NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

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

Committee papers

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MULTIPLE TECHNOLOGY APPRAISAL

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

Contents:

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

MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 134985

Completed 23 March 2022

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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
Sarah Nevitt	Reviewed statistical clinical effectiveness evidence, including study selection, data extraction, synthesis and interpretation. Carried out indirect network analyses
James Mahon	Development of the economic model
Sophie Beale	Critique of clinical and economic evidence
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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

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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.

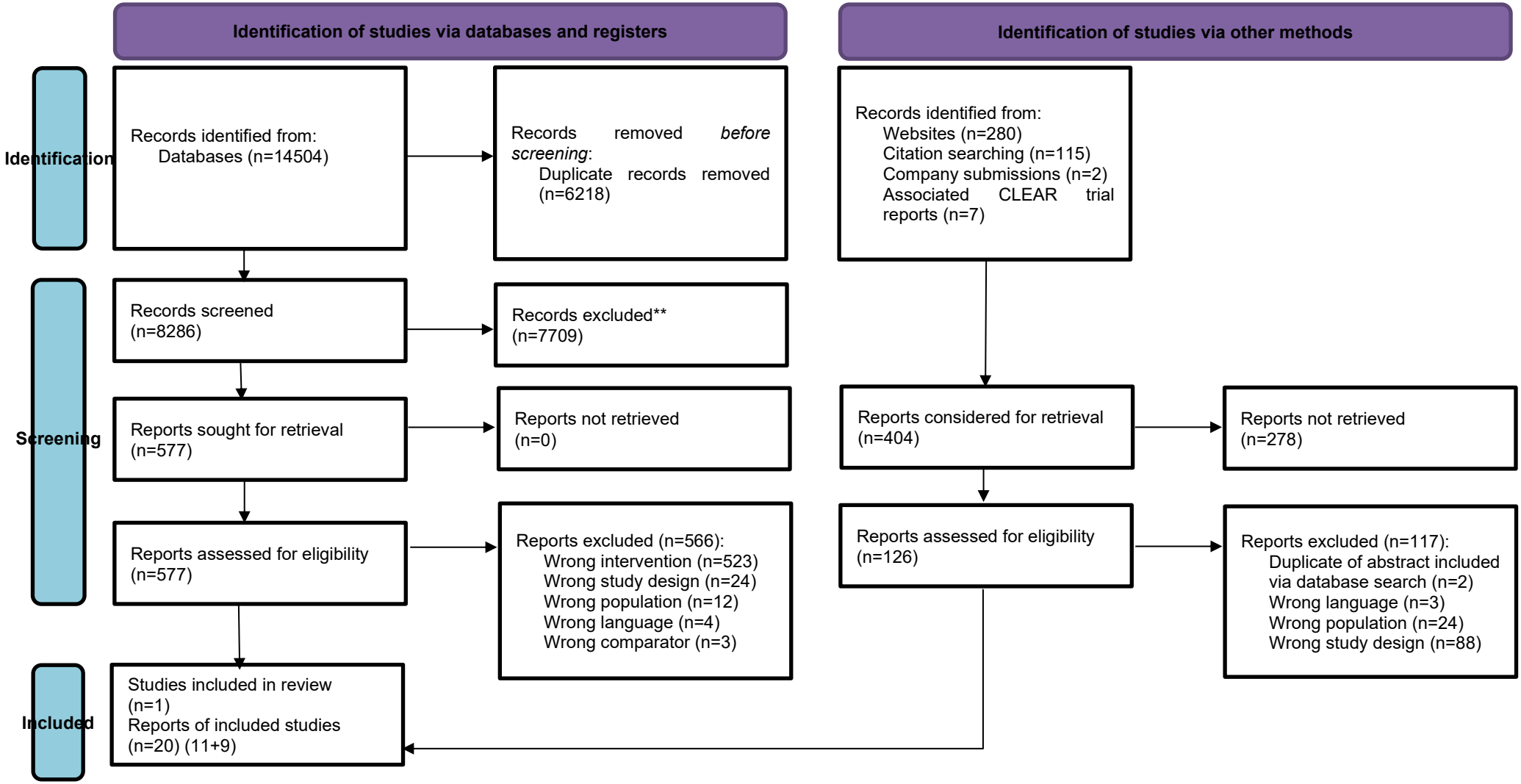

Figure 1 PRISMA flow diagram: direct clinical effectiveness evidence*

* 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).

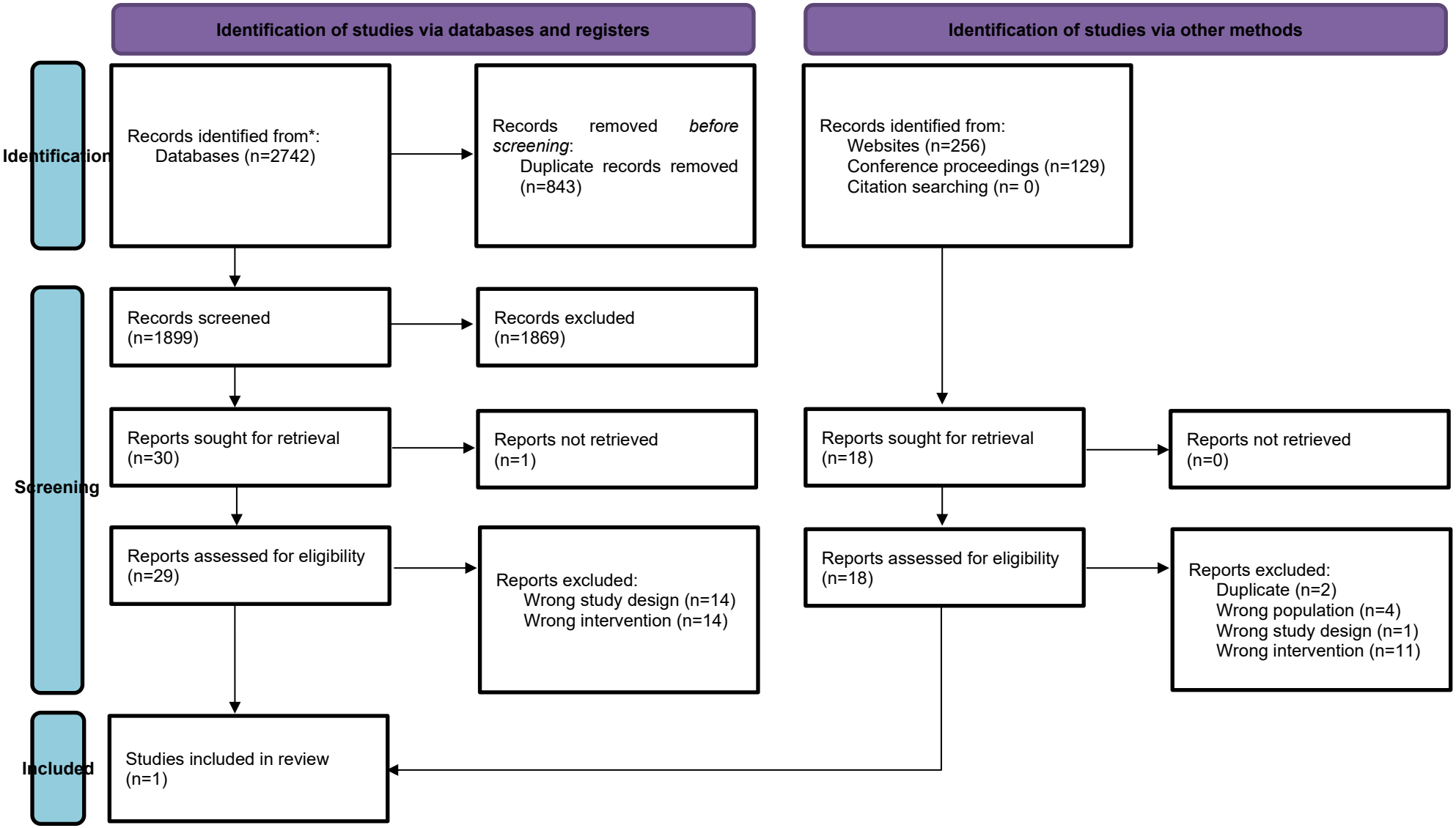

Figure 2 PRISMA 2020 flow diagram for cost effectiveness systematic review

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.

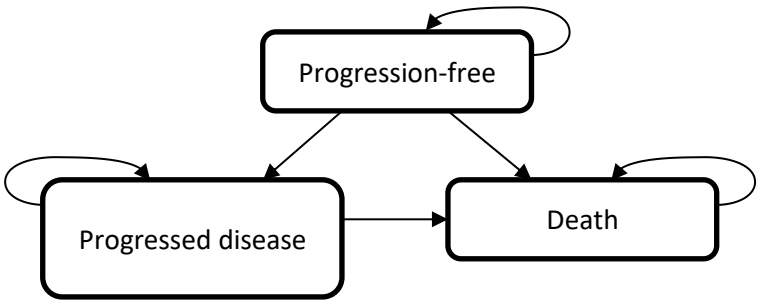

Figure 3 Structure of MSD and MSD/AG company model

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			[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)

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			[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; 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

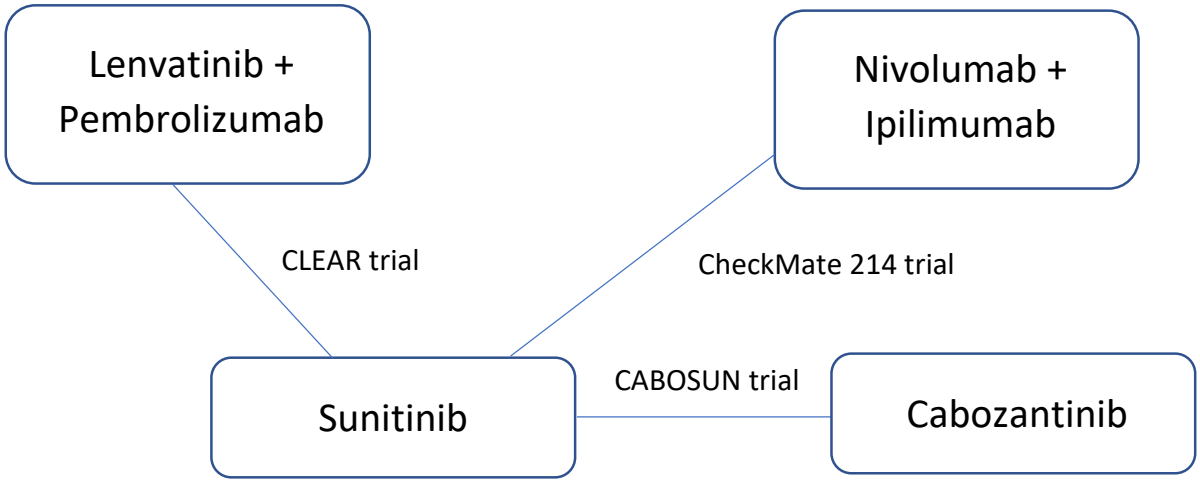

Figure 29 Network diagram for the AG NMAs for the intermediate/poor risk subgroup (PFS, OS and ORR)

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

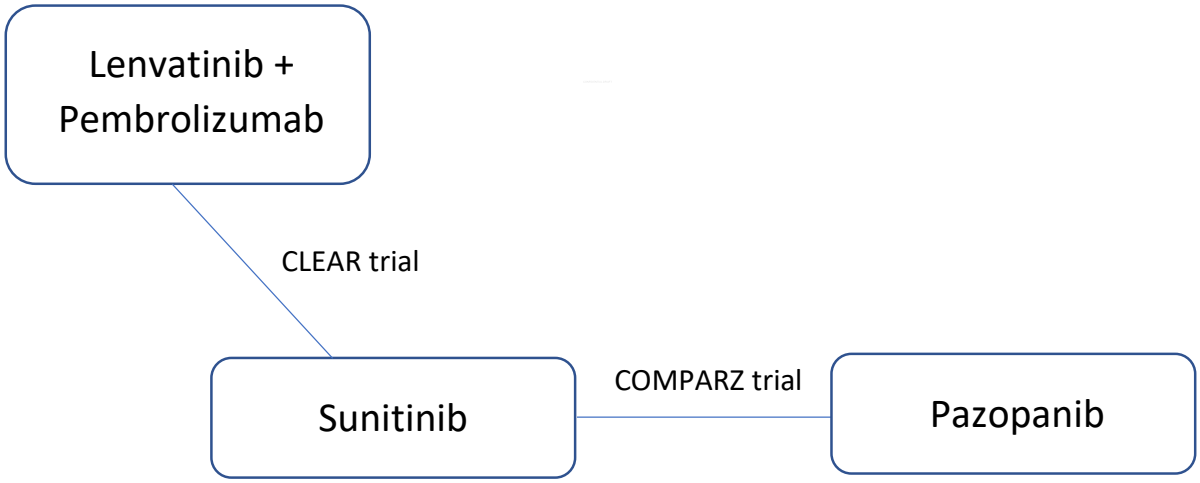

Figure 30 Network diagram for the AG NMAs for the all-risk population (OS and ORR) and for the favourable risk subgroup (PFS, OS, Grade ≥3 AEs)

AE=adverse events; AG=Assessment Group; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

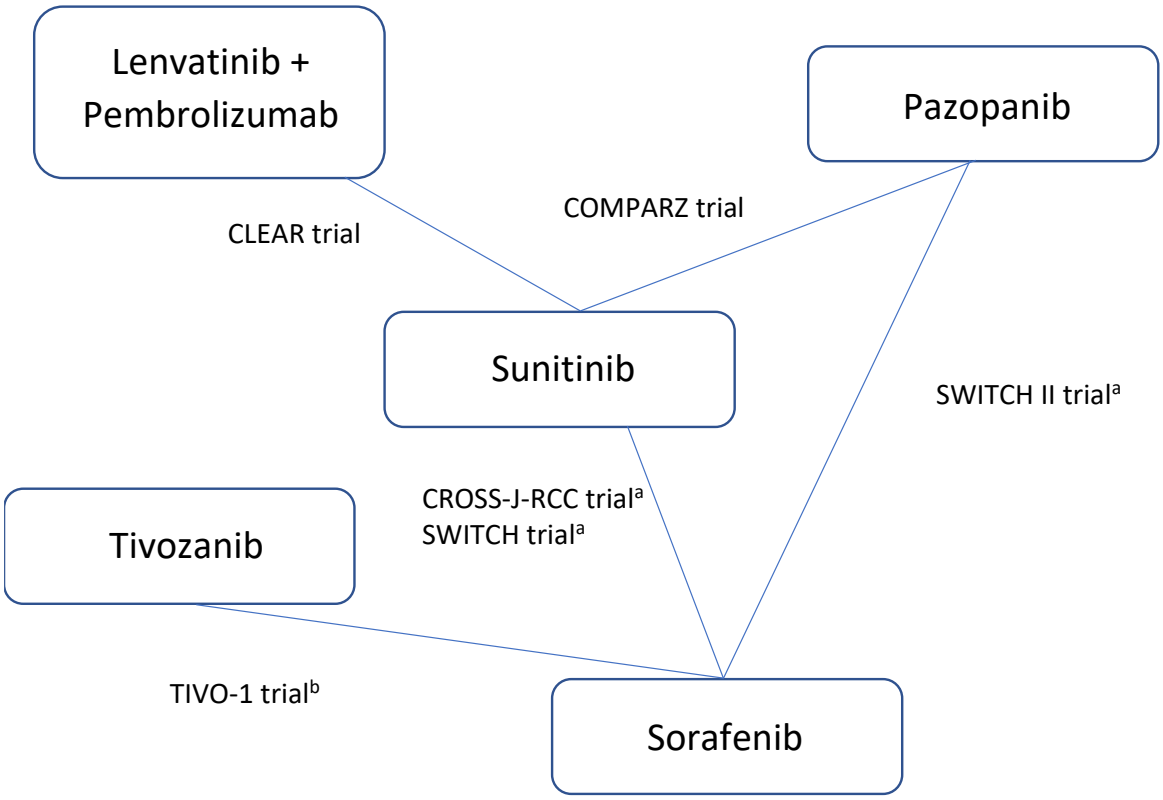

Figure 31 Network diagram for the AG PFS NMA for the all-risk population

[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

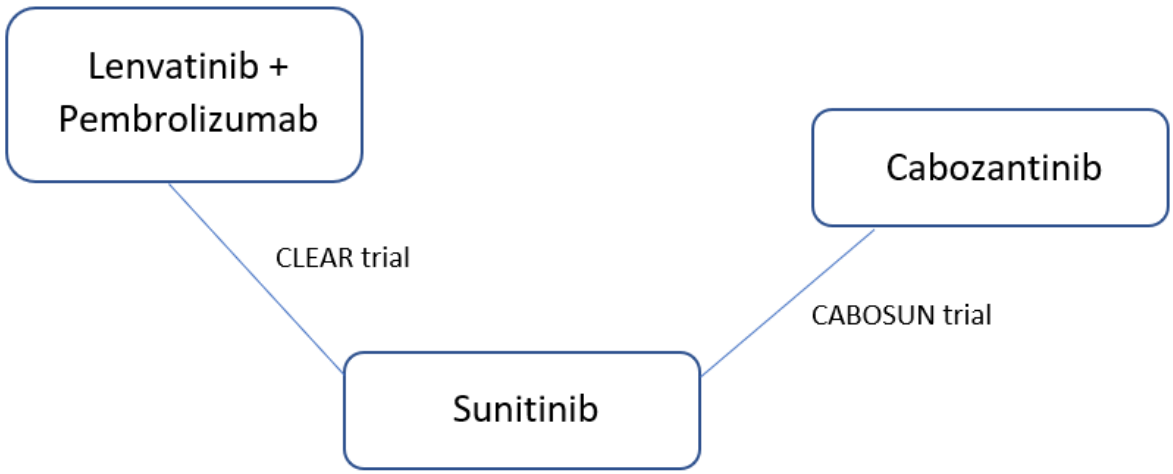

Figure 32 Network diagram for the AG NMAs for the intermediate/poor risk subgroup (Grade ≥3 AEs)

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]

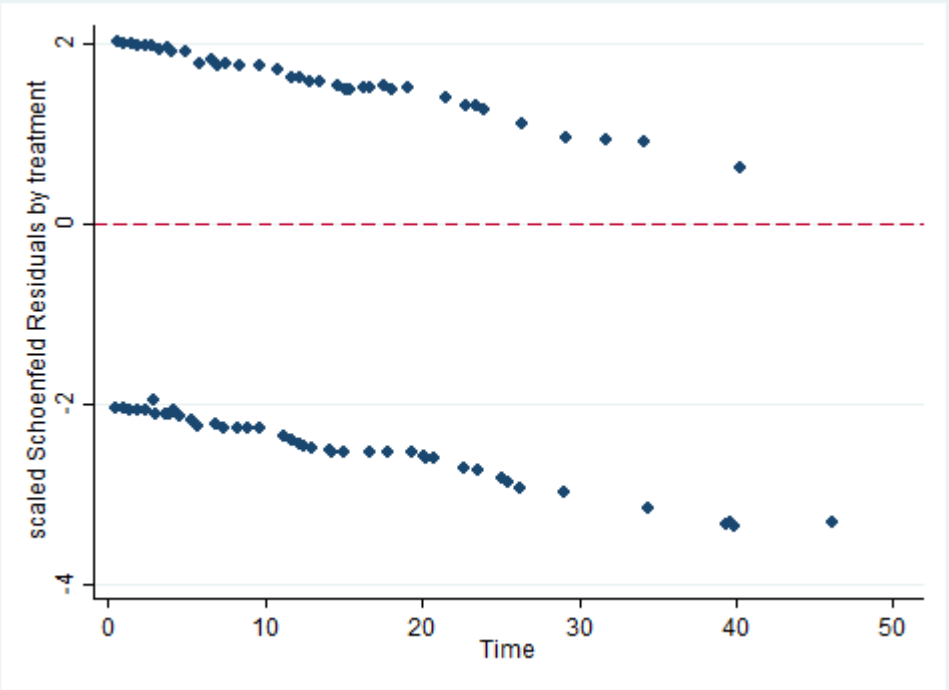

Figure 33 Schoenfeld residuals plot for PFS (CheckMate 214 trial, intermediate/poor risk subgroup)

PFS=progression-free survival

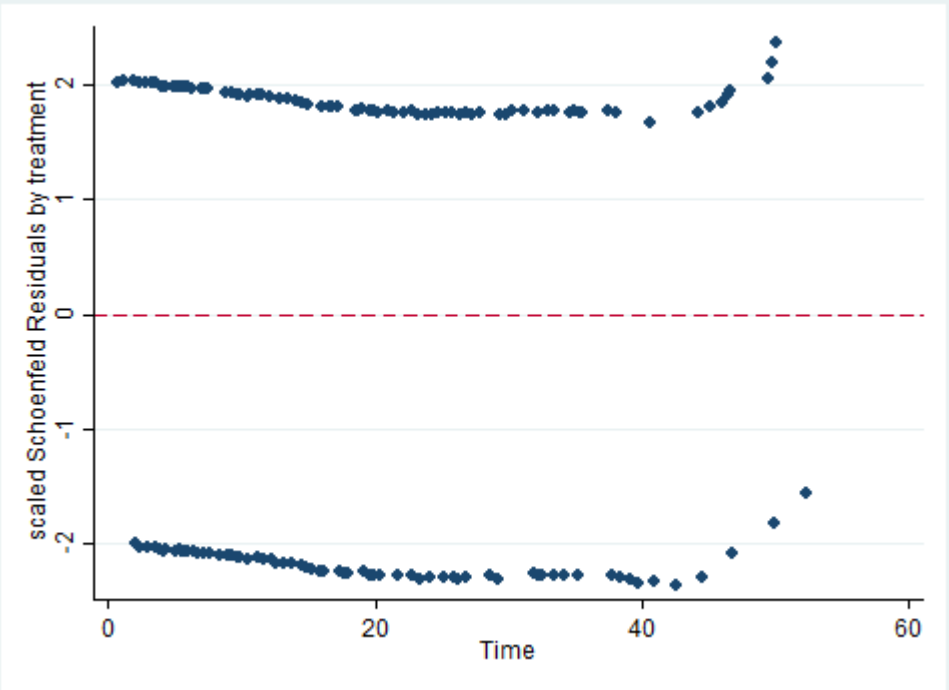

Figure 34 Schoenfeld residuals plot for OS (CheckMate 214 trial, intermediate/poor risk subgroup)

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

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

Eisai Response to the Assessment Report

June 2022

Eisai provides the following comments on the Assessment Report:

1. The assessment group (AG) has conducted an analysis for a subgroup of patients with favourable risk disease which deviates from the final scope

Medicine and Healthcare products Regulatory Agency (MHRA) (1, 2) and European Medicines Agency (EMA) (3) approval were granted on 29th November 2021 and 26th November 2021, respectively, for lenvatinib (LEN, Kisplyx®) for the treatment of adults with advanced renal cell carcinoma (aRCC) in combination with pembrolizumab (PEM), as first-line treatment. The indication represents the entire untreated aRCC population, not differentiated by disease risk subgroups. Accordingly, Eisai seeks reimbursement for LEN+PEM in the overall aRCC population.

This is reflected in the population in the final scope. In addition, the final scope states *"If the evidence allows, the following subgroups will be considered. These include:*

- *People with advanced RCC that is intermediate or poor risk, as defined in IMDC criteria".*

For this subgroup, the final scope lists cabozantinib (CAB) and nivolumab + ipilimumab (NIV+IPI) (subject to ongoing appraisal) as comparators. This reflects the marketing authorisation for both treatments, and the associated National Institute and Care Excellence (NICE) guidance TA542 (4) and TA780 (5), respectively, which are specifically for patients with intermediate or poor risk disease.

In contrast to the final scope, the AG presents cost-effectiveness results for the favourable risk subgroup, per International Metastatic RCC Database Consortium (IMDC) criteria, in addition to the intermediate or poor risk subgroup. Results for the overall population are reported only within Appendix 17. Eisai disagree with the AG's approach and believe that analysis of the favourable risk subgroup should not be considered by the committee for the following reasons:

- **The final scope does not specify the favourable risk subgroup**. Therefore, Eisai consider the use of this population for decision-making to be outside of the scope of this appraisal.
- **Rationale provided by the AG for presenting results for this subgroup is factually inaccurate**.
    - On page 37, the AG state that "*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… 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."* It is true that, by definition, patients without intermediate/poor risk disease would have

favourable risk disease. However, favourable risk patients are part of the overall population that includes all risk types. As there are no treatments specifically recommended by NICE for patients with favourable risk, we disagree that the risk groups being mutually exclusive is sufficient reason to deviate from the scope.

- The AG report states (page 38) that *"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.".* This statement is not factually accurate, as, if a NICE recommendation is not for a specific risk group, that does not automatically mean it is only recommended for the favourable risk group due to the existence of other NICE recommendations specifically for intermediate/poor risk disease. Instead, these treatments are recommended for all patients regardless of risk.
- The AG report incorrectly states (page 155) that "*NICE has recommended different treatments for patients with untreated aRCC with different levels of disease risk (intermediate/poor risk and favourable risk subgroups).*" However, NICE has not made any recommendations specifically for the favourable risk subgroup.

- **The favourable risk subgroup was not considered in the previous appraisals of untreated aRCC for avelumab with axitinib (TA645) (6) and pembrolizumab with axitinib (TA650) (7)**. Avelumab in combination with axitinib (AVE+AXI) (8) and pembrolizumab in combination with axitinib (PEM+AXI) (9) also have marketing authorisation for the first-line treatment of adult patients with aRCC. During the associated NICE appraisals, the committees did not consider the favourable risk subgroup in decision making.

2. The interpretation of favourable risk subgroup data is implausible

Notwithstanding the inclusion of the favourable risk subgroup detailed in Issue 1, Eisai also disagrees with the interpretation of the favourable risk subgroup data as implemented within the AG's economic analysis.

The AG assume that plausible extrapolations in this subgroup should include "*a sustained survival benefit for patients treated with sunitinib versus patients treated with lenvatinib plus pembrolizumab"*. The AG do not justify this statement. It should be noted that at the time of the updated OS analysis (IA4), the difference in OS between LEN+PEM and sunitinib for this subgroup is not statistically significant (HR: [redacted]). Furthermore, a statistically significant benefit in favour of LEN+PEM was observed in this subgroup for response (objective response rate odds ratio [OR]: [redacted]), progression-free survival (PFS) at the time of the final PFS analysis (IA3 HR: 0.41 [95% CI: 0.28, 0.62]; p<0.0001) and PFS on the second line of therapy (10) (HR: 0.57 [95% CI: 0.32, 1.00]; [redacted]). Eisai therefore believe the AG's assumption of a sustained survival benefit for sunitinib vs. LEN+PEM lacks clinical validity.

Methodologically, the CLEAR trial design was not statistically powered for subgroup analyses, only for the overall aRCC population. As stated in the EMA's European public assessment report (EPAR) (11), Section 3.3, "*The OS data are currently immature to allow for the informative analyses in the key subgroups, in particular IMDC and MSKCC favourable prognosis subgroups, while the updated analysis in the overall population*

supports benefit, with hazard ratio (HR) of 0.72 (0.55, 0.93)". The AG state *"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 *** of patients were alive at the end of the trial follow up period."* Over [redacted] of patients in the favourable risk population were alive across both arms of the trial at the time of updated OS analysis (IA4). The sample size of the IMDC favourable risk group was also limited (110 [31.0%] and 124 [34.7%] patients in the LEN+PEM and sunitinib arms, respectively). Eisai therefore do not consider the data for the IMDC favourable risk subgroup alone suitable for use in decision-making.

Given response is an established surrogate for OS in RCC (12-15) and patients in the favourable risk subgroup treated with LEN+PEM have better response, PFS and PFS2 but worse OS compared to sunitinib, this suggests the current OS data are too immature to draw conclusions about the relative efficacy of LEN+PEM in this subgroup. Clinical opinion obtained by Eisai suggested that at least 10 years of follow-up would be required for favourable risk patients in order to observe a difference in OS (16). As stated by the AG on page 19: "*there were too few events in the favourable risk subgroup for robust OS conclusions to be drawn"*.

Indeed, this view is supported by the European Society for Medical Oncology (ESMO) clinical guidelines (17), which states "*The OS signals in the IMDC favourable-risk patients treated with VEGFR-PD-1 combinations are immature and not yet superior to sunitinib. Better response and PFS data, however, support the use of the combination in this exploratory and under-powered subset"*. The European clinical guidelines also state that "*Lenvatinib-pembrolizumab… joins other VEGFR-PD-1 inhibitor-targeted combinations (axitinib-pembrolizumab or cabozantinib-nivolumab) to be recommended for first-line treatment of advanced ccRCC, irrespective of the IMDC risk groups*".

On the basis of the immaturity of data, limited sample size, and statistical power, Eisai do not believe the data for the IMDC favourable risk subgroup can be used in isolation for decision-making. Consequently, Eisai consider it inappropriate to use *"a sustained survival benefit"* for sunitinib as a criteria for selecting extrapolations for the favourable risk subgroup, irrespective of the relevance of this subgroup to the decision problem (Issue 1).

3. The method used by the AG for extrapolation of overall survival has been criticised previously (18) and does not appear to have been clinically validated

For the overall and intermediate/poor risk populations, the AG model assumes OS in the long-term follows an exponential distribution estimated on the hazards observed between specific time periods (between [redacted], and [redacted] for LEN+PEM and sunitinib in the overall population, respectively, and between [redacted] for LEN+PEM in the intermediate/poor risk population). This approach therefore uses a subset of the available follow-up and different periods of follow-up in each arm, to estimate the long-term hazards.

The justification for this approach provided in the AG report is *"…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 AGs approach seems to be based on the principle that the analyst should *"Concentrate attention on using the later stable portion of the available data as the basis for projecting outcomes* beyond the available data*"* (19). However, it is not clear that these data are more "stable", and critically, why selection of a "stable" portion of the data (or a specific portion with a constant hazard) will provide a clinically plausible long-term extrapolation.

Based on the AG report, the time intervals used to estimate the hazards and the resulting extrapolations do not appear to have been informed or validated by clinical experts (16); a key recommendation from the NICE DSU (20) when exploring model fit. Eisai believe the AG's approach has generated clinically implausible estimates of the relative treatment effect for LEN+PEM vs sunitinib in the overall population, which is detailed in Issue 4.

More generally, Eisai believe that the data informing the long-term extrapolation should include the beginning of the survival curve, rather than only a subset of the available data. Including data from the early part of the survival curve avoids losing information, as well as the need to select a cut point from which to begin extrapolation, as described by Latimer (18).

As such, Eisai's original submission used independent exponential distributions to extrapolate OS for LEN+PEM and sunitinib in the overall population, including the beginning of the survival curve from CLEAR. This approach was adopted following steps outlined by the NICE DSU (20) incorporating clinical validation (16). Eisai maintain this approach is more appropriate than that adopted by the AG.

4. The assumptions made by the AG and associated OS extrapolations in the overall population are clinically implausible (Appendix 17)

For the overall population, the AG assumes OS follows an exponential distribution estimated on the hazards observed between [redacted] for LEN+PEM, and [redacted] for sunitinib, which is applied from [redacted] onwards (with Kaplan-Meier data used until this point). Eisai's concerns with the use of this methodology and underlying assumptions are detailed in Issue 3. In this section, we specifically address the implied assumptions about the relative efficacy of LEN+PEM vs sunitinib in the overall population which arise from this methodology.

Because exponential distributions are used (and hazards are therefore constant in each arm), a HR is implicitly assumed between LEN+PEM and sunitinib. In the AG model, the estimated hazards for LEN+PEM and sunitinib yield a HR of approximately [redacted] for LEN+PEM vs sunitinib. This means the risk of death for patients receiving LEN+PEM is approximately [redacted] than for sunitinib (and pazopanib and tivozanib) in patients who have survived to Week 120. In contrast, the HR for LEN+PEM vs sunitinib observed in the updated OS analysis (IA4) from CLEAR [0.72 (95% CI: 0.55, 0.93)] was statistically significant in favour of LEN+PEM. Moreover, the equivalent HR for OS implied by Eisai's extrapolation approach for the overall population was [redacted], which closely aligns with CLEAR. Eisai therefore believe the AG's extrapolation approach is clinically implausible.

The AG extrapolations (Figure 1) generate lower absolute survival for LEN+PEM than sunitinib beyond approximately [redacted] for the remainder of the time horizon. In contrast, clinical feedback obtained during advisory boards conducted in July 2021 (21) and September 2021 (16) stated that poorer OS with LEN+PEM is unlikely, given the high objective response rate (ORR; 71.0% vs 36.1% for sunitinib; odds ratio [OR]: 4.35

[95% CI: 3.16, 5.99]; nominal p-value <0.0001) and PFS gain associated with LEN+PEM compared with sunitinib (median PFS: 23.9 months [95% CI: 20.8, 27.7] for LEN+PEM vs 9.2 months [95% CI: 6.0, 11.0] for sunitinib; HR: 0.39 [95% CI: 0.32, 0.49]; p<0.0001). As discussed in TA645 (6), previous appraisals (22, 23) have acknowledged that there is an OS benefit for immuno-oncology (IO) combinations in aRCC in both first- and second-line. Moreover, clinicians also confirmed that with longer follow-up, it is unlikely that the curves will continue to cross (16). Consequently, Eisai believe the AG's extrapolation approach for OS is clinically implausible (as mentioned in Issue 3).

Figure 1: AG model OS extrapolations for the overall population†

†Note sunitinib, pazopanib, and tivozanib are assumed to have equal efficacy and therefore these curves overlie each other.

One reason for the convergence observed in the current OS data in CLEAR is likely to be an imbalance in subsequent anti-cancer therapy between treatment arms (received subsequent treatment in the LEN+PEM arm and % in the sunitinib arm). In clinical practice, subsequent treatment use may be higher than observed in the LEN+PEM arm of CLEAR; comments from Professor Peter Clarke (NHS England Chemotherapy Lead and Clinical Lead for the Cancer Drugs Fund) in TA581 (22) state that the proportion of patients who would go on to receive subsequent treatment following both NIVO+IPI or a tyrosine kinase inhibitor (TKI) would be 50%. Clinical experts consulted during TA650 also estimated that over 50% of patients who had first-line treatment would have subsequent treatment (7). Therefore, fewer patients receiving subsequent treatment in the LEN+PEM arm of CLEAR may have led to an underestimation of OS benefit for LEN+PEM vs sunitinib.

In addition, adjusted OS for switching to any subsequent anti-cancer medication in Eisai's original submission estimated HRs between compared with the unadjusted HR of 0.72 (95% CI: 0.55, 0.93). Overall, these post-hoc analyses indicated that imbalances in subsequent anti-cancer medication may underestimate the reduction in the risk of death for patients treated with LEN+PEM vs sunitinib.

Furthermore, it should be noted that the number of events is low and there are a high number of patients censored towards the tail of the OS curve; at month 42 (prior to convergence of the curves) fewer than and patients remained at risk in the LEN+PEM and sunitinib arms, respectively (IA4 analysis). Additional data from the final OS analysis of CLEAR ( ) may address this uncertainty.

Therefore, Eisai believes the AG extrapolations of OS in the overall population are clinically implausible, and that the approach used in Eisai's original submission, which does not imply higher OS for sunitinib than LEN+PEM in the long-term and was supported by clinicians as clinically plausible (16), is appropriate.

5. The AG has applied a cost of administration for lenvatinib and other oral therapies

Lenvatinib is a tablet, administered orally, once daily. Treatment with LEN should be initiated and supervised by a healthcare professional experienced in the use of anti-cancer therapies (3). In the economic model submitted by Eisai, it was assumed that the initial administration of oral therapies would occur in an outpatient setting, with the cost captured as part of background medical management. After initiation, it was assumed that no administration costs would be associated with oral therapies as patients would self-administer.

The AG model assumes that costs for the administration of LEN and other oral therapies are incurred at treatment initiation, and thereafter an additional cost of a hospital-based pharmacist is incurred in subsequent cycles. However, Eisai believe that the AG have not applied the oral administration costs as they have explained. Please see Issue 8b for more detail.

Administration costs for LEN were not included in the model used for decision-making in NICE TA551 (LEN for untreated advanced hepatocellular carcinoma) (24). During TA650 (PEM+AXI in untreated aRCC) (7), the company had included administration costs for oral therapies and the ERG had set this to zero, with the NICE technical team stating "*The technical team recognises that the company may have double counted the cost of oral drug administration given a follow-up outpatient consultation is included (equating to approximately 1 consultation every 4 weeks). The technical team therefore agrees with the ERG base case assumption of zero cost for the administration of oral drugs*".

By applying administration costs in addition to other medical resource use, Eisai believe that the AG model double-counts any costs of administration for LEN and other oral therapies, and should therefore be removed.

6. The AG do not assume treatment with pembrolizumab is stopped at 2 years

The AG model includes the KM curves for PEM time-to-discontinuation (TTD) from CLEAR and use this to calculate the drug costs for pembrolizumab. This leads to a proportion of patients continuing treatment with pembrolizumab beyond Year 2 (for the overall population, [redacted] remain on treatment at Year 2).

In TA650 (PEM+AXI in untreated aRCC), treatment with pembrolizumab was stopped at 2 years (7) and the committee concluded that capping pembrolizumab at 2 years was appropriate for RCC, and was in line with the clinical- and cost-effectiveness evidence (7). Therefore, Eisai believe that drug costs for pembrolizumab should also be stopped at 2 years in this appraisal.

7. The approach to calculating utility values does not take into account utilities differing by other predictors such as treatment or progression status

The AG's model uses a time-to-death approach to predict health-related quality of life (HRQoL). This assumes that proximity to death is the sole predictor of HRQoL, rather than progression status and/or treatment, which are routinely used to differentiate health state utilities in oncology HTAs (5, 6).

To date, all other NICE appraisals of combination treatments for RCC have modelled utilities by health state, except one which used time to death utilities (PEM+AXI, TA650) (7). In that appraisal, the committee concluded that post-progression utilities were important and acceptable for decision making (7). Moreover, the difference in progression-free utilities between the LEN+PEM and sunitinib arms in CLEAR was statistically significant [redacted] (25). Consequently, treatment-specific utility values from CLEAR were used for the progression-free health state in the Eisai submission. A simple test of difference in means also found a statistically significant difference between pre- and post-progression utility scores [redacted].

Eisai believe that as the difference in pre-progression EQ-5D between LEN+PEM and sunitinib, and also, as the difference in utilities between pre- and post-progression health states are both statistically significant, the utilities used in Eisai's original submission are more appropriate, in line with other NICE appraisals in RCC.

8. Errors identified in AG model

a. Error in tivozanib engine for adverse event costs

Within the tivozanib engine, the AG's amendment around adverse event costs has not been included in Column DA, whereas this has been included in all other engines.

b. Error in application of oral administration costs

The AG state they "*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*."

Eisai have interpreted this as: the oral cost applies in the first cycle of the model, and then the pharmacy cost applies every month (every 4 cycles of the model) assuming medicines are dispensed monthly. However, no oral chemotherapy cost has been applied within the engines. The formulae in Column CO only use the cost in Cell CO22 when the treatment is an IV treatment.

Oral administration costs also apply to subsequent treatments. However, on the subsequent treatments sheet, it seems the oral chemotherapy cost (£226) is being multiplied by the number of administrations per month, thereby overestimating the administration costs for subsequent treatments. In addition, the £11 pharmacy cost does not appear to be used anywhere for subsequent treatments. This may represent an error in the economic model.

c. Patient characteristics reported in the AG report

The AG report states that: "*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 includes the FAS population for all three arms combined (LEN + everolimus, LEN+PEM, SUN), and not representing only the participants from the European sites.

9. **Finally, Eisai would like to highlight the following factual inaccuracies in the report:**

   a. **Page 3 "This report should be referenced as follows: Fleeman N, Houten R, Nevitt S, Mahon J, Beale S, Boland A, Greenhalgh J, Edwards K, Maden M, Bhattacharyya D, Chaplin M, McEntee J, Chow S, Waddell T. Lenvatinib plus pembrolizumab for untreated advanced renal cell carcinoma [ID3760]: A Multiple Technology Appraisal. LRiG, University of Liverpool, 2018"**

Eisai would like to note that the reference has the year 2018 instead of 2022.

   b. **Page 18, "The AG has, therefore, included it as a comparator and a NICE recommendation is expected to be released on 24 March 2021."**

Eisai would like to note that the NIV+IPI recommendation was expected to be released on 24th March 2022, not 2021.

   c. **Page 112, "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."**

Eisai would like to highlight that Table 49 implies log-logistic is the base case, however, it appears to be a scenario (page 116).

   d. **Page 155, "NICE has recommended different treatment for patients with untreated aRCC with different levels of disease risk (intermediate/poor risk and favourable risk subgroups)."**

There are no UK clinical recommendations specifically for the favourable risk subgroup.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

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

MSD response to Assessment Group report

June 2022

File name	Version	Contains confidential information	Date
MSD response to Assessment Group report [REDACTED]	Final	Yes	24/06/2022

Issue 1: Assessment Group (AG) do not consider the cost-effectiveness results reported for the trial intention-to-treat (ITT) population to be relevant for decision making.

AG report text and reference:
Section 5.22.1 – page 133
"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;…"

MSD Response:

MSD consider the cost-effectiveness results for the all-risk population to be relevant for decision making.

As mentioned in the AG report, "*Lenvatinib plus pembrolizumab is licensed to treat all patients with aRCC irrespective of risk status*." Furthermore, European Society for Medical Oncology (ESMO) clinical practice guidelines recommend the combination as a treatment option for all-risk patients[1]. Hence, the appropriate comparator treatments for a combination with this indicated population are those associated with a similar clinical profile, independent of a patient's IMDC risk status.

MSD acknowledges that a patient's risk status is a factor in a clinician's decision about which treatment to offer an advanced renal cell carcinoma (aRCC) patient in the first-line setting. However, risk status-agnostic treatment options such as pembrolizumab + lenvatinib provide additional clinical flexibility and have the potential to displace those treatments with a similar indicated population currently available for routine use in the NHS. Hence MSD's position remains that those comparators listed in the appraisal scope as appropriate comparators when considering the all-risk population are the most relevant, and the all-risk cost-effectiveness results used to inform those comparisons are the most appropriate for decision making. This is consistent with the NHS England and NHS Improvement budget impact analysis submission for this appraisal made in January 2022[2], where a treatment option with an equivalent indicated population was identified as the most appropriate comparator ("*Lenvatinib plus pembrolizumab will provide an alternative TKI plus IO option for all risk categories.*"), rather than treatments whose use is restricted to specific IMDC risk categories. The AG and MSD agree that the technology in question (i.e. avelumab + axitinib) is currently available through the Cancer Drugs Fund (CDF) and hence cannot be considered as a relevant comparator for this appraisal[3].

MSD's position also aligns with the previous NICE appraisal of an immunotherapy + tyrosine kinase inhibitor (IO + TKI) combination in first-line aRCC (TA645), where a treatment available to all-risk patients was under consideration and the most appropriate comparators were identified as those which all patients are eligible to receive (*"Comparisons with sunitinib and pazopanib are the most relevant for decision making…")*[4]. Despite the AG approach to treating the all-risk population as a collection of disaggregated subgroups, MSD have not identified justification for a divergent approach in this IO + TKI combination appraisal (ID3760).

The AG report states that their clinical advice indicates that in general, nivolumab plus ipilimumab or cabozantinib are the preferred first-line treatment options for patients with intermediate/poor risk disease. However, in line with the product licenses and NICE guidelines, there is a subgroup of these patients who clinicians choose to treat with TKI monotherapy (e.g. sunitinib) in the first-line, and hence the approach proposed by the AG means those NHS patients are not represented in this appraisal. Considering the all-risk population allows these patients to be accounted for in the appraisal.

Issue 2: AG have included nivolumab in combination with ipilimumab as a comparator in the intermediate + poor risk subgroup analysis.
AG report text and reference: *Section 2.1.2 – page 37* *"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 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*."
MSD Response: **Nivolumab + ipilimumab should not be a relevant comparator in this appraisal, according to NICE's position statement on the consideration of products recommended for use in the CDF as comparators in future appraisals.** MSD does not consider nivolumab in combination with ipilimumab (nivolumab + ipilimumab) to be a relevant comparator within this appraisal. MSD has consistently maintained this position throughout the appraisal process to date, as per our response to the consultation on the draft scope as well as in our evidence submission dated 10 November 2021 and our response to clarification questions The AG report justified the inclusion of nivolumab + ipilimumab as a relevant comparator following advice from the NICE technical team. It is important to note that nivolumab + ipilimumab only received a positive NICE recommendation (following their CDF guidance review – TA780[5]) on 24 March 2022. This date falls after both the date of receipt of the invitation to participate in this appraisal (ID3760) and MSD's evidence submission deadline for this appraisal. As nivolumab + ipilimumab was not available through baseline commissioning at the time of the invitation to participate being issued by NICE or the evidence submission deadline, it is inappropriate to consider it as established standard of care, or a factor to inform decision making during the appraisal of pembrolizumab + lenvatinib. MSD's view that nivolumab + ipilimumab should not be considered a comparator of relevance in ID3760 is informed and supported by NICE's position statement ("*Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product*") issued in January 2019[3], which states: *"…products recommended for use in the Cancer Drugs Fund after 1st April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. Companies of new cancer products under appraisal should therefore not include treatments recommended for use in the Cancer Drugs Fund as comparators, or treatment sequence products in their economic modelling*." This position statement, which was available for public information at the initiation of the appraisal, does not contain provision for exceptions to this rule to be made in circumstances where potential comparators exit the CDF following the commencement of an appraisal, as has occurred during the course of the ID3760 appraisal. Furthermore, the appraisal scope listed nivolumab + ipilimumab as a comparator, with the caveat that this was "subject to ongoing appraisal". MSD considers that the correct interpretation of this caveat is that nivolumab + ipilimumab would only be a comparator of relevance in ID3760 if the combination was to successfully exit the CDF and enter baseline commissioning prior to the initiation of the current appraisal. Consulting the dates

for this appraisal outlined above, this scenario has not occurred; consequently, the inclusion of nivolumab + ipilimumab as a comparator for this appraisal, or as a treatment to be included in the network for an indirect treatment comparison, is unjustified.

Issue 3: The survival estimates predicted by the AG analysis for the all-risk population who receive sunitinib are overly optimistic.

AG report reference:
Section 9.17 – page 238-251

MSD Response:

MSD considers the submitted approach to extrapolating the sunitinib trial data to better reflect clinical plausibility, and that the AG approach overestimates the survival for this treatment arm.

PFS:
Both MSD and the AG followed the fully extrapolated approach to modelling PFS data, utilising all of the currently available CLEAR (KEYNOTE-581) trial data for extrapolation of both treatment arms. The AG outlined their process for selecting the appropriate distribution to use, and in the case of the sunitinib arm, the log-normal distribution was selected on the basis of long-term clinical plausibility. This model predicts a PFS rate of [redacted] of patients after 7 years and also that some patients will remain alive and progression-free on this treatment after 10 years. MSD believe this lacks clinical plausibility and that this outcome is not supported by the trial median PFS value of 9.2 months, indicating that a significant subset of patients would need to be driving this long tail that the AG-preferred distribution predicts.

The AG choice of the gamma distribution for extrapolating pembrolizumab + lenvatinib PFS produces more pessimistic longer-term estimates than are suggested by the trial median PFS of 23.9 months and the trial HR (0.39; 95% CI [0.32-0.49]). When extrapolating such a mature dataset as this, clinical plausibility should be a priority assessment criterion over goodness-of-fit and visual inspection. MSD continue to view the exponential distribution as the most appropriate for extrapolating PFS.

OS:
MSD followed a fully extrapolated approach to modelling OS data, whereas the AG employed a two-piece approach for both treatment arms, using trial KM data up to week 120, and fitting extrapolated data beyond this timepoint. Supporting evidence for this choice of cut-point (e.g. Chow test plot) has not been provided. For the sunitinib arm, the AG used the average hazard observed between weeks 50-120 for all subsequent timepoints (estimated to be [redacted]), however a comparison with the hazard observed in the trial data for weeks 120-179 indicates this to be too optimistic, as the average trial hazard for this time period appears to be [redacted] – hence the AG approach appears to predict a lower risk of death for these patients at this timepoint than was observed in the CLEAR (KEYNOTE-581) trial. Furthermore, an assessment of the longer-term survival rate predicted by the AG model indicates the model generates an overly optimistic estimate of [redacted] at 10 years, which exceeds rates reported in previous trials and a real-world study[6], as well as clinical opinion received by MSD. The MSD approach of fully extrapolating using the gamma distribution predicts a less optimistic OS estimate of [redacted] at 10 years, which, whilst also exceeding historical benchmarks, is closer to a clinically plausible estimate, and utilises the full CLEAR (KEYNOTE-581) trial dataset for extrapolation.

A similar AG approach was followed for the pembrolizumab + lenvatinib arm's OS extrapolation. In this arm, the average hazard between weeks 80-120 was used to project survival at subsequent timepoints. However, it appears the AG model uses the average hazard beyond week 120 (i.e. [redacted]) for these later timepoints, rather than what appears to be the week 80-120 average (i.e. [redacted]), as stated. This erroneous application of a greater risk of death leads to more pessimistic survival estimates with the combination treatment. MSD believe that the originally submitted fully extrapolated approach (using the exponential distribution) remains the most appropriate predictor of long-term survival for pembrolizumab + lenvatinib. For comparisons with the AG approach, the AG model should be updated to reflect the average hazard between weeks 80-120.

Issue 4: The survival estimates predicted by the AG analysis for the intermediate + poor risk population who receive cabozantinib are overly optimistic.

AG report reference:
Section 5.13.1, 5.14.1 – page 103-105, 110-112

MSD Response:

MSD considers our approach to extrapolating the cabozantinib trial data in this population to better reflect clinical plausibility, and that the AG approach overestimates the survival for this treatment arm.

PFS:
In the absence of head-to-head data, results of an indirect treatment comparison were required for the comparison with cabozantinib. The inclusion of an additional treatment in the AG network (i.e. nivolumab + ipilimumab) does not appear to have impacted the results for the comparison of pembrolizumab + lenvatinib vs. cabozantinib in this population, as the MSD NMA and the AG NMA report a similar HR (i.e. [redacted]). In the PFS analyses conducted by both MSD and the AG, the assumption of proportional hazards was deemed to be violated, hence it is unreasonable to assume a constant HR for this comparison. However, the AG analysis applies a constant HR ([redacted]) for pembrolizumab + lenvatinib vs. cabozantinib in this population. Furthermore, a comparison of the median PFS predicted by the AG model (i.e. [redacted]) with that reported for cabozantinib in the CABOSUN trial (i.e. 8.6 months)[7] indicates an almost [redacted] increase in the median estimate with this approach, and should be viewed as overly optimistic. The fractional polynomial approach followed by MSD predicts a more appropriate median PFS for the cabozantinib arm (i.e. [redacted]). There is a precedent of accepting this more flexible modelling approach in previous NICE appraisals in this therapeutic area when the use of a time-varying HR is more appropriate (TA463, TA512)[8,9]. MSD believe that although the AG report outlines limitations related to difficulties interpreting fractional polynomials, this should not be a rationale for excluding their use for decision making.

OS:
An indirect treatment comparison was also required for comparative OS results. The inclusion of an additional treatment in the AG network (i.e. nivolumab + ipilimumab) does not appear to have impacted the results for the comparison of pembrolizumab + lenvatinib vs. cabozantinib in this population, as the MSD NMA and the AG NMA report a similar HR (i.e. [redacted]). The AG report states that no violation of the proportional hazards assumption was observed for OS in this population. Hence they applied a constant HR ([redacted]) for pembrolizumab + lenvatinib vs. cabozantinib. However, as stated in the company submission, MSD considers that the assumption is violated in this population and that the application of time-varying hazards is more appropriate. The Schoenfeld residual plot and

summary of Cox proportional hazard modelling summary as presented in Figure *1* and Table *1* below. The Schoenfeld residual test p value was estimated to be <0.05 for the CLEAR (KEYNOTE-581) trial. The Bayesian constant HR analysis should not be used to infer any statistically significant difference (or lack of statistically significant difference) for outcomes that report a violation of this assumption. Furthermore, as reported in NICE DSU TSD 14, it is generally considered unnecessary to rely on the proportional hazards assumption when patient-level data is available[10]. As outlined, fractional polynomial models were fitted in line with guidance, in order to provide an estimate of treatment differences where a hazard changes over time. As with the PFS, a comparison between the median OS predicted by the AG model (i.e. [redacted]) and that reported for cabozantinib in the CABOSUN trial (i.e. 26.6 months)[7] indicates the AG model to provide an overly optimistic survival estimate for patients receiving cabozantinib. The fractional polynomial approach followed by MSD predicts a more appropriate median PFS for the cabozantinib arm (i.e. [redacted]).

Similar to the approach in the all-risk analysis of OS, the AG model uses the average OS hazard for weeks 50-120 to project survival with pembrolizumab + lenvatinib beyond week 120. However, it appears the AG model uses the average hazard beyond week 120 (i.e. [redacted]) for these later timepoints, rather than what appears to be the week 50-120 average (i.e. [redacted]), as stated. The erroneous application of this greater risk of death leads to more pessimistic survival estimates with the combination treatment. In the absence of an external benchmark with which to validate the survival estimates, the updated AG model (i.e. with the average hazard from week 50-120) and the fully extrapolated approach submitted by MSD (using the exponential distribution) both provide similar and plausible estimates of longer-term survival in the intermediate/poor risk population. Clinical expert input will be useful in validating the approaches.

Figure 1: Schoenfeld residual plot for graphical diagnosis of proportional hazards in Overall Survival between intermediate + poor risk patients treated with pembrolizumab + lenvatinib vs. sunitinib in CLEAR (KEYNOTE-581)

Table 1: Summary of COX proportional hazard modelling for intermediate + poor risk patients treated with pembrolizumab + lenvatinib vs. sunitinib in CLEAR (KEYNOTE-581)

coef	exp(coef)	se(coef)	z	Pr(>|z|)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Issue 5: The survival estimates predicted by the AG analysis for the favourable risk population who receive pembrolizumab + lenvatinib lack clinical plausibility.

AG report reference:
Section 5.14.2 – page 112-114

MSD Response:

MSD considers the AG survival estimate for patients treated with pembrolizumab + lenvatinib to be an underestimate, and that a lower survival projection than for sunitinib patients is clinically implausible in this population.

OS:
The AG report states that the favourable risk results from the CLEAR (KEYNOTE-581) trial are associated with considerable uncertainty. MSD agrees with this statement, attributable to low patient numbers and low numbers of events experienced by these patients (the clinical profile of a favourable risk patient means that death events are likely to be rarer than in the aRCC population as a whole). However, the AG report then cites the trial OS KM data and HR data shared by MSD to justify that a sustained survival benefit with sunitinib over pembrolizumab + lenvatinib should be modelled, based on a suggestion from these data. MSD disagree with this plausibility principle, which is used to anchor the AG choice of extrapolation curves. Clinical advice received by MSD is that the benefit of TKI monotherapy typically manifests early on in a patient's treatment, so if there is a survival advantage with sunitinib, it would be expected to present in survival rates in the short term. However, the 2-year survival rate observed with pembrolizumab + lenvatinib (approximately [redacted]) exceeds that of the sunitinib arm (approximately [redacted]). This, in addition to the wide confidence intervals around the OS HR reported (1.22; 95% CI [0.66 – 2.26], undermines the assertion that sunitinib should be modelled to provide a sustained survival benefit in this population.

MSD's preferred distributions for modelling sunitinib OS (i.e. gamma and Weibull) predict a similar 5-year rate of [redacted], and the AG agree with the choice of gamma. This distribution provides an optimistic estimate relative to historical benchmarks[6], however to select any other distribution would increase this survival prediction even further. MSD agree with the AG assertion that survival projections for the favourable risk population should be higher than for intermediate + poor risk group, in order to preserve clinical plausibility. The AG report contains a typo, which MSD have subsequently clarified, and the AG choice of distribution has been confirmed as log-logistic. However, this distribution produces a long-term survival projection for pembrolizumab + lenvatinib (5-year OS rate of [redacted]) which is less than that for sunitinib. As discussed above, MSD consider this clinical outcome (i.e. improved survival with sunitinib) to be implausible and it is not supported by the OS rates in the observed data. The QALY gain reported for the pembrolizumab + lenvatinib combination treatment in the MSD submission is a more clinically plausible outcome than the negative incremental QALY (and hence dominance) reported by the AG in the favourable risk population.

Issue 6: The AG analysis underestimates the subsequent therapy costs for cabozantinib and overestimates the subsequent therapy costs for pembrolizumab + lenvatinib.

AG report reference:
Section 5.21 – page 132

MSD Response:

MSD believes the proportion of cabozantinib patients expected to receive nivolumab as a second-line treatment in the NHS is higher than that estimated by the AG. Furthermore, the AG's assumption that all progression-free patients will receive a subsequent treatment is not likely to be the case in clinical practice.

The AG received clinical advice that 60% of patients treated with cabozantinib would receive subsequent treatment with nivolumab and 40% of patients would receive a TKI in the second line. MSD have received alternative clinical opinion that these proportions are more likely to be 80% and 20% respectively. This latter group are likely to only be those patients who have shown a durable response whilst receiving TKI therapy, which is rare, or those who are unhappy to attend the hospital setting for IO therapy. Clinical opinion is that these patient profiles are likely to comprise a lower proportion than 40%. Hence the treatment costs allocated to the cabozantinib arm in the AG analysis are likely to be an underestimate of those incurred by the NHS in the treatment of these patients.

The AG analysis also contains the implicit assumption that 100% of patients in the progression-free (PF) health state will ultimately progress and receive a subsequent treatment. However, it is possible that patients will move from the PF health state without receiving a subsequent treatment, through death from other causes, or by electing not to receive any subsequent therapies. In the CLEAR (KEYNOTE-581) trial, the proportion of PF patients who progressed was observed to be [redacted] for the pembrolizumab + lenvatinib arm and [redacted] for the sunitinib arm. Adopting the AG's assumption of 100% leads to an overestimate of the subsequent therapy costs in the analysis.

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Multiple Technology Appraisal (MTA)

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

Comments on Assessment Report

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Comments

On Page 18 it is highlighted that the comparators are Cabozantinib and Ipilimumab and Nivolumab in the poor and intermediate risk group and comparison with Axitinib and Avelumab is not made in the document. Whilst an appreciation is given to the fact the combination of Axitinib and Avelumab is only available on CDF, I would argue as a treatment that is used routinely at present, it provides a really useful bench mark to consider the response rate (RR), progression free survival (PFS) and Overall Survival (OS) against as both treatments are immunotherapy (IO) and tyrosine kinase inhibitor (TKI) combinations.
For the overall groups, the comparators are single agent TKI which would not be standard of care for most renal cancer treating consultants in 2022.

On page 19 the statistically significant PFS advantage of the combination of lenvatinib with pembrolizumab is highlighted. In my opinion this results in both statistically significant but also extremely clinically meaningful outcomes with a hazard ratio of 0.39 and a PFS of 23.9 months. Sunitinib PFS was 9.2 months, consistent with the range one would expect of single agent TKI for sunitinib, pazopanib and tivozanib in their respective registration trials. The treatment switching analysis provided by Eisai which continued to show a statistically significant advantage for patients treated with lenvatinib plus pembrolizumab versus sunitinib. This is further supported by data presented at ASCO 2022 which investigated PFS-2 which evaluates the ability to be salvaged by 2nd line therapy and is a surrogate for overall survival (OS). The definition of PFS2 is the time from randomization to disease progression on next line of treatment, or death from any cause (whichever occurs first). Of note, this includes

time periods that patients are on second line therapy: Among all patients, PFS2 was longer with lenvatinib + pembrolizumab than with sunitinib (median not reached vs 28.7 months; HR 0.50, 95% CI 0.39–0.65 (1)

On Page 19 it is also noted that the combination treatment of lenvatinib and pembrolizumab had higher rates of all toxicities, grade 3 toxicities and discontinuation. Whilst this is true, the reality in real life clinical practice is that most of toxicity is contributed to by TKI rather than IO and outcomes were still statistically significantly improved despite these required discontinuations. Despite superior outcomes, as discussed on page 19 there were no clinically meaningful differences in quality of life (QOL).

On page 20 it is noted that there is no overall survival advantage of the combination of lenvatinib and pembrolizumab over cabozantinib or the Ipilimumab and Nivolumab combination. Yet if we look at the 24 month survival rates 79.2% (2) of patients in the Lenvatinib and pembrolizumab arm are alive, compared to at 18 months follow up of Ipilimumab and Nivolumab the overall survival (3) was only 75% and with Cabozantinib it is less than 60% at 2 years with median overall survival being 26.6 months in the phase 2 Cabosun trial (4). The overall survival data for the favourable risk group remains limited by a low number of events.

It is noted on page 21 that there is a statistically significant improvement in response rate of the combination of lenvatanib and pembrolizumab vs ipilimumab and nivolumab but not against cabozantanib. This is despite an overall response rate of 70% and complete response rate of 16% compared to a response rate of 20% in the Cabosun trial (with no complete response rates in the first data cut).

On page 22 it is noted that there were more grade >3 toxicities in the lenvatinib and pembrolizumab group compared to cabozantanib. This needs to be considered within the context of the 20mg dose of lenvatanib that needed to be dose reduced in 69% of patients. It is accepted that with TKI treatment in general it is about finding the right dose that an individual patient can tolerate. Thus I would and thus more >grade 3 toxicities would be expected to be seen at a starting dose of 20mg.

On page 30 it is noted that European guidelines do not make specific recommendations regarding favourable risk disease. However in the most recent update of the ESMO guidelines (2021) three IO-TKI combinations (including lenvatinb and pembrolizumab) are recommended (Figure 1).

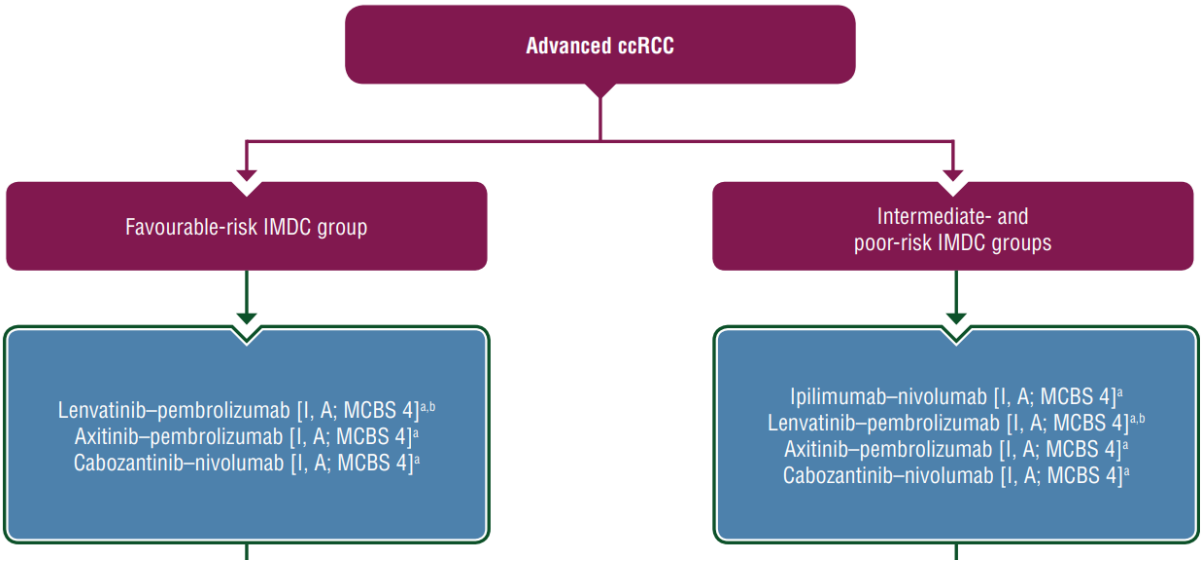

Figure 1: ESMO guidelines of first line treatment for advanced clear cell carcinoma (5)

On page 31 it is noted that pembrolizumab infusion is only 30 minutes (3 or 6 weekly) compared to 60 minutes 2 weekly for Avelumab, This has significant implications for patient's particularly in this time of Covid and post Covid where many cancer centres are struggling with treatment capacity and waiting lists and many patients are having delays to starting infusional treatments.

On page 33 it is rightly outlined that 5 reviews highlighted that combination treatments have statistically improved RR and PFS compared with the comparator sunitinib. In four further reviews the combination of lenvatinib and pembrolizumab ranked highest for overall survival. On page 33 there is a comment that the PD1 treatment Pembrolizumab was less well tolerated compared to other PD1 inhibitors. Having used pembrolizumab for a number of years in clinical practice this has certainly not been my experience.

On page 33 I note the compared PFS and OS for combination therapies versus sunitinib 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.
On page 33 I note the comment regarding favourable risk disease with improvement in PFS but not OS. This is very likely due to small number of events and improved later line therapies and I believe the OS advantage will be observed over the longer term.

As discussed on page 52 PFS was improved at all PFS landmarks. 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, PFS rates were higher in the lenvatinib plus pembrolizumab arm than in the sunitinib arm at 12, 18, 24 and 36 months. ‘
As discussed on page 52, all PFS subgroup analysis was statistically significantly in favour of the combination of lenvatinib and pembrolizumab.

On page 54 it is outlined that there were early survival differences between patients treated with lenvatinib plus pembrolizumab and those treated with sunitinib; OS rates at 12 months, 18 months, 24 months and 36 months were consistently higher for patients treated with lenvatinib plus pembrolizumab compared with patients treated with sunitinib. We know that with other comparator arms there is a numerically increased number of patients with primary progression compared to the combination of lenvatinib and pembrolizumab who as a result of this primary progression are not fit enough to receive a second line therapy. This improved early overall survival advantage and reduced primary progression is thus clinically meaninigful in my experience. With regard to overall survival in the favourable risk group, as discussed there has only been a limited number of events thus far 20/110 and 21/124 in terms of deaths in the lenvatinib plus pembrolizumab and sunitinib arms respectively).

When considering treatment beyond progression it is highlighted that nearly twice as many patients in the sunitinib arm received subsequent treatment. It is noted that up to 33 months there is OS benefit of the combination of lenvatinib and pembrolizumab. We know that there is a significant drop off rate between first and second line treatment and therefore patients who only receive single agent TKI in the first settling have a real possibility of not receiving an

immunotherapy agent for their advanced renal cancer and thus miss the opportunity of, in my opinion, the chance of being cured.

When considering subsequent treatment on page 54 we see that 42.6 % of patients in the sunitinib arm went on to receive nivolumab or another checkpoint inhibitor treatment which is likely to be part of the explanation for the later crossing of the OS curves. Similar trends are observed in the overall group, favourable risk and the intermediate/poor risk group.

On page 59 overall response rates and duration of response are discussed. Both of these as well as being statistically significant are extremely clinically significant and as end point is often the one most asked about by patients. The complete response rate of 16% is also clinically significant in my opinion and there is an increasing body of evidence that supports patients who have a deep partial or complete response have better outcomes (5).

Regarding safety on page 59, it is noted that more patients in the combination lenvatinib and pembrolizumab arm experienced adverse events. This is to be expected due to the starting dose of lenvatinib of 20mg. This safety data should however be considered in the context that median duration of treatment was longer in the lenvatinib plus pembrolizumab arm than in the sunitinib arm (17.0 months versus 7.8 months) despite the apparent toxicity.

On page 61 all grade AEs are outlined. The majority of these seen are driven by the TKI rather than the checkpoint inhibitor in my experience. MSD reported and higher than expected rate of hepatic AEs and certainly in clinical practice the rates I have seen across different tumour types are not usually this high. On page 63 side effects of special interest (AEOSIs) for pembrolizumab were experienced by 60.8% of patients in the lenvatinib plus pembrolizumab arm and 30.9% of patients in the sunitinib arm. The most common of which was hypothyroidism which in routine clinical management is normally relatively easy to manage with replacement levothyroxine.

In the quality of life data, discussed on page 64, lenvatinib and pembrolizumab resulted in higher physical functioning scores and lower fatigue, dyspnea and constipation scores than sunitinib. As reported by Motzer, 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. Statistically significant differences were also found in the median TuDD in favour of lenvatinib plus pembrolizumab versus sunitinib for all scales, except for the cognitive domain and financial difficulties symptom scales.

On page 66 the interpretation of evidence of the clear trial is outlined. I would agree completely that the trial was well designed and generalizable to clinical practice. Whilst only of one the comparators (sunitinib) was included in the clear trial. Similar efficacy end points in terms of PFS and response rates are seen with pazopanib and tivozanib in other trials. The PFS and RR improvements in the overall group, favourable and intermediate/poor risk are clinically meaningful for patients. The CLEAR trial the OS survival rates at 12 months, 18 months, 24 months and 36 months all favour lenvatinib plus pembrolizumab versus sunitinib. I would agree that the hazard ratio 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.

On page 80, Table 30 demonstrates impressive hazard ratios for PFS against all comparator arms (all hazard ratios below 1). Similar patterns are seen for overall survival in the all-risk group and poor/intermediate risk groups. 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).

On Page 82 response rates are discussed with 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). Whilst the confidence interval is wide in the latter group the response rates were 72% for lenvatinib and pembrolizumab in the intermediate/poor risk group and 20% in the cabozantanib group in

the Cabosun phase 2 trial. Similarly the combination of lenvatinib and pembrolizumab compares favourably when compared to ipilimumab and Nivolumab in poor/intermediate risk disease in CheckMate214 which had a response rate of 42%. Finally the complete response rate of 16% is superior numerically to any complete response rate seen for any of the comparator agents.

Summary

In summary, in my opinion the combination of lenvatinib and pembrolizumab represents a step change in advanced renal cancer. Never before have we seen PFS approaching 2 years a response rate of 70% and a complete response rate of 16%. If I was unfortunate enough to develop advanced renal cancer in 2022 this combination is the treatment I would want to receive. Whilst other TKI/IO combinations are not included here as comparators, they are included in national international guidelines such as ESMO and ASCO. Even with all these possible combinations considered (in addition to the comparators highlighted here) the improved endpoints of PFS, RR and complete response rate with the combination of lenvatinib and pembrolizumab are in my opinion both statistically significant and clinically meaningful.

My final concern is that with other combinations of IO/TKI available to patients in other devolved nations, we are at a real risk in England and Wales of providing inferior care and options to patients if this combination is not reimbursed and made available routinely in the NHS.

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AG response to consultation comments

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib plus pembrolizumab for untreated advanced renal cell carcinoma [ID3760]: A Multiple Technology Appraisal

AG response to company consultation comments

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 134985

Completed 4 July 2022

CONTAINS COMMERCIAL IN CONFIDENCE DATA (CiC)

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ALL TABLES IN THIS REPORT ARE CONFIDENTIAL

1 INTRODUCTION

During the consultation process, Eisai and MSD provided extensive comments relating to the MSD/AG model. The AG has produced revised cost effectiveness results in response to the two comments that relate specifically to AG modelling errors.

1.1 Errors identified by Eisai

In their response to consultation, Eisai identified two modelling errors:

- tivozanib engine for AE costs
- application of oral administration costs

1.1.1 Error in tivozanib engine for adverse event costs

Eisai correctly identified that the AG did not limit AE costs to the first cycle. The AG had implemented this amendment in the original MSD/AG model for all other treatments; therefore, only the costs of tivozanib will change with this correction.

1.1.2 Error in application of oral administration costs

Eisai correctly identified that there were errors in the AG application of oral administration costs. In response, the AG, has removed oral administration costs from the AG/MSD model. Revised results show that oral administration costs (inclusion or exclusion) have a minimal effect on AG base case ICERs per QALY gained.

1.2 Impact of the errors identified by Eisai on AG base case results

The impact of the two errors identified by Eisai on the AG base case cost effectiveness results is presented for each of the following groups: intermediate/poor risk subgroup, favourable risk subgroup and all-risk population in Table 1 to Table 8. The AG has presented pair-wise deterministic results generated using list prices for all drugs.

1.2.1 Intermediate/poor risk subgroup

The AE error does not apply to the intermediate/poor risk subgroup as tivozanib is not a relevant comparator for this population.

Table 1 Intermediate/poor risk subgroup: AG base case

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	4.933	[redacted]	-	-	-	-
CABO	[redacted]	4.080	[redacted]	[redacted]	0.852	[redacted]	£166,249
NIV+IPI	[redacted]	4.707	[redacted]	[redacted]	0.226	[redacted]	£133,362

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

Table 2 Intermediate/poor risk subgroup: **oral treatment administration costs removed from AG base case**

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	4.933	[redacted]	-	-	-	-
CABO	[redacted]	4.080	[redacted]	[redacted]	0.852	[redacted]	£161,714
NIV+IPI	[redacted]	4.707	[redacted]	[redacted]	0.226	[redacted]	£132,969

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

1.2.2 Favourable risk subgroup

Table 3 Favourable risk subgroup: AG base case

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	6.017	[redacted]	-	-	-	-
SUNITINIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	LEN+PEM is dominated
PAZOPANIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	
TIVOZANIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	

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

Table 4 Favourable risk subgroup: **one-off AE costs for tivozanib included in AG base case**

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	6.017	[redacted]	-	-	-	-
SUNITINIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	LEN+PEM is dominated
PAZOPANIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	
TIVOZANIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	

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

Table 5 Favourable risk subgroup: **oral treatment administration costs removed from AG base case**

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	6.017	[redacted]	-	-	-	-
SUNITINIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	LEN+PEM is dominated
PAZOPANIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	
TIVOZANIB	[redacted]	7.993	[redacted]	[redacted]	-1.976	[redacted]	

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

1.2.3 All-risk population

Table 6 All-risk population: AG base case

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	5.463	[redacted]	-	-	-	-
SUNITINIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,205,044
PAZOPANIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,167,492
TIVOZANIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,048,514

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

Table 7 All-risk population: **one-off AE costs for tivozanib included in AG base case**

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEN	[redacted]	5.463	[redacted]	-	-	-	-
SUNITINIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,205,044
PAZOPANIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,167,492
TIVOZANIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,051,199

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

Table 8 All-risk population: **oral treatment administration costs removed from AG base case**

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	5.463	[redacted]	-	-	-	-
SUNITINIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,151,860
PAZOPANIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£4,116,623
TIVOZANIB	[redacted]	5.419	[redacted]	[redacted]	0.043	[redacted]	£3,997,647

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

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

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
ID3760_LEN+PEM_RCC_company submission	1	Yes	10th Nov 2021

Contents

Tables and figures

Abbreviations

Acronym	Definition
AE	Adverse event
aRCC	Advanced renal cell carcinoma
BMI	Body mass index
BOR	Best overall response
CDF	Cancer Drugs Fund
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
EMA	European Medicines Agency
EORTC	European Organisation for the Research and Treatment of Cancer
EPAR	European public assessment report
EQ-5D-3L	EuroQoL 5 Dimension 3 Level version
FAS	Full analysis set
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms
HR	Hazard ratio
HRQoL	Health-related quality of life
IFN-γ	Interferon gamma
IIR	Independent imaging review
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immune-oncology
IPCW	Inverse probability of censoring weights (IPCW)
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LEN	Lenvatinib
LSM	Least squares mean
MHC	Major histocompatibility complex
MSKCC	Memorial Sloan Kettering Cancer Center
NHS	National Health Service
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

Acronym	Definition
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDGFRα	Platelet-derived growth factor receptor alpha
PEM	Pembrolizumab
PFS	Progression-free survival
PFS2	Progression-free survival during next-line therapy
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response
PS	Performance status
PY	Patient-year
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QD	Once daily
QLQ-C30	Quality of life questionnaire
QoL	Quality of life
QTc	Corrected QT interval
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RTK	Receptor tyrosine kinase
SD	Standard deviation
SoC	Standard-of-care
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
TTD	Time to treatment discontinuation
US	United States
VEGF	Vascular endothelial growth factor

1. Executive summary

Renal cell carcinoma (RCC) is the most common form of kidney cancer, representing around 85% of all cases. Each year, over 3,000 patients diagnosed with advanced stage kidney cancer in England

- Kidney cancer is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases (1)
- RCC is the most common subtype (2), and is responsible for up to 85% of all renal malignancies (3, 4)
- During 2018, 1,753 (21.9%) and 1,695 (21.2%) patients in England were diagnosed with Stage III or Stage IV kidney cancer, respectively (5)
- Kidney cancer is responsible for approximately 4,600 deaths annually (6)

Advanced RCC (aRCC) represents a substantial clinical, humanistic, and economic burden

- aRCC imposes a considerable burden on patients in terms of morbidity, health-related quality of life (HRQoL), and mortality
    - HRQoL for patients with aRCC is particularly impaired by disease-related symptoms, including fatigue, weakness, pain, constipation, diarrhoea, shortness of breath, and treatment-related adverse events (AEs) (7)
    - Patients with advanced or metastatic RCC have a poor prognostic outlook, with 5-year net survival rates of approximately 12% (6, 8, 9)
- RCC poses a significant economic burden, with the majority of costs associated with inpatient hospital care and prescriptions. The majority of patients with aRCC require hospitalisation and other types of healthcare resource usage following diagnosis (10, 11)
- Despite improved clinical outcomes with targeted therapies, most patients receive multiple lines of treatment due to disease progression or treatment-related toxicity (12), potentially increasing associated costs

There are currently no immune-oncology (IO) and tyrosine kinase inhibitor (TKI) combination therapies recommended by NICE for routine commissioning. An unmet need remains for treatments that improve progression-free survival (PFS) and overall survival (OS) beyond that currently obtained by standard-of-care (SoC) therapy

- Systemic therapy has improved clinical outcomes for patients with aRCC, however median PFS rates are varied (e.g. 7.2–22.6 months with first-line sunitinib (13, 14))
- Furthermore, there remains a challenge in overcoming innate and acquired resistance mechanisms to monotherapy (15-17). The use of combination therapies to simultaneously target multiple pro-tumourigenic signalling pathways may overcome such resistance mechanisms which greatly impact response to therapy
- Avelumab plus axitinib has been recommended as a treatment option for advanced RCC in the Cancer Drugs Fund (CDF)

Lenvatinib + pembrolizumab (LEN+PEM) is indicated for [redacted]

- MHRA approval is anticipated in [redacted]
- European CHMP positive opinion was received on the 14th October 2021 (18)
- LEN 20 mg will be administered orally, once daily; PEM will be administered intravenously (IV) at 200 mg every 3 weeks or 400 mg every 6 weeks

LEN+PEM was investigated as a first-line therapy in the Phase 3 clinical study CLEAR. The combination demonstrated statistically significant and clinically meaningful improvements in PFS, OS and in objective response rate (ORR) vs sunitinib. Approximately four-times the number of patients achieved complete response (CR) in the LEN+PEM arm vs sunitinib

- The CLEAR study met its primary efficacy endpoint, with LEN+PEM providing a statistically significant improvement in PFS vs sunitinib

- Median PFS: 23.9 months vs 9.2 months; hazard ratio (HR): 0.39 (95% CI: 0.32, 0.49); p<0.001

- LEN+PEM showed statistically significant improvements in OS and ORR vs sunitinib
  - OS at the time of final PFS analysis; data-cut 28th August 2020; HR: 0.66 (95% CI: 0.49, 0.88); p=0.005; median OS not reached in either treatment arm
  - Updated OS data; data-cut 31st March 2021; HR: 0.72 (0.55, 0.93); median OS not reached in either treatment arm
  - ORR: 71.0% in the LEN+PEM arm vs 36.1% in the sunitinib arm; [redacted]
  - The proportion of patients who achieved a confirmed CR with LEN+PEM was approximately four-times of that observed in the sunitinib arm (16.1% and 4.2%, respectively)
  - Progressive disease was observed in 5.4% of patients treated with LEN+PEM compared with 14.0% of patients treated with sunitinib
- [redacted]

LEN+PEM was generally well-tolerated in patients with aRCC

- The safety profile of LEN+PEM was generally consistent with established safety profiles of LEN and PEM when used as monotherapies, and AEs were effectively managed with standard medical care or dose modification
- The most common treatment-emergent AEs (TEAEs; >30% of patients) in the LEN+PEM arm were diarrhoea, hypertension, hypothyroidism, decreased appetite, fatigue, nausea, and stomatitis
- Additional network meta-analyses (NMA) suggest that LEN+PEM generally outperforms comparators relevant in England and Wales with regard to survival and response

- LEN+PEM generally outperformed sunitinib, pazopanib, and cabozantinib (intermediate/poor risk only) on survival endpoints (OS, PFS) and response endpoints (ORR, CR)

LEN+PEM, has the potential to be cost-effective as a first-line therapy in patients with aRCC

- A cost-utility analysis with a 40-year time horizon was conducted to evaluate the cost-effectiveness of LEN+PEM vs current comparators in England
- In the base-case analysis of all patients with aRCC, LEN+PEM was associated with an incremental cost-effectiveness ratio (ICER) of £118,286 per quality adjusted life year (QALY) gained vs sunitinib, £115,303 per QALY gained vs pazopanib, and £128,671 per QALY gained vs tivozanib
- In subgroup analyses of intermediate and poor risk patients with aRCC, LEN+PEM was associated with an ICER of £110,075 per QALY gained vs cabozantinib

2. The technology

2.1. Decision problem

This submission covers the technology's full marketing authorisation for this indication. The company submission is generally consistent with the NICE scope (19) and the NICE reference case (20). The population, comparators, and outcomes are in line with the final NICE scope. Differences in the intervention, and subgroups are outlined in Table 1.

This submission focusses on the combination of lenvatinib and pembrolizumab (LEM+PEM) for the first-line treatment of adults with aRCC (18). Reimbursement is not being sought for LEN plus everolimus in this submission.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	• Lenvatinib with everolimus • Lenvatinib with pembrolizumab	Lenvatinib with pembrolizumab (LEN+PEM)	Evidence for lenvatinib with everolimus has not been submitted for regulatory approval, and therefore should not be considered within this submission
Comparator(s)	• Pazopanib • Sunitinib • Tivozanib • Cabozantinib (only for intermediate or poor risk disease as defined in the IMDC criteria) • Nivolumab with ipilimumab (only for intermediate or poor risk disease as defined in the IMDC criteria); subject to ongoing CDF review	All comparators are addressed as per scope, apart from nivolumab with ipilimumab	The list of comparators reflects the standard options for first line treatment in the NHS. Nivolumab + ipilimumab is currently included within the CDF, but its inclusion is due to be reviewed after the data collection period ends in August 2021 (21). Under the current NICE process this would not be considered a comparator unless routinely commissioned prior to the start of this appraisal
Subgroups to be considered	N/A	IMDC intermediate/poor risk subgroup	Separate consideration for the IMDC intermediate-/poor risk subgroups would be applicable for the comparison with cabozantinib only

Abbreviations: CDF, cancer drugs fund; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; LEN, lenvatinib; N/A, not applicable; NICE, National Institute for Health and Care Excellence; PEM, pembrolizumab.

2.2. Description of the technology being appraised

The summary of product characteristics (SmPC) is presented in Appendix C.

Table 2 summarises the technology being appraised in this submission.

Table 2: Technology being appraised

UK approved name and brand name	Lenvatinib (Kisplyx®) with pembrolizumab (Keytruda®)

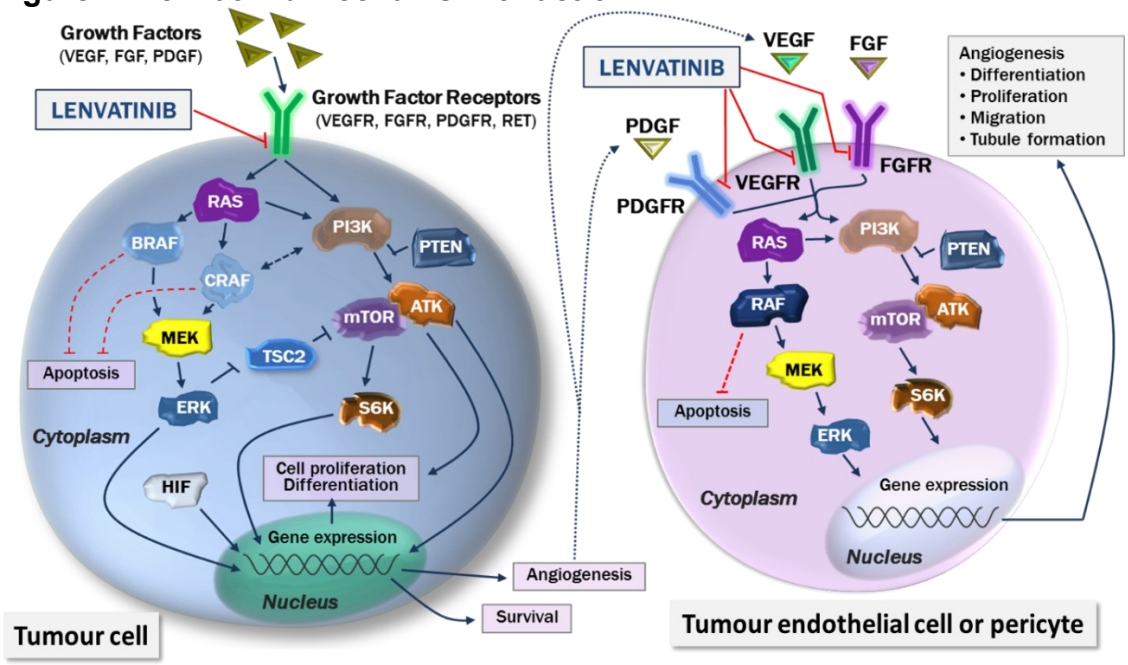
Marketing authorisation/CE mark status	European CHMP positive opinion was received on 14th October 2021 (18) LEN+PEM does not currently have marketing authorisation in the UK for untreated aRCC. UK approval is anticipated in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The LEN+PEM indication for this submission is [redacted] In addition, LEN (Kisplyx®) is currently licensed for the following indication (22): • in combination with everolimus for the treatment of adult patients with aRCC following one prior VEGF-targeted therapy
Method of administration and dosage	• LEN 20 mg is administered orally, once daily • PEM is administered IV, at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks (up to a maximum duration of 2 years)
Additional tests or investigations	None
List price and average cost of a course of treatment	• LEN: 4 mg or 10 mg tablets, £1,437.00 for 30 tablets PEM: 100 mg, £2,630.00 for 1 vial • Cost per treatment cycle: £[redacted] • Average cost of a course of treatment: £[redacted]†
Patient access scheme (if applicable)	LEN is subject to a PAS discount of [redacted]: 4 mg or 10 mg tablets, £[redacted] for 30 tablets PEM is subject to a commercial access agreement, but this information is CiC

†Cost per course assuming time to discontinuation as in the cost-effectiveness model.
Abbreviations: aRCC; advanced renal cell carcinoma; CiC, commercial in confidence; IV, intravenous; LEN, lenvatinib; PAS, patient access scheme; PEM, pembrolizumab; UK, United Kingdom; VEGF, vascular endothelial growth factor.

2.2.1. Lenvatinib

Lenvatinib is a novel multiple receptor tyrosine kinase (RTK) inhibitor which harnesses a distinct binding mechanism to selectively inhibit the kinase activity of vascular endothelial growth factor receptors 1–3 (VEGFR1–3), in addition to other proangiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor receptors 1–4 (FGFR1–4), platelet-derived growth factor receptor alpha (PDGFRα), KIT proto-oncogene, and rearranged during transfection proto-oncogene (RET) (23, 24).

Figure 1: Lenvatinib mechanism-of-action



Adapted from: Andrae et al., 2008; de Groot et al., 2006; Matsui et al., 2008a; Matsui et al., 2008b; Turner et al., 2010 and Folkman 2002 (24-29).

2.2.2. Pembrolizumab

Pembrolizumab is a monoclonal, humanised IgG4 antibody which binds to and inhibits programmed cell-death protein 1 (PD-1), a cell surface receptor which, along with its cognate ligands (programme cell-death ligand 1 and -2; PD-L1 and PD-L2), serves as a negative regulator of T-cells to control local inflammatory responses and maintain self-tolerance (30). PD-L1 is upregulated in a number of malignancies in response to interferon-gamma (IFN-γ) signalling, and other inflammatory mediators (e.g. VEGF (31)), and may also ligate to cluster of differentiation protein 80 (CD80) on activated T-cells (30, 32, 33).

Tumour cells can display antigens on their cell surface, which may be recognised by host T-cells. When tumours adopt the PD-1/PD-L1 immunomodulatory checkpoint, an imbalance between tumour growth and host surveillance occurs (30), allowing tumour cells to evade the immune system by impeding T-cell response (34). Pembrolizumab restores the T-cell mediated immune response against tumour cells (35, 36), and has demonstrated efficacy in improving ORRs and/or PFS in a number of malignancies, including non-small cell lung cancer (37), melanoma (38), Hodgkin's lymphoma (39), breast (40-42), urothelial (43) and gastric cancer (44).

2.2.3. Lenvatinib plus pembrolizumab (LEN+PEM)

Preclinical studies provide a rationale for the complementary mechanisms of VEGF inhibition and PD-1 blockade. VEGF inhibitors, such as lenvatinib, decrease the population of immunosuppressive tumour-associated macrophages (TAMs), leading to higher levels of interferon gamma (IFN-γ) and an increase in IFN-γ^+ cytotoxic ($CD8^+$) T-cells (45). IFN-γ-mediated signalling activates an immunostimulatory tumour microenvironment via increased expression of β2-microglobulin, chemokines, major histocompatibility complex (MHC), and PD-L1, which collectively act to increase tumour cell antigen presentation, immune cell recruitment, and antitumor effects (46, 47). Within the tumour microenvironment, FGFR signalling suppresses the immunostimulatory outcomes of IFN-γ signalling, leading to reduction of these downstream anti-tumour effects (45-48).

Lenvatinib also acts as an FGFR inhibitor, which restores the immunostimulatory effects of IFN-γ; however, increased PD-L1 expression resulting from IFN-γ signalling may lead to PD-1/PD-L1-mediated T-cell exhaustion, providing a potential tumour escape route (45-48). Pairing lenvatinib with an anti-PD-1 antibody results in simultaneous inhibition of three key signalling pathways (VEGF, FGF, and PD-1), inducing immunostimulatory IFN-y signalling effects while blocking the PD-1/PD-L1 escape mechanism (45, 46, 49-51). In syngeneic murine tumour models, lenvatinib combined with an anti-PD-1 monoclonal antibody decreased the TAM population, increased activated cytotoxic T cells, and demonstrated greater anti-tumour activity compared with either drug alone (45). Pembrolizumab, as described in Section 2.2.2, is an anti-PD-1 monoclonal antibody which blocks the interaction between the PD-1 receptor and its ligands, thereby releasing the natural break on the immune system (52).

The early Phase 1b/2 clinical study (Study 111/KEYNOTE-146; NCT02501096) demonstrated the benefit of LEN+PEM in patients with advanced or metastatic RCC; treatment with LEN+PEM resulted in notable and durable tumour reductions and had a manageable safety profile (53, 54).

2.3. Innovation

At present, there are no IO+TKI combinations available for routine reimbursement in the treatment of first-line aRCC in England and Wales. Currently, avelumab plus axitinib is available through the Cancer Drugs Fund, while the immune-oncology combination therapy nivolumab plus ipilimumab is indicated for patients who are intermediate or poor risk only (available through the Cancer Drugs Fund).

As discussed in Section 2.2.3, the unique combination of LEN+PEM amalgamates PD-1 and VEGF signalling inhibition to impede pro-angiogenic and pro-tumourigenic signalling and enhance anti-tumour activity (45). 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(55).

The LEN+PEM treatment regimen offers convenient dosing and administration, with the option for less frequent infusion visits vs many comparator therapies. During treatment with LEN+PEM, pembrolizumab is administered as a 30-minute intravenous (IV) infusion at an interval of either once every 3 weeks (200 mg dose) or once every 6 weeks (400 mg dose) (56, 57). Treatment schedules for the IV-administered components of other key combination therapies may be less convenient for the patient compared with pembrolizumab, including 60-minute infusions administered once every 2 weeks for avelumab, and 30- or 60-minute infusions of nivolumab administered once every 2 to 4 weeks depending on the treatment phase and dose level (58-61). Furthermore, the oral route of administration for lenvatinib is likely to be preferable for patients. Lenvatinib can be taken with or without food, and patients can ingest the capsule(s) dissolved in a glass of water or apple juice (22). In comparison, both cabozantinib and axitinib must be swallowed whole, and cabozantinib must be administered after a ≥2 hour fast (62-65).

3. Health condition and position of the technology in the treatment pathway

Kidney cancer is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases (1). RCC is the most common subtype of kidney cancer, arising from the parenchyma/cortex of the kidney (2), and is responsible for up to 85% of all renal malignancies (3, 4). When diagnosed at its earliest stage (Stage I), approximately 87% of patients will survive for 5 years or more, compared with an approximate 12% 5-year survival rate for those who are diagnosed with advanced stage disease (6, 8, 9).

3.1. Epidemiology

Approximately 13,100 new cases of kidney cancer are diagnosed annually in the UK (1). Kidney cancer is the 14th most common cause of cancer-related death in UK females and the 10th most common cause of cancer-related death in UK males, and is responsible for approximately 4,600 deaths annually (6). Risk factors for RCC include older age, smoking, obesity and hypertension (4).

During 2018, 1,753 (21.9%) and 1,695 (21.2%) patients in England were diagnosed with Stage III or Stage IV kidney cancer, respectively (5).

3.1.1. Prognostic classification system

While staging of RCC (e.g. Tumour, Node, Metastasis [TNM] classification) is an important factor in determining prognosis, other factors are considered which are not only indicative of prognosis, but guide treatment. The two systems commonly used are the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (66). 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 systems use 5-6 factors which categorise patients into favourable, intermediate or poor risk prognostic groups (4) (Table 3).

Table 3: Summary of MSKCC and IMDC prognostic criteria

Prognostic criteria	MSKCC (66, 67)	IMDC (4)
Serum haemoglobin below lower limit of normal	✓	✓
High corrected serum calcium (>10 mg/dL)	✓	✓
High blood lactate dehydrogenase (>1.5x upper limit of normal)	✓	×
Platelets greater than the upper limit of normal	×	✓
Neutrophils greater than the upper limit of normal	×	✓
Time from diagnosis to need for systemic treatment <1 year	✓	✓
Karnofsky performance status (PS) <80%	✓	✓

Adapted from: Escudier et al, 2019 (4), Kidney Cancer: Early Detection, Diagnosis and Staging" from the American Cancer Society (66), and Motzer et al, 1999 (67).

For each system, patients who do not harbour any of the factors presented in Table 3 are considered to be low risk and therefore have a good prognosis. Patients with one-two factors are considered intermediate risk, while patients with three or more factors are considered high risk, have poor prognosis and are less likely to benefit from systemic therapy (66). A summary of OS estimates for MSKCC and IMDC risk groups in first-line and second-line metastatic RCC are presented in Table 4 and Table 5, respectively.

Table 4: Median OS estimates in first-line and previously treated metastatic RCC according to MSKCC risk groups

		Median OS (Months)	
No. of risk factors	Risk category	First-line (N=353) (68)	Treated[†] (N=234) (69)
0	Favourable	28.6	91.0
1–2	Intermediate	14.6	33.6
3–5	Poor	4.5	15.2

[†]Patients treated with first-, second- or third-line therapy.
Adapted from: Mekhail et al, 2005 (68) and Tamada et al, 2018 (69).
Abbreviations: OS, overall survival.

Table 5: Median OS estimates in first- and second-line metastatic RCC according to IMDC risk groups

		Median OS (Months)	
No. of risk factors	Risk category	First-line (N=1,028) (70)	Second-line (N=1,021) (71)
0	Favourable	43.2	35.3
1–2	Intermediate	22.5	16.6
3–6	Poor	7.8	5.4

Adapted from: MDCalc, IMDC Risk Model (72), Heng et al, 2013 (70), and Ko et al., 2015 (71).
Abbreviations: OS, overall survival.

3.2. Disease burden

3.2.1. Clinical burden

Advanced RCC imposes a considerable burden on patients in terms of morbidity, HRQoL, and mortality. While prognosis for early-stage disease is favourable, patients with RCC often display few, if any, signs or symptoms, which can result in delayed diagnosis and more time for the disease to advance before detection. Patients with advanced or metastatic RCC have a poor prognostic outlook, with 5-year net survival rates of approximately 12% (6, 8, 9).

The most common presenting symptoms of aRCC are haematuria, a palpable mass in the flank or abdomen, and abdominal pain. Other, non-specific symptoms include fever, night sweats, malaise (nausea) and weight loss. Although rare, some patients may experience symptoms of metastatic disease, such as bone pain or respiratory problems (2, 73).

3.2.2. Humanistic burden

HRQoL for patients with aRCC is particularly impaired by disease-related symptoms, including fatigue, weakness, pain, constipation, diarrhoea, shortness of breath, and treatment-related adverse events (AEs) (7). For patients with aRCC, treatment is usually palliative with the intent to relieve tumour burden and extend survival, thus patients continually balance quality with quantity of life (74). HRQoL typically declines when patients with aRCC experience disease progression (75, 76). For patients with metastatic RCC, the presence of symptoms and the application of radiotherapy are associated with lower EQ-5D utilities (77), which measure HRQoL to determine the clinical and economic benefits of an intervention. Advanced RCC can also have an impact on the quality-of-life (QoL) of family and friends, particularly if they are providing informal care for the patient.

3.2.3. Economic burden

The majority of costs associated with RCC are related to inpatient hospital care, accounting for 70–80% of total costs (78). At present, UK cost or healthcare resource use data are not available for RCC. However, in 2019–2020, there were 22,987 finished consultant episodes (FCE), 19,744 hospital admissions, and 51,971

FCE bed days within National Health Service (NHS) England for patients with malignant neoplasm of the kidney (excluding renal pelvis) (79).

Despite improved clinical outcomes with targeted therapies, most patients receive multiples lines of therapy due to disease progression or treatment-related toxicity (12), potentially increasing associated costs. Management of treatment-related AEs contributes to the cost burden of RCC, with the most costly AEs including dyspnoea and nausea/vomiting (80). RCC is also associated with a number of indirect costs, particularly from informal carers who spend a significant portion of their time in supporting patients with RCC (81), resulting in reduced productivity and time at work.

Although UK-specific data are not available, studies from France and Greece estimated the total direct cost of first-line treatment to be €19,132–€39,843 per patient (82-84). In Europe, the main cost drivers were outpatient pharmacy costs, oral targeted therapy, and inpatient/hospitalisation costs (11, 82, 85). A study based in Denmark estimated indirect costs, including age pension, early retirement and sick pay to cost €8,851 per patient, per year (86). In a US study, informal carers spent an average of 11.4 months providing care to patients with kidney cancer. The average cost of informal carer time over 2 years following diagnosis was $53,541 (81).

3.3. Current clinical practice & guidelines

Approximately 40% of patients with localised RCC will develop metastatic lesions following surgical resection. Furthermore, between 20–30% of patients present with aRCC during initial diagnosis. The goals of treatment are to extend life and delay disease progression for patients with aRCC, however, improving HRQoL by relieving symptoms and tumour burden is an important clinical outcome for patients (87).

Advanced RCC is largely resistant to chemotherapy and radiotherapy, and therefore, first-line treatment of aRCC consists of targeted systemic therapy, immunotherapy or a combination of both. Patients with metastatic RCC may receive surgery to alleviate tumour burden or to remove metastatic lesions, which may or may not be in addition to drug therapy (4).

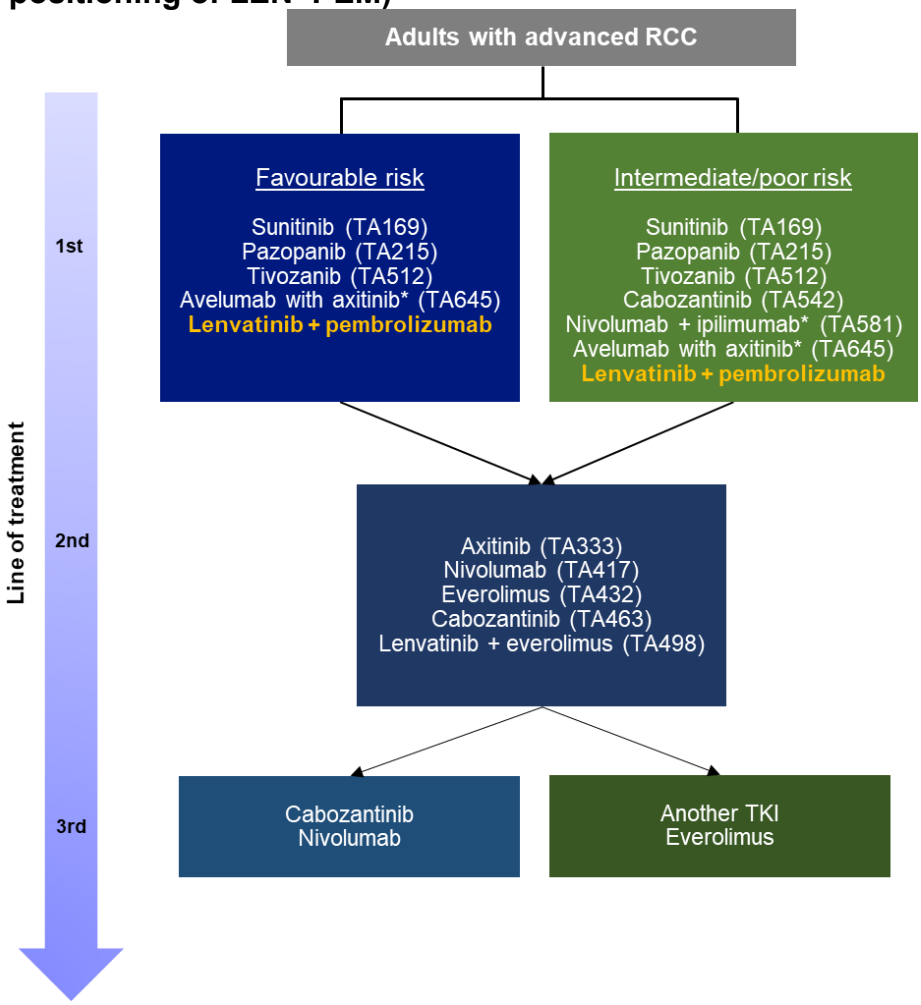
In England, NICE recommends sunitinib (TA169) (88), pazopanib (TA215) (89) and tivozanib (TA512) (90) for the first-line treatment of aRCC. Avelumab with axitinib is

recommended for use within the Cancer Drugs Fund (CDF), conditional on the adherence of a managed access agreement (91), while nivolumab with ipilimumab (within the CDF) (21), and cabozantinib (92) are recommended for adults with untreated RCC that is intermediate- or poor-risk, as defined by the IMDC prognostic criteria.

3.4. Clinical pathway of care

The clinical pathway of care (including the proposed positioning of LEN+PEM) for managing untreated aRCC is presented in Figure 2.

Figure 2: Clinical pathway of care for managing untreated aRCC (including proposed positioning of LEN+PEM)



Risk groups are based on IMDC criteria.
*at the time of submission, avelumab with axitinib and nivolumab with ipilimumab were recommended for use within the Cancer Drugs Fund, subject to the conditions within a managed access agreement (21, 91).
Abbreviations: RCC, renal cell carcinoma.

3.5. Unmet need and place for LEN+PEM in first-line aRCC

Historically, first-line treatment for advanced or metastatic RCC has consisted of VEGF-targeted monotherapy, resulting in suboptimal outcomes due to limited response and progression following development of drug resistance (93-97). Over the last two decades, a number of TKIs and novel immune checkpoint inhibitors (e.g. PD-1/PD-L1 inhibitors) which target multiple pro-tumourigenic signalling pathways have been developed (15). While immune-oncology based combinations demonstrate improved efficacy vs VEGF-targeted monotherapy, they provide ~2.5 years OS and ~1 year PFS (93, 98, 99), while overall response rates remain ≤60% (95, 96, 100-105). Furthermore, there remains a challenge in overcoming innate and acquired resistance mechanisms to monotherapy (15-17). Therefore, despite recent advances, there remains an unmet need for improved clinical outcomes.

Mechanisms of immune evasion, i.e. evading the immune system's ability to recognise and reject tumour cells, are common in many different types of cancer, including RCC (106). However, the immune system is not always adequately primed to attack and eliminate tumour cells (107). Often dysregulated in malignancy, the PD-1/PD-L1 axis is a negative regulator of T-cell immunity, inhibiting T-cell activation and thus contributing to evasion of the anti-tumour immune response (108, 109). Pembrolizumab disrupts this PD-1-mediated inhibition of T-cell immunity; encouraging the immune system to identify and eradicate tumour cells.

As previously discussed (Section 2.2), lenvatinib has demonstrated immunomodulatory effects in preclinical models, increasing tumour infiltration of CD8+ T-cells and decreasing TAM population within the tumour microenvironment (45). Together, LEN+PEM impede oncogenic molecular signalling pathways (e.g. angiogenesis via excessive VEGF and FGF signalling), and immune inhibitory signalling via PD-1 (110), and thereby offer complimentary modulation of different aspects of tumour immunobiology to potentially increase response to therapy or overcome resistance mechanisms and offer improved efficacy in RCC.

Currently, there are no IO therapeutic combinations recommended for routine reimbursement for the treatment of aRCC. A combination of LEN+PEM offers

convenient dosing and administration, offering less frequent infusion visits (for pembrolizumab) vs many other comparator therapies for aRCC. LEN is administered orally, once daily, while pembrolizumab can be administered intravenously every 3 or 6 weeks, allowing for fewer outpatient visits.

4. Clinical effectiveness

4.1. Identification and selection of relevant studies

A systematic literature review (SLR) (111) was conducted to identify clinical evidence for first-line treatments for aRCC. The original search was conducted on 27th March 2019, with updates performed on 1st September 2020, 5th January 2021, and 4th June 2021. In total, nine studies (26 publications) were deemed relevant to the NICE decision problem and included in the NMA (Table 6). Further details on SLR methodology, and quality assessments are available in Appendix D.

Table 6: RCTs identified by the clinical effectiveness SLR relevant to the NICE decision problem

Study	Treatment
CABOSUN (97, 98, 112-115)	Cabozantinib Sunitinib
CLEAR (116-118)	LEN + everolimus LEN+PEM Sunitinib
COMPARZ (99, 119-121)	Pazopanib Sunitinib
CROSS-J-RCC (122-124)	Sunitinib (followed by sorafenib†) Sorafenib (followed by sunitinib†)
Escudier, 2009 (125-128)	IFN alfa-2a Sorafenib
Motzer, 2007 (93, 129, 130)	Sunitinib IFN alfa-2a
SWITCH (131)	Sorafenib (followed by sunitinib†) Sunitinib (followed by sorafenib†)
SWITCH II (132)	Sorafenib (followed by pazopanib†) Pazopanib (followed by sorafenib†)
TIVO-1 (133)	Tivozanib Sorafenib

†Even though the protocol defined a specific second-line treatment for these studies, only data from the first-line phase of treatment has been collected in this review.
Abbreviations: IFN, interferon; IL-2, interleukin-2; RCT, randomised controlled trial.

4.2. Relevant clinical effectiveness evidence

The Phase 3 clinical trial, CLEAR (Study 307/KEYNOTE-581; Table 7) provides the clinical evidence and is used in the economic model for LEN+PEM for the first-line treatment of aRCC. Data presented for CLEAR is sourced from Motzer et al, 2021 (118), supplemented with data from the clinical study report (134), an updated OS analysis report (data cut: 31st March 2021) and conference poster presented at KCRS 2021 (135, 136), and an OS adjustment report (137).

Table 7: Clinical effectiveness evidence (CLEAR)

Study title	A multicentre, open-label, randomised, Phase 3 trial to compare the efficacy and safety of LEN in combination with everolimus or PEM vs sunitinib alone in first-line treatment of subjects with aRCC (CLEAR)				
Study design	Phase 3, multicentre, randomised (1:1:1), open-label study				
Population	Adults ≥18 years of age with aRCC without any previous systemic anti-cancer therapy				
Intervention(s)	LEN 20 mg QD + PEM 200 mg Q3W during a 21-day cycle				
Comparator(s)	Sunitinib 50 mg QD, 4 weeks on, 2 weeks off				
Indicate if trial supports application for marketing authorisation	**Yes**	✓	Indicate if trial used in the economic model	**Yes**	✓
	No			**No**	
Rationale for use/non-use in the model	CLEAR is the pivotal RCT in this indication				
Reported outcomes specified in the decision problem	• **PFS** • **OS** • Response rates • **Adverse effects of treatment** • **HRQoL**				
All other reported outcomes	• Duration of response (DOR) • Disease control rate (DCR) • Clinical benefit rate (CBR)				

Outcomes in **bold** are incorporated into the economic model.
Abbreviations: aRCC, advanced renal cell carcinoma; HRQoL, health-related quality of life; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; Q3W, every 3 weeks; QD, once daily; RCT, randomised controlled trial.

4.3. Summary of methodology of the relevant clinical effectiveness evidence

A summary of the study aim and methodology is presented in Table 8.

Table 8: Summary of CLEAR methodology

Study	CLEAR (Study 307/KEYNOTE-581; NCT02811861)
Trial design	Phase 3, randomised, open-label, multicentre, active-controlled study
Aim	To assess and compare the efficacy and safety of LEN in combination with PEM or everolimus vs sunitinib as first-line treatment in patients with aRCC *Note: data from the LEN + everolimus treatment arm is not included in this submission*
Key inclusion criteria	• Adults ≥18 years at time of informed consent • Histological or cytological confirmation of RCC with a clear-cell component • Documented evidence of aRCC • ≥1 measurable target lesion according to RECIST 1.1 • Adequate liver, bone marrow, blood coagulation, and renal function • KPS ≥70 • Adequately controlled blood pressure with or without antihypertensive medications
Key exclusion criteria	• Any systemic anti-cancer therapy for RCC, including PD-1/PD-L1 inhibitor treatment, or adjuvant treatment • Presence of significant cardiac impairment ≤12 months • History of or current non-infectious pneumonitis which required steroid treatment • History of organ allograft • Positive for HIV, hepatitis B or hepatitis C • Presence of CNS metastases, unless patient has completed local therapy (e.g. whole brain radiation therapy, surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for ≥4 weeks before study treatment
Settings and locations where the data were collected	Data were collected globally at 181 sites in 20 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Japan, Korea, Poland, Russia, Spain, Switzerland, The Netherlands, UK and the USA UK data comes from 8 sites (26 patients)
Trial drugs (the interventions for each group with sufficient details to allow replications, including how and when they were administered) Intervention(s), n; comparator(s), n	**Intervention:** combination of LEN 20 mg QD, every 21-day cycle, plus PEM 200 mg administered Q3W, N=355 **Comparator:** sunitinib 50 mg QD for 4 weeks, followed by 2 weeks off (schedule 4/2), N=357 Both LEN and sunitinib were administered orally, while PEM was administered intravenously
Randomisation	• 1069 patients were randomised 1:1:1 • Stratified according to MSKCC risk group (favourable, intermediate or poor), and geographic region (Western Europe/North America vs rest of the world)

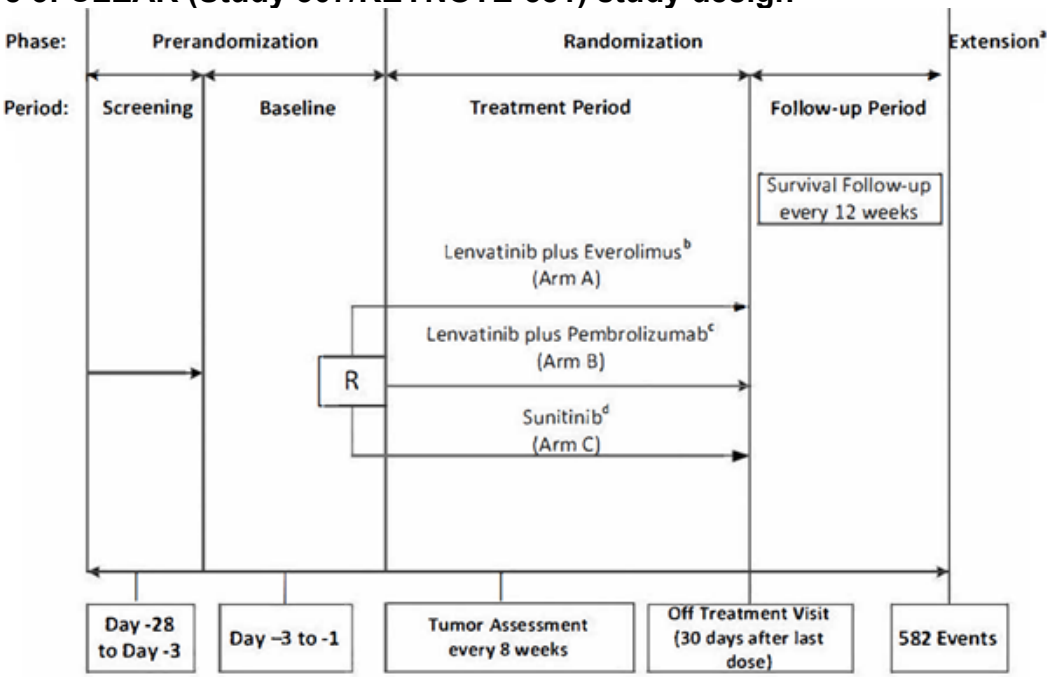
Permitted and disallowed concomitant medication	**Permitted:** • Physiologic doses of corticosteroids (e.g. >10 mg/day of prednisone or equivalent) • Inhaled steroids for management of asthma or seasonal allergies • Thyroid hormone suppressive therapy • Adjuvant hormonal therapy for history of definitely treated breast or prostate cancer • Anticoagulants including low molecular weight heparin, warfarin, and anti-Xa agents • Anti-inflammatory drugs • Antihypertensive therapy, including antihypertensive treatment as appropriate of BP increases once patient was enrolled • Palliative radiotherapy of up to two painful, pre-existing, non-target bone metastases • Surgery. If patient was receiving LEN and required surgery during the study, the stop time and restart time of LEN was: o For minor procedures: stop LEN ≥2 days before the procedure and restart ≥2 days after, once there is evidence of adequate healing and no risk of bleeding o For major procedures: stop LEN ≥1 week (5 half-lives) prior to surgery and then restart ≥1 week after, once there is evidence of adequate healing and no risk of bleeding
	Prohibited: • Concurrent anti-cancer therapies, e.g. TKIs, chemotherapy, anti-tumour interventions, cancer immunotherapy or radiotherapy (except for palliative radiotherapy for up to two painful, pre-existing, non-target bone metastases) • Other concurrent investigational drugs • Live vaccinations • Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that was suspected to have immunologic aetiology
Primary endpoint	PFS by IIR per (RECIST 1.1)
Key additional endpoints	Key secondary endpoints: • OS • ORR by IIR using RECIST 1.1 • Other secondary endpoints: • PFS based on investigator assessment per RECIST 1.1 • PFS on next-line of therapy (PFS2) as reported by investigator • HRQoL assessed using FKSI-DRS, EORTC-QLQ-C30, and EQ-5D-3L

	• Exploratory endpoints: • DOR by IIR and investigator assessment using RECIST 1.1 • ORR by investigator assessment using RECIST 1.1 • DCR (complete response [CR], partial response [PR] or stable disease) by IIR and investigator assessment using RECIST 1.1 • CBR (CR, PR, stable disease) by IIR and investigator assessment using RECIST 1.1 • Safety • TEAEs
Pre-planned subgroups	Planned subgroup analyses for efficacy endpoints (PFS, OS and ORR) were performed for the following subgroups: • Age group (<65 years or ≥65 years) • Sex (male or female) • Race (White, Asian, all others) • Geographic region per IxRS (West Europe, North America, Rest of World) • MSKCC risk group per IxRS • IMDC risk group • KPS score group • Baseline bone metastasis • Baseline liver metastasis • Baseline lung metastasis • PD-L1 status • Prior nephrectomy • Histologic clear cell component with sarcomatoid features

Abbreviations: AE, adverse event; aRCC, advanced renal cell carcinoma; BP, blood pressure; CBR, clinical benefit rate; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECG, electrocardiogram; EQ-5D-5L, Euro-QoL 5 Dimension 3 Level version; EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IIR, independent imaging review; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IxRS, interactive voice and web response system; KPS, Karnofsky Performance Status; LEN, lenvatinib; LVEF, left ventricular ejection fraction; MSKCC, Memorial Sloan-Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PEM, pembrolizumab; PFS, progression-free survival; QD, once daily; Q3W, every 3 weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours; TEAE, treatment-emergent adverse event; UK, United Kingdom; USA, United States of America.

CLEAR is comprised of three phases; a pre-randomisation phase, randomisation phase, and extension phase (Figure 3).

Figure 3: CLEAR (Study 307/KEYNOTE-581) study design



[a]Extension phase includes a treatment and follow-up period. All patients still on treatment at the end of the randomisation phase will enter the extension phase and continue to receive the same study treatment they received in the randomisation phase; [b]Lenvatinib 18 mg plus everolimus 5 mg given orally once daily; [c]Lenvatinib 20 mg once daily plus pembrolizumab 200 mg intravenously every 3 weeks; [d]Sunitinib 50 mg once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).
NOTE: The lenvatinib + everolimus treatment arm is excluded from this submission.
Abbreviation: R, randomisation.

During the follow-up period, patients were treated by the investigator according to the prevailing local standard-of-care. Patients were followed every 12 weeks (±1 week) for PFS during next-line therapy (PFS2), survival, and all subsequent anti-cancer treatments received. Patients who discontinued study treatment before disease progression continued to undergo tumour assessments every 8 weeks, and a bone scan every 24 weeks in the follow-up period until disease progression was documented and confirmed by IIR or a new anti-cancer therapy was initiated, unless the patient withdrew consent or was lost to follow-up.

All patients who were still receiving study treatment or who were in the follow-up phase by the 28th August 2020 (final PFS analysis) entered the extension phase.

4.4. Statistical analysis and analysis populations

The following analysis populations were utilised in CLEAR:

- Full analysis set (FAS): All randomised patients regardless of the treatment actually received. This was the primary analysis population used for all efficacy analyses, which was based on the intention-to-treat principle

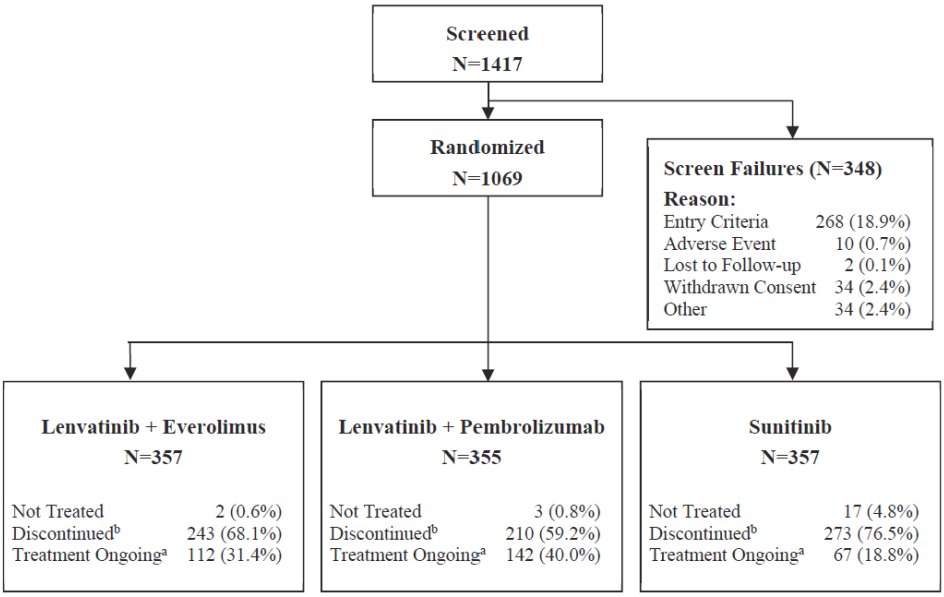
- Safety analysis set: Used for all safety analyses, and comprised all patients who received at least one dose of any study drug
- Per protocol (PP) analysis set: All patients who received at least one dose of any study drug, who had no major protocol deviations, and had both baseline and at least one post-baseline tumour assessment. Patients who died prior to the first post-baseline tumour assessment were also included. The PP analysis set was the secondary analysis set for efficacy endpoints
- HRQoL analysis set: All patients who had any HRQoL data and received at least one dose of study treatment.

A summary of the statistical analysis of CLEAR is presented in Appendix L.

4.5. Patient population and participant flow

A summary of the flow of patients in CLEAR is presented in Figure 4, and a summary of analysis populations (defined in Section 4.4) is presented in Table 9.

Figure 4: Patient disposition in CLEAR



[a]Ongoing in study at data cut-off date; [b]Discontinued treatment includes patients who discontinued sunitinib or both study drugs in combination arm.
NOTE: As of the final PFS data cut-off date (28th August 2020), 142 patients (40.0%) in the LEN+PEM arm and 67 (18.8%) in the sunitinib arm were still receiving study treatment.
The lenvatinib + everolimus arm is not included in this submission.

Table 9: Analysis populations in CLEAR

Analysis population, n	LEN+PEM (N=355)	Sunitinib (N=357)
Randomised	355	357
FAS	[redacted]	[redacted]
Per protocol	[redacted]	[redacted]
HRQoL	[redacted]	[redacted]
Safety	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HRQoL, health-related quality of life; LEN, lenvatinib; PEM, pembrolizumab.

4.5.1. Baseline characteristics

Baseline demographics were generally well balanced between treatment arms (Table 10). At baseline, distribution between MSKCC and IMDC risk groups was comparable.

Table 10: Demographic and baseline characteristics, FAS

	LEN+PEM (N=355)	Sunitinib (N=357)
Baseline characteristics		
Age (years)		
Mean (SD)	[redacted]	[redacted]
Sex, n (%)		
Male	255 (71.8)	275 (77.0)
Female	100 (28.2)	82 (23.0)
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
BMI (kg/m^2)		
Mean (SD)	[redacted]	[redacted]
KPS score group, n (%)		
100–90	295 (83.1)	294 (82.4)
80–70	60 (16.9)	62 (17.4)
Missing	0 (0.0)	1 (0.3)
Disease history and characteristics		
Time since first RCC diagnosis to randomisation (months)		
Mean (SD)	[redacted]	[redacted]
Age at first diagnosis (years)†		
Mean (SD)	[redacted]	[redacted]

	LEN+PEM (N=355)	Sunitinib (N=357)
RCC diagnosis classification, n (%)		
Clear cell	[redacted]	[redacted]
Clear cell with additional features‡ Papillary Chromophobe Sarcomatoid Other	[redacted]	[redacted]
Other (not clear cell)	[redacted]	[redacted]
RCC sarcomatoid component by histology, n (%)		
Yes	28 (7.9)	21 (5.9)
No	[redacted]	[redacted]
Time since advanced/metastatic RCC diagnosis to randomisation (months)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Lesion organ/site location‡,¶, n (%)		
Lung	[redacted]	[redacted]
Lymph Node	[redacted]	[redacted]
Bone	[redacted]	[redacted]
Kidney	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Adrenal	[redacted]	[redacted]
Brain	[redacted]	[redacted]
Other	[redacted]	[redacted]
Number of metastatic organs/sites involved¶,§, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Stage group at diagnosis, n (%)		
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Not Assigned	[redacted]	[redacted]
MSKCC prognostic group at baseline, n (%)		
Favourable risk	96 (27.0)	97 (27.2)
Intermediate risk	227 (63.9)	228 (63.9)
Poor risk	32 (9.0)	32 (9.0)

	LEN+PEM (N=355)	Sunitinib (N=357)
IMDC prognostic group at baseline††, n (%)		
Favourable risk	110 (31.0)	124 (34.7)
Intermediate risk	210 (59.2)	192 (53.8)
Poor risk	33 (9.3)	37 (10.4)
Could not be evaluated	2 (0.6)	4 (1.1)
PD-L1 status‡‡, n (%)		
Positive (CPS≥1)	107 (30.1)	119 (33.3)
Negative (CPS<1)	112 (31.5)	103 (28.9)
Not Available	136 (38.3)	135 (37.8)
Previous nephrectomy, n (%)		
Yes	262 (73.8)	275 (77.0)

Data cut-off date: 28th August 2020. Percentages are based on the total number of patients in the Full Analysis Set within the relevant treatment group.
†Age at first diagnosis (years): Age – [(Date of informed consent signed – Date of Diagnosis)/365.25]; ‡Patients may be represented in more than 1 category; ¶Lesion organ/sites involved were derived from independent imaging review; §Kidney is not included in the number of metastatic organs/sites; ††IMDC prognostic group at baseline is based on total risk score from 6 prognostic factors at baseline: KPS, haemoglobin, corrected serum calcium, neutrophils, platelets, and time from first RCC diagnosis to randomisation; ‡‡PD-L1 status was determined using an investigational version of the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent, Santa Clara, California, USA) and a provisional CPS, which is defined as the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100. The CPS cut-off value is 1.
Abbreviations: BMI, body mass index; CPS, Combined Positive Score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky Performance Status; LEN, lenvatinib; MSKCC, Memorial Sloan-Kettering Cancer Center; PD-L1, programmed cell death ligand-1; PEM, pembrolizumab; RCC, renal cell carcinoma.

4.6. Clinical effectiveness results of CLEAR

Clinical effectiveness results for CLEAR are based on the final PFS analysis, with a data cut-off of 28th August 2020, and updated OS analysis (data cut-off of 31st March 2021), which was requested by the European Medicines Agency (EMA). The primary (PFS assessed by independent imaging review [IIR] assessment) and key secondary endpoints (overall survival [OS] and ORR by IIR using RECIST 1.1) are presented in Sections 4.6.1–4.6.2. Other secondary endpoints (PFS assessed by investigator assessment, PFS on next-line therapy, and a change from baseline in HRQoL measurements), and exploratory secondary endpoints (duration of response by IIR and investigator assessment, ORR by investigator assessment, and disease control rate) are presented in Appendix M. Pre-specified subgroup analyses (e.g. IMDC/MSKCC risk groups) are presented in Appendix E.

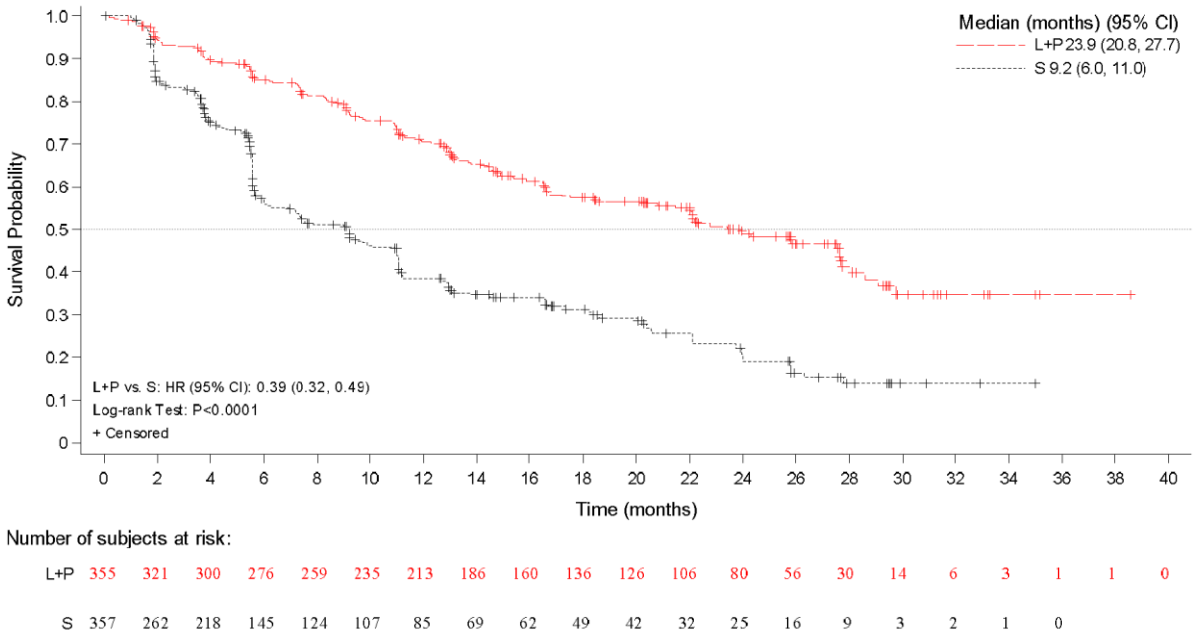
4.6.1. Primary efficacy endpoint: PFS assessed by IIR per RECIST 1.1

During CLEAR, two alternative censoring rules for PFS data were used:

- PFS according to the Food and Drug Administration (FDA) censoring criteria included: progression date assigned to the earliest date when any RECIST 1.1-defined disease progression is observed without missing more than one adequate radiologic assessment (138). PFS per FDA censoring rules was utilised for the primary efficacy endpoint. More detail about FDA censoring rules is presented in Table 102, Appendix L.
- PFS according to EMA censoring criteria included: using the actual reported date of progression by independent imaging review or death to define PFS regardless of missing assessments, or use of new anti-cancer therapy (139) (Appendix E and Appendix M).

CLEAR met its primary efficacy endpoint of PFS assessed by IIR per RECIST 1.1. Treatment with LEN+PEM resulted in a statistically significant improvement in PFS compared with sunitinib (Figure 5 and Table 11). Median PFS was 23.9 months (95% CI: 20.8, 27.7) for LEN+PEM and 9.2 months (95% confidence interval [CI]: 6.0, 11.0) for sunitinib (HR: 0.39 [95% CI: 0.32, 0.49]; p<0.001. The observed improvement in PFS for patients treated with LEN+PEM demonstrated a 2.5-fold increase in PFS, and a 61.0% reduction in the risk of disease progression or death compared with sunitinib.

Figure 5: Kaplan-Meier plot of PFS by IIR using RECIST 1.1, final PFS analysis (28th August 2020), FAS



Data cut-off: 28th August 2020 (final PFS analysis).
Abbreviations: CI, confidence interval; HR, hazard ratio; L, lenvatinib; P, pembrolizumab; S, sunitinib.

Table 11: PFS by IIR per RECIST 1.1, final PFS analysis (28th August 2020), FAS

Category	LEN+PEM N=355	Sunitinib N=357
Patients with events, n (%) Progressive disease Death	160 (45.1) [redacted]	205 (57.4) [redacted]
Censored, n (%) No baseline tumour assessment No adequate post-baseline tumour assessment No progression and alive at time of data cut-off New anti-cancer treatment started Death or progression after >1 missing assessment	[redacted]	[redacted]
PFS (months)† Median (95% CI) Q1 (95% CI) Q3 (95% CI)	23.9 (20.8, 27.7) [redacted]	9.2 (6.0, 11.0) [redacted]
LEN+PEM vs sunitinib Stratified HR (95% CI)‡, ¶ Stratified Log-rank Test p-value¶	0.39 (0.32, 0.49) p<0.001	
PFS rate (%) (95% CI)§ at: 6 months 12 months 18 months 24 months	[redacted]	[redacted]

Category	LEN+PEM N=355	Sunitinib N=357
Follow-up time for PFS (months)[†, ††] Median (95% CI) Q1 (95% CI) Q3 (95% CI)	[redacted]	[redacted]

Data cut-off: 28th August 2020 (final PFS analysis).
[†]Quartiles were estimated by Kaplan–Meier method, and the 95% CIs ere estimated with a generalised Brookmeyer and Crowley method; [‡]Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties; [¶]Stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and MSKCC prognostic groups (favourable, intermediate, and poor risk) in IxRS; [§]Progression-free survival rate and 95% CIs are calculated using Kaplan–Meier product-limit method and Greenwood Formula;
[††]Estimates for PFS follow-up time are calculated in the same way as the Kaplan–Meier estimate of PFS but with the meaning of 'censor' and 'event' status indicator reversed.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; LEN, lenvatinib; NE, not estimable; PEM, pembrolizumab; PFS, progression-free survival, Q, quartile.

Sensitivity analysis of the primary efficacy endpoint, and analysis of PFS in the per protocol analysis set are presented in Appendix M.

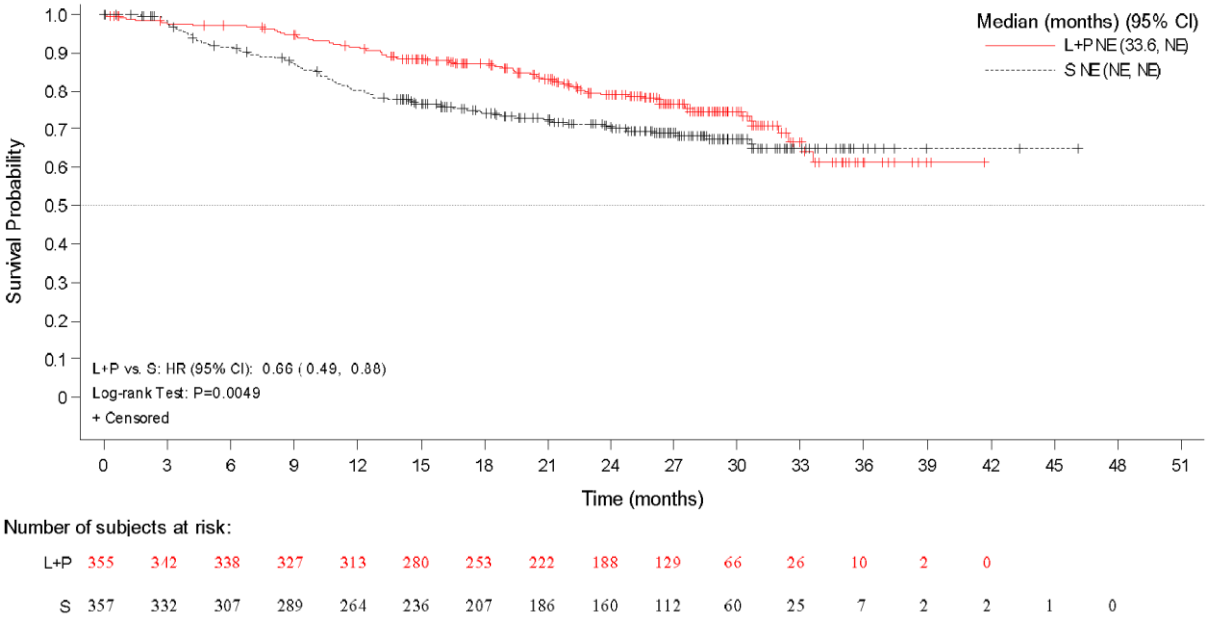
4.6.2. Key secondary efficacy endpoints

4.6.2.1. OS – at the time of final PFS analysis (data cut-off 28th August 2020)

At the time of final PFS analysis (28th August 2020), there was a statistically significant improvement in OS between the LEN+PEM and sunitinib arms. At a median duration of survival follow-up of 26.6 months, the OS HR was 0.66 (95% CI: 0.49, 0.88); p=0.005. Median OS was not reached in either treatment arm (Figure 6 and Table 12).

[redacted].

Figure 6: Kaplan-Meier plot of OS, final PFS analysis (28th August 2020), FAS



Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; L, lenvatinib; NE, not estimable; OS, overall survival; P, pembrolizumab; S, sunitinib.

Table 12: OS, final PFS analysis (28th August 2020), FAS

Category	LEN+PEM N=355	Sunitinib N=357
Death, n (%)	[redacted]	[redacted]
Censored, n (%) Lost to follow-up Withdrawal of consent Alive	[redacted]	[redacted]
OS (months)† Median (95% CI) Q1 (95% CI) Q3 (95% CI)	NE (33.6, NE) [redacted] NE (NE, NE)	NE (NE, NE) [redacted] NE (NE, NE)
LEN+PEM vs sunitinib Stratified HR (95% CI)‡, ¶ Stratified Log-rank Test p-value¶	0.66 (0.49, 0.88) 0.005	
OS rate (%) (95% CI)§ at: 12 months 18 months 24 months	[redacted]	[redacted]
Duration of survival follow-up (months)†, †† Median (95% CI) Q1 (95% CI) Q3 (95% CI)	[redacted]	[redacted]

†Quartiles were estimated by Kaplan–Meier method, and the 95% CIs ere estimated with a generalised Brookmeyer and Crowley method; ‡Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties; ¶Stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and MSKCC prognostic groups (favourable, intermediate, and poor risk) in IxRS; §OS rate and 95% CIs are calculated using Kaplan–Meier product-limit method and Greenwood Formula; ††Estimates for survival follow-up time are calculated in the same way as the Kaplan–Meier estimate of OS but with the meaning of 'censor' and 'event' status indicator

reversed.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IxRS, interactive voice and web response system; LEN, lenvatinib; MSKCC, Memorial Sloan-Kettering Cancer Center; NE, not estimable; OS, overall survival; PEM, pembrolizumab; Q, quartile.

4.6.2.2. OS – updated OS analysis (data cut-off 31st March 2021)

At the regulatory-requested updated OS analysis 163 patients were receiving treatment; 114 in the LEN+PEM arm and 49 in the sunitinib arm. A total of 529 patients discontinued treatment across the treatment arms; the primary reason for which was radiological disease progression.

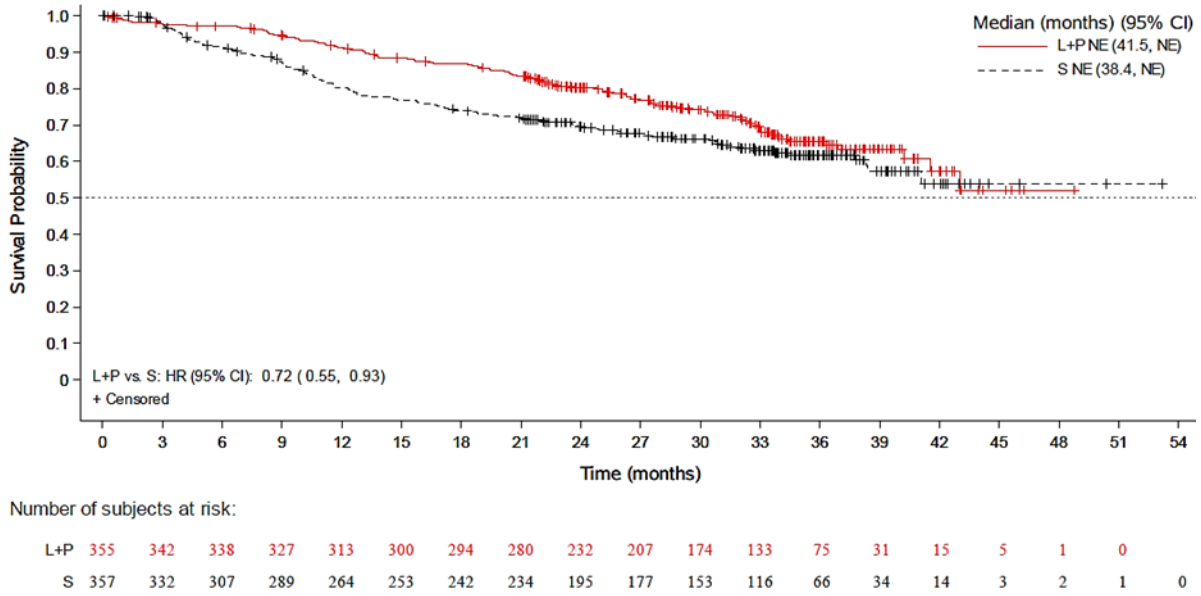
In the updated OS analysis, patients treated with LEN+PEM retained the OS benefit observed in the planned OS analysis compared with those treated with sunitinib, with a 28% reduction in risk of death (HR: 0.72 [95% CI: 0.55, 0.93]). Median OS was not reached in either treatment arm. Overall survival rates at Months 12, 18 and 24 were consistently higher in the LEN+PEM arm compared with the sunitinib arm. [redacted]

Table 13: OS, updated OS analysis (31st March 2021), FAS

Category	LEN+PEM N=355	Sunitinib N=357
Death, n (%)	105 (29.6)	122 (34.2)
Censored, n (%) Lost to follow-up Withdrawal of consent Alive	250 (70.4) 10 (2.8) 15 (4.2) 225 (63.4)	235 (65.8) 8 (2.2) 30 (8.4) 197 (55.2)
OS (months)† Median (95% CI) Q1 (95% CI) Q3 (95% CI)	NE (41.5, NE) [redacted]	NE (38.4, NE) [redacted]
LEN+PEM vs sunitinib Stratified HR (95% CI)‡, ¶	0.72 (0.55, 0.93)	
OS rate (%) (95% CI)§ at: 12 months 18 months 24 months 36 months	[redacted]	[redacted]
Duration of survival follow-up (months)†, †† Median (95% CI) Q1 (95% CI) Q3 (95% CI)	33.7 (32.8, 34.4) [redacted]	33.4 (32.5, 34.1) [redacted]

Data cut-off: 31st March 2021 (updated OS analysis).
†Quartiles were estimated by Kaplan–Meier method, and the 95% CIs ere estimated with a generalised Brookmeyer and Crowley method; ‡Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties; ¶Stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and MSKCC prognostic groups (favourable, intermediate, and poor risk) in IxRS; §OS rate and 95% CIs are calculated using Kaplan–Meier product-limit method and Greenwood Formula; ††Estimates for survival follow-up time are calculated in the same way as the Kaplan–Meier estimate of OS but with the meaning of 'censor' and 'event' status indicator reversed.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IxRS, interactive voice and web response system; LEN, lenvatinib; MSKCC, Memorial Sloan-Kettering Cancer Center; NE, not estimable; OS, overall survival; PEM, pembrolizumab; Q, quartile.

Figure 7: Kaplan-Meier plot of OS, updated OS analysis (31st March 2021), FAS



Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; L, lenvatinib; NE, not estimable; OS, overall survival; P, pembrolizumab; S, sunitinib.

4.6.2.3. ORR by IIR using RECIST 1.1, final PFS analysis (28th August 2020)

The ORR in the LEN+PEM treatment arm was approximately double the ORR in the sunitinib arm; at 71.0% compared with 36.1% [redacted] The proportion of patients who achieved a confirmed complete response (CR) with LEN+PEM was approximately four-times of that observed in the sunitinib arm (16.1% and 4.2%, respectively). A total of 54.9% of patients achieved a confirmed partial response (PR) in the LEN+PEM arm compared with 31.9% of patients in the sunitinib arm (Table 14).

Table 14: ORR assessed by IIR using RECIST 1.1, final PFS analysis (28th August 2020), FAS

Category	LEN+PEM N=355	Sunitinib N=357
Best overall response, n (%)		
CR	57 (16.1)	15 (4.2)
PR	195 (54.9)	114 (31.9)
Stable disease	68 (19.2)	136 (38.1)
PD	19 (5.4)	50 (14.0)
Unknown/NE	16 (4.5)	42 (11.8)
ORR (CR + PR), n (%)	252 (71.0)	129 (36.1)
95% CI†	(66.3, 75.7)	(31.2, 41.1)
LEN+PEM vs sunitinib	[redacted]	
Difference, % (95% CI)†		
Odds ratio (95% CI)‡		
p-value (nominal)‡		

Note: Stable disease was ≥7 weeks after randomisation.
†95% CI is constructed using the method of Normal Approximation; ‡Odds ratio and nominal p-value are calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS.
Abbreviations: CI, confidence interval; CR, complete response; IxRS, interactive voice and web response system; LEN, lenvatinib; NE, not estimable; ORR, overall response rate; PD, progressive disease; PEM, pembrolizumab; PR, partial response.

4.6.3. Post-hoc adjusted OS analyses

At the time of the updated OS analysis (31st March 2021), a higher proportion of patients in the sunitinib arm ([redacted]) received subsequent anti-cancer medication during survival follow-up compared with the LEN+PEM arm ([redacted]) (Table 15). Moreover, a lower proportion of patients in the LEN+PEM arm ([redacted]) received subsequent PD-1/PD-L1 checkpoint inhibitor therapy compared with the sunitinib arm ([redacted]). The median duration of subsequent anti-cancer medication was [redacted] in the LEN+PEM arm and [redacted] in the sunitinib arm (Table 15). To account for this difference, post-hoc analyses were conducted to evaluate the impact of subsequent treatment on OS.

Table 15: Summary of anti-cancer medications during survival follow-up, updated OS analysis (31st March 2021), FAS

Category	LEN+PEM (N=355) n (%)	Sunitinib (N=357) n (%)
Patients started study treatment	[redacted]	[redacted]
Patients discontinued study treatment	[redacted]	[redacted]
Patients received any subsequent systemic anti-cancer medication during survival follow-up by type	[redacted]	[redacted]
Anti-VEGF therapy	[redacted]	[redacted]
PD-1/PD-L1 checkpoint inhibitor	[redacted]	[redacted]

Category	LEN+PEM (N=355) n (%)	Sunitinib (N=357) n (%)
MTOR Inhibitor	[redacted]	[redacted]
CTLA-4 Inhibitor	[redacted]	[redacted]
Number of regimens		
1	[redacted]	[redacted]
2+	[redacted]	[redacted]
Duration of first anti-cancer medication during survival follow-up (months)		
Mean (SD)	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Time from randomisation to first anti-cancer medication during survival follow-up (months)		
Mean (SD)	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Percentages are based on the total number of patients in the FAS within the relevant treatment group; Patients with two or more anti-cancer medications may be counted in multiple categories.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LEN, lenvatinib; Max, maximum; Min, minimum; mTOR, mammalian target of rapamycin; PD-1/PD-L1, programmed cell death/programmed cell death ligand-1; PEM, pembrolizumab; Q, quartile; SD, standard deviation; VEGF, vascular endothelial growth factor.

4.6.3.1. Post-hoc OS subgroup analysis: subsequent anti-cancer therapy (data cut-off: 31st March 2021)

In the updated OS analysis, median OS was compared between patients who received subsequent anti-cancer therapy and those who did not (OS analysis per subsequent treatment at the time of final PFS analysis is presented in Appendix E).

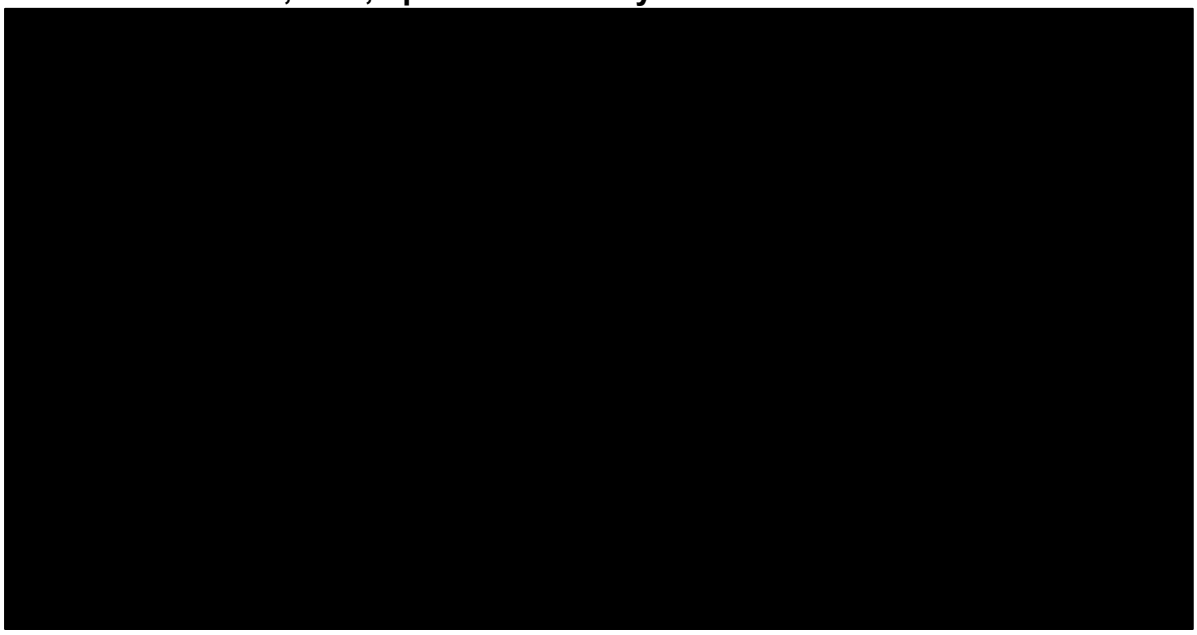
[redacted] (Figure 8; Figure 9).

The median OS for patients who received subsequent therapy was [redacted].

Figure 8: Kaplan-Meier plot of OS by patients receiving subsequent anti-cancer medication, FAS, updated OS analysis

Data cut-off date: 31st March 2021 (updated OS analysis).
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; L, lenvatinib; NE, not evaluable; OS, overall survival; P, pembrolizumab; S, sunitinib.

Figure 9: Kaplan-Meier plot of OS by patients not receiving subsequent anti-cancer medication, FAS, updated OS analysis



Data cut-off date: 31st March 2021 (updated OS analysis).
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; L, lenvatinib; NE, not evaluable; OS, overall survival; P, pembrolizumab; S, sunitinib.

4.6.3.2. Adjusted OS using two-stage estimation, updated OS analysis (31st March 2021)

Post-hoc analyses using two-stage estimation and inverse probability of censoring weights (IPCW) modelling were performed to evaluate the impact of subsequent Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

anti-cancer medication on the OS comparison. These analyses were initially conducted based on the final PFS analysis (28th August 2020; Appendix O). The two-stage estimation approach was updated subsequently for the updated OS analysis (31st March 2021).

A two-stage approach to adjust for receiving subsequent therapy was preferred over IPCW due to the capability of the two-stage approach to generate two counterfactual scenarios where (1) no patients receive subsequent therapy and (2) all patients receive subsequent therapy and combine both of these estimates to generate additional scenarios with varying proportions of patients receiving subsequent therapy to more closely reflect real-world practice.

In the two-stage estimation, OS is defined similarly as in the overall population (Section 4.6.2.2), but the survival time for patients switching to subsequent anti-cancer medication is adjusted. Specifically, the survival time after discontinuation from study treatment is adjusted using an acceleration factor (AF) determined in Stage 1. The primary two-stage estimation approach applies the adjustment for switching without re-censoring due to the potentially substantial impact of re-censoring. Further detail on the methodology and results of the two-stage estimation and IPCW approach is detailed in the two-stage estimation and IPCW report (140).

During the final PFS analysis (28th August 2020), the two-stage estimation, without and with re-censoring, resulted in a decrease in the OS HR compared with the HR based on the overall population analysis; [redacted]. The two-stage estimation results obtained during the updated OS analysis data cut (31st March 2021) were consistent with those from the final PFS analysis (Table 16; Figure 10; Figure 11).

Overall, these post-hoc analyses indicated that subsequent anti-cancer medication impacted the OS analysis in the overall population, underestimating the reduction in the risk of death for patients treated with LEN+PEM vs sunitinib.

Table 16: Unadjusted and adjusted OS results for switching to any subsequent anti-cancer medication by two-stage estimation method with different models

	LEN+PEM (N=355)	Sunitinib (N=357)
Unadjusted OS results		
Number of events	[redacted]	[redacted]
Unadjusted HR (95% CI)[†]	[redacted]	
Adjusted OS results for switching to any subsequent anti-cancer medication		
Log-normal AF without/with re-censoring		
Number of events	[redacted]	[redacted]
Adjusted HR1 (Bootstrap 95% CI)[†]	[redacted]	
Adjusted HR2 (Bootstrap 95% CI)[‡]	[redacted]	
Log-logistic AF without/with re-censoring		
Number of events	[redacted]	[redacted]
Adjusted HR1 (Bootstrap 95% CI)[†]	[redacted]	
Adjusted HR2 (Bootstrap 95% CI)[‡]	[redacted]	
Weibull AF without/with re-censoring		
Number of events	[redacted]	[redacted]
Adjusted HR1 (Bootstrap 95% CI)[†]	[redacted]	
Adjusted HR2 (Bootstrap 95% CI)[‡]	[redacted]	

Data cut-off date: 31 March 2021.

[†]HR (lenvatinib + pembrolizumab vs sunitinib) is based on a Cox proportional hazard model including treatment group as a factor, stratified by geographic region and MSKCC prognostic groups in IxRS; [‡]HR (lenvatinib + pembrolizumab vs sunitinib) is based on a Cox proportional hazard model including treatment group and the selected baseline covariates (IMDC prognostic risk group, number of metastatic organs/sites involved, and prior nephrectomy) as factors. The selected baseline covariates were determined by a multivariate Cox model on the unadjusted original OS data using the backward variable selection method with alpha=0.05.

Abbreviations: AF, acceleration factor; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IxRS, interactive voice and web response system; MSKCC, Memorial Sloan Kettering Cancer Center; RCC, renal cell carcinoma.

Figure 10: KM curves of adjusted OS for switching to any anti-cancer medication by two-stage estimation method without re-censoring based on log-normal model for acceleration factor estimation

Date: 31st March 2021 (updated OS analysis)
Abbreviations: KM, Kaplan-Meier; L, lenvatinib; P, pembrolizumab; S, sunitinib.

Figure 11: KM curves of adjusted OS for switching to any anti-cancer medication by 2-stage estimation method with re-censoring based on log-normal model for acceleration factor estimation

Date: 31st March 2021 (updated OS analysis)
Abbreviations: KM, Kaplan-Meier; L, lenvatinib; P, pembrolizumab; S, sunitinib.

4.7. *Indirect treatment comparisons*

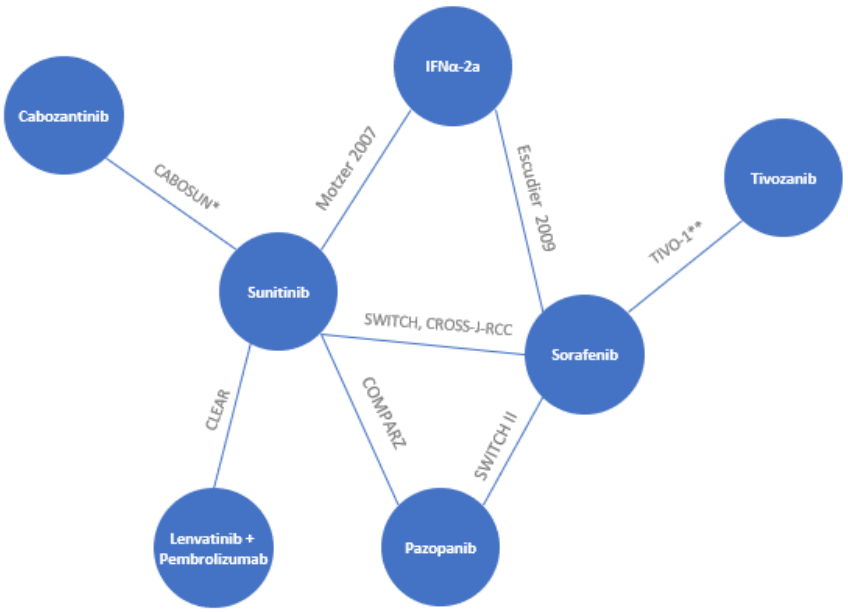
4.7.1. NMA methodology

In the absence of head-to-head trials comparing LEN+PEM with all other comparators than sunitinib, Bayesian and fractional polynomial (FP) NMAs were performed to assess the relative effectiveness and safety of LEN+PEM versus other treatments.

A total of nine RCTs identified by the SLR (111) had eligible populations, comparators, and outcomes of interest for the NMAs and therefore formed the network for the analyses (Figure 12). The eligible patient population for the NMAs included adults with aRCC with a clear-cell histology who have received no prior systemic therapy.

A summary of the trials assessed for eligibility for the NMAs including reasons for exclusion, where relevant, and further details on the NMA feasibility assessment are presented in Appendix D. An overview of the Bayesian and FP NMA methodologies are presented in Appendix D2.2 and D2.3, respectively.

Figure 12: Network diagram for first-line aRCC



*Due to the enrolment of only intermediate- and poor-risk patients, the CABOSUN trial was not included in the base-case analysis but was included in risk subgroup analyses; **Only a treatment-naïve subgroup of patients from the TIVO-1 trial was included.
Abbreviations: IFNα-2a, interferon-alpha 2a.

Although IFNα-2a and sorafenib are not comparators of interest within the scope, their inclusion in the network allowed an indirect comparison to be made between

LEN+PEM and tivozanib. NMA results include IFNα-2a and sorafenib, however, they are not relevant for this analysis and are therefore not discussed further.

Seven outcomes were included in the Bayesian NMA:

- OS
- PFS, independent review committee[a] (IRC) or investigator assessed – FDA censoring rule[b]
- PFS, IRC or investigator assessed – EMA censoring rule[c]
- ORR; defined as complete + partial response
- Complete response (CR)
- Patients with at least one all-cause Grade ≥3 AE
- Treatment discontinuation due to AEs.

Two outcomes were included in the FP NMA:

- OS
- PFS.

4.7.2. NMA results

In the Bayesian NMA, LEN+PEM generally outperformed all comparators relevant in England and Wales on survival endpoints (OS, PFS) and response endpoints