sunitinib**		**Incremental**		***ICER*** **£/QALY**
	Cost	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,205,044
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,498,809
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
LEN+PEM PFS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,197,889
LEN+PEM PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,197,048
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,211,511
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,169,615
MSD SUNITINIB PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,191,672
LEN+PEM OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£263,613
Eisai SUNITINIB OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
MSD SUNITINIB OS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241,564
Eisai LEN+PEM TTD (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,356,024
Eisai LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,281,938
Eisai LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,381,303
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,157,860
Eisai SUNITINIB TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,364,812
Eisai SUNITINIB TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,050,501
Eisai SUNITINIB TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,256,635
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,871,468
Eisai health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£859,692
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,203,370
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,206,717
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,128,236
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,281,851

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 133 AG scenario analyses: lenvatinib plus pembrolizumab versus pazopanib (list prices)

AG scenarios ***All-risk population***	**Lenvatinib plus pembrolizumab**		**Pazopanib**		**Incremental**		***ICER*** **£/QALY**
	Cost	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,167,492
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,487,254
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
LEN+PEM PFS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,160,337
LEN+PEM PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,159,496
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,173,960
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,132,063
MSD SUNITINIB PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,158,249
LEN+PEM OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£261,289
Eisai SUNITINIB OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
MSD SUNITINIB OS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£239,468
Eisai LEN+PEM TTD (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,318,472
Eisai LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,244,386
Eisai LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,343,751
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,120,308
Eisai SUNITINIB TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,336,576
Eisai SUNITINIB TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,004,184
Eisai SUNITINIB TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,221,966
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,854,755
Eisai health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£852,015
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,191,262
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,143,721
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,090,684
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,244,299

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 134 AG scenario analyses: lenvatinib plus pembrolizumab versus tivozanib (list prices)

AG scenarios ***All-risk population***	**Lenvatinib plus pembrolizumab**		**Tivozanib**		**Incremental**		***ICER*** **£/QALY**
	Cost	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYs**	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,048,514
Discount rate 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,041,860
Discount rate 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
LEN+PEM PFS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,630,398
LEN+PEM PFS (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,604,639
LEN+PEM PFS (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,003,596
LEN+PEM PFS (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,168,137
MSD SUNITINIB PFS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,742,343
LEN+PEM OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£253,739
Eisai SUNITINIB OS (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
MSD SUNITINIB OS (gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£233,603
Eisai LEN+PEM TTD (exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,839,917
Eisai LEN+PEM TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,821,429
Eisai LEN+PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,845,753
MSD LEN+PEM TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,788,521
Eisai SUNITINIB TTD (generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,711,271
Eisai SUNITINIB TTD (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,904,812
Eisai SUNITINIB TTD (log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,773,649
MSD health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,801,804
Eisai health state utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£827,691
AE costs doubled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,058,317
AE costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,038,712
Subsequent treatment costs increased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,971,707
Subsequent treatment costs decreased by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,125,322

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; TTD=time to treatment discontinuation

9.18 Appendix 18: AG table of scenario analyses

Table 135 AG scenario analyses

Scenario analysis	Intermediate/poor risk	Favourable risk	All-risk population
Discounting	6%	6%	6%
	0%	0%	0%
PFS	**LEN+PEM distributions within 5 AIC points**	**LEN+PEM distributions within 5 AIC points**	**LEN+PEM distributions within 5 AIC points**
	Gamma	Exponential	Exponential
	Generalised gamma	Gamma	Generalised gamma
	Gompertz	Gompertz	Gompertz
	Log-logistic	Log-logistic	Log-logistic
	Log-normal	Log-normal	MSD gamma distribution for SUN
	Weibull	Weibull	-
	CABO MSD FP PFS NMA HR	**SUN distributions within 5 AIC points**	**Eisai/MSD exponential distribution for LEN+PEM**
	-	Gamma	Eisai exponential distribution for SUN
	-	Generalised gamma	MSD gamma distribution for SUN
	-	Log-logistic	-
	-	Weibull	-
OS	Eisai/MSD exponential distribution for LEN+PEM	AG OS NMA HR for SUN	LEN+PEM distributions within 5 AIC points (exponential)
	Eisai CABO OS	SUN OS=LEN+PEM OS	Eisai SUN OS exponential
	MSD CABO FP OS	-	MSD SUN OS gamma
	CABO OS=LEN+PEM OS	-	-
	NIV+IP OS=LEN+PEM OS	-	-
TTD	**LEN+PEM distributions within 5 AIC points**	**LEN+PEM distributions within 5 AIC points**	**LEN+PEM distributions within 5 AIC points**
	Exponential	Generalised gamma	Eisai exponential
	Gompertz	Gamma	Eisai gompertz
	Weibull	Gompertz	Eisai Weibull
	MSD generalised gamma	Log-logistic	MSD generalised gamma
	Eisai CABO TTD within 5 AIC points	Weibull	Eisai SUN generalised gamma
	Weibull	**SUN distributions within 5 AIC points**	Eisai SUN generalised gamma
	Log-normal	Gamma	Eisai SUN gompertz
	Exponential	Generalised gamma	Eisai SUN log-normal
	Generalised gamma	Gompertz	-
	Gompertz	Log-logistic	-
	MSD CABO FP TTD	Log-normal	-
	NIV+IPI=Eisai PEM TTD (Weibull)	Weibull	-

Scenario analysis	Intermediate/poor risk	Favourable risk	All-risk population
Utility values	MSD treatment independent health state utility values	MSD treatment independent health state utility values	MSD treatment independent health state utility values
	Eisai treatment dependent health state utility values	-	Eisai treatment dependent health state utility values
Adverse events	Double AE costs	Double AE costs	Double AE costs
	Set AE costs to zero	Set AE costs to zero	Set AE costs to zero
Subsequent treatments	Increase costs by 20%	Increase costs by 20%	Increase costs by 20%
	Decrease costs by 20%	Decrease costs by 20%	Decrease costs by 20%

AE=adverse events; AG=Assessment Group; AIC=Akaike Information Criterion; FP=fractional polynomial; HR=hazard ratio; OS=overall survival; NMA=network meta-analysis; PFS=progression-free survival; TTD=time to treatment discontinuation

9.19 Appendix 19: AG OWSA and PSA parameters

Table 136 AG intermediate/poor risk: OWSA and PSA parameters

Parameter	Base case value	Lower bound	Upper bound	Distribution	Distribution parameters
Age at model start	61	55.21	67.48	Normal	SE=0.405
Percentage of males	74.61%	0.67	0.82	Normal	α=529 β=180
Patient weight	79.40	71.46	87.34	Normal	SE=0.693
OS HR CABO	1.28*	1.05	1.56	Log-normal	SE=0.128
OS HR, NIV+IPI	1.06*	0.87	1.29	Log-normal	SE=0.106
PFS HR (constant), CABO	1.33*	1.10	1.62	Log-normal	SE=0.133
PFS HR (constant), NIV+IPI	2.08*	1.71	2.53	Log-normal	SE=0.208
RDI - PEM	[redacted]	[redacted]	[redacted]	Beta	[redacted]
RDI - CABO	0.94	0.91	0.97	Beta	α=229.149 β=13.851
Drug costs: admin costs, oral prescription cost	£11.00	8.84	13.16	Normal	SE=1.100
Drug costs: admin costs, IV - simple, first	£221.35	177.97	264.73	Normal	SE=22.135
Drug costs: admin costs, IV - simple, subsequent	£365.91	294.19	437.62	Normal	SE=36.591
Drug costs: admin costs, IV - complex, first	£352.24	283.20	421.28	Normal	SE=35.224
Drug costs: admin costs, oral chemo admin, first	£226.45	182.07	270.83	Normal	SE=22.645
EOL cost: NICE ID1426 (ERG)	8,073.00	6,490.72	9,655.28	Normal	SE=807.300
Subsequent treatment costs – LEN+PEM	[redacted]	[redacted]	[redacted]	Uniform	-
Subsequent treatment costs - CABO	[redacted]	[redacted]	[redacted]	Uniform	-
Subsequent treatment costs – NIV+IPI	[redacted]	[redacted]	[redacted]	Uniform	-
AE costs – LEN+PEM	[redacted]	[redacted]	[redacted]	Uniform	-
AE costs - CABO	[redacted]	[redacted]	[redacted]	Uniform	-
AE Costs – NIV+IPI	[redacted]	[redacted]	[redacted]	Uniform	-
Resource use: health state cost, progression-free (first cycle)	£255.01	£205.03	£305.00	Normal	SE=25.501
Resource use: health state cost, progression-free (subsequent cycles)	£59.89	£48.15	£71.63	Normal	SE=5.989
Resource use: health state cost, disease progression	£59.89	£48.15	£71.63	Normal	SE=5.989
Resource use: frequency - PF first cycle - outpatient consultation	1.00	0.80	1.20	Normal	SE=0.100
Resource use: frequency - PF first cycle - blood test	1.00	0.80	1.20	Normal	SE=0.100
Resource use: frequency - PF subsequent cycle - outpatient consultation	0.25	0.20	0.30	Normal	SE=0.025

Parameter	Base case value	Lower bound	Upper bound	Distribution	Distribution parameters
Resource use: frequency - PF subsequent cycle - CT scan	0.08	0.06	0.10	Normal	SE=0.008
Resource use: frequency - PF subsequent cycle - blood test	0.25	0.20	0.30	Normal	SE=0.025
Resource use: frequency - PD - Outpatient consultation	0.25	0.20	0.30	Normal	SE=0.025
Resource use: frequency - PD - CT scan	0.08	0.06	0.10	Normal	SE=0.008
Resource use: frequency - PD - blood test	0.25	0.20	0.30	Normal	SE=0.025
Time to death utilities**	See description in text				

AE=adverse event; AG=Assessment Group; CABO=cabozantinib; CT=computed tomography; EOL=end of life; ERG=Evidence Review Group; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; LEN+PEM=lenvatinib plus pembrolizumab; NIV+IPI=nivolumab plus ipilimumab; OS=overall survival; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity; SE=standard error;
* Reciprocal of AG NMA HR used in the AG/MSD model
** Only varied in PSA

Table 137 AG favourable risk: OWSA and PSA parameters

Parameter	Base case value	Lower bound	Upper bound	Distribution	Distribution parameters
Age at model start	62.18	55.96	68.40	Normal	SE=0.501
Percentage of males	74.71%	0.67	0.82	Normal	α=260 β=88
Patient weight (kg)	84.32	75.89	92.75	Normal	SE=0.993
RDI - PEM	[redacted]	[redacted]	[redacted]	Beta	[redacted]
RDI – SUN	[redacted]	[redacted]	[redacted]	Beta	[redacted]
RDI - PAZO	0.86	0.81	0.90	Beta	α=208.980 β=34.020
RDI - TIVO	0.94	0.91	0.97	Beta	α=228.420 β=14.580
Drug costs: admin costs, oral prescription cost	£11.00	£8.84	£13.16	Normal	SE=1.100
Drug costs: admin costs, IV - simple, first	£221.35	£177.97	£264.73	Normal	SE=22.135
Drug costs: admin costs, IV - simple, subsequent	£365.91	£294.19	£437.62	Normal	SE=36.591
Drug costs: admin costs, IV - complex, first	£352.24	£283.20	£421.28	Normal	SE=35.224
Drug costs: admin costs, oral chemo admin, first	£226.45	£182.07	£270.83	Normal	SE=22.645
EOL cost: NICE ID1426 (ERG)	£8,073.00	£6,490.72	£9,655.28	Normal	SE=807.300
Subsequent treatment costs – LEN+PEM	[redacted]	[redacted]	[redacted]	Uniform	-
Subsequent treatment costs – SUN/PAZO/TIVO	[redacted]	[redacted]	[redacted]	Uniform	-
AE costs – LEN+PEM	[redacted]	[redacted]	[redacted]	Uniform	-
AE costs - SUN	[redacted]	[redacted]	[redacted]	Uniform	-
AE Costs – PAZO	[redacted]	[redacted]	[redacted]	Uniform	-
AE Costs – TIVO	[redacted]	[redacted]	[redacted]	Uniform	
Resource use: health state cost, progression-free (first cycle)	£255.01	£205.03	£305.00	Normal	SE=25.501
Resource use: health state cost, progression-free (subsequent cycles)	£59.89	£48.15	£71.63	Normal	SE=5.989
Resource use: health state cost, disease progression	£59.89	£48.15	£71.63	Normal	SE=5.989
Resource use: frequency - PF first cycle - outpatient consultation	1.00	0.80	1.20	Normal	SE=0.100
Resource use: frequency - PF first cycle - blood test	1.00	0.80	1.20	Normal	SE=0.100
Resource use: frequency - PF subsequent cycle - outpatient consultation	0.25	0.20	0.30	Normal	SE=0.025
Resource use: frequency - PF subsequent cycle - CT scan	0.08	0.06	0.10	Normal	SE=0.008
Resource use: frequency - PF subsequent cycle - blood test	0.25	0.20	0.30	Normal	SE=0.025

Parameter	Base case value	Lower bound	Upper bound	Distribution	Distribution parameters
Resource use: frequency - PD - outpatient consultation	0.25	0.20	0.30	Normal	SE=0.025
Resource use: frequency - PD - CT scan	0.08	0.06	0.10	Normal	SE=0.008
Resource use: frequency - PD - blood test	0.25	0.20	0.30	Normal	SE=0.025
Time to death utilities*	See description in text				

* Only varied in PSA

AE=adverse event; AG=Assessment Group; CT=computed tomography; EOL=end of life; ERG=Evidence Review Group; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; LEN+PEM=lenvatinib plus pembrolizumab; OS=overall survival; PAZO=pazopanib; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity; SE=standard error; SUN=sunitinib; TIVO=tivozanib

Table 138 AG all-risk population: OWSA and PSA parameters

Parameter	Base case value	Lower bound	Upper bound	Distribution	Distribution parameters
Age at model start	62.18	55.96	68.40	Normal	SE=0.501
Percentage of males	74.71%	0.67	0.82	Normal	α=260 β=88
Patient weight (kg)	84.32	75.89	92.75	Normal	SE=0.993
RDI - PEM	[redacted]	[redacted]	[redacted]	Beta	[redacted]
RDI - SUN	[redacted]	[redacted]	[redacted]	Beta	[redacted]
RDI - PAZO	0.86	0.81	0.90	Beta	α=208.980 β=34.020
RDI - TIVO	0.94	0.91	0.97	Beta	α=228.420 β=14.580
Drug costs: admin costs, oral prescription cost	£11.00	£8.84	£13.16	Normal	SE=1.100
Drug costs: admin costs, IV - simple, first	£221.35	£177.97	£264.73	Normal	SE=22.135
Drug costs: admin costs, IV - simple, subsequent	£365.91	£294.19	£437.62	Normal	SE=36.591
Drug costs: admin costs, IV - complex, first	£352.24	£283.20	£421.28	Normal	SE=35.224
Drug costs: admin costs, oral chemo admin, first	£226.45	£182.07	£270.83	Normal	SE=22.645
EOL cost: NICE ID1426 (ERG)	£8,073.00	£6,490.72	£9,655.28	Normal	SE=807.300
Subsequent treatment costs – LEN+PEM	[redacted]	[redacted]	[redacted]	Uniform	-
Subsequent treatment costs – SUN/PAZO/TIVO	[redacted]	[redacted]	[redacted]	Uniform	-
AE costs – LEN+PEM	[redacted]	[redacted]	[redacted]	Uniform	-
AE costs - SUN	[redacted]	[redacted]	[redacted]	Uniform	-
AE Costs – PAZO	[redacted]	[redacted]	[redacted]	Uniform	-
AE Costs – TIVO	[redacted]	[redacted]	[redacted]	Uniform	
Resource use: health state cost, progression-free (first cycle)	£255.01	£205.03	£305.00	Normal	SE=25.501
Resource use: health state cost, progression-free (subsequent cycles)	£59.89	£48.15	£71.63	Normal	SE=5.989
Resource use: health state cost, disease progression	£59.89	£48.15	£71.63	Normal	SE=5.989
Resource use: frequency - PF first cycle - outpatient consultation	1.00	0.80	1.20	Normal	SE=0.100
Resource use: frequency - PF first cycle - blood test	1.00	0.80	1.20	Normal	SE=0.100
Resource use: frequency - PF subsequent cycle - outpatient consultation	0.25	0.20	0.30	Normal	SE=0.025

Parameter	Base case value	Lower bound	Upper bound	Distribution	Distribution parameters
Resource use: frequency - PF subsequent cycle - CT scan	0.08	0.06	0.10	Normal	SE=0.008
Resource use: frequency - PF subsequent cycle - blood test	0.25	0.20	0.30	Normal	SE=0.025
Resource use: frequency - PD - outpatient consultation	0.25	0.20	0.30	Normal	SE=0.025
Resource use: frequency - PD - CT scan	0.08	0.06	0.10	Normal	SE=0.008
Resource use: frequency - PD - blood test	0.25	0.20	0.30	Normal	SE=0.025
Time to death utilities*	See description in text				

AE=adverse event; AG=Assessment Group; CT=computed tomography; EOL=end of life; ERG=Evidence Review Group; HR=hazard ratio; INMB=incremental net monetary benefit; IV=intravenous; LEN+PEM=lenvatinib plus pembrolizumab; OS=overall survival; PAZO=pazopanib; PD=progressed disease; PF=progression free; PFS=progression-free survival; RDI=relative dose intensity; SE=standard error; SUN=sunitinib; TIVO=tivozanib
* Only varied in PSA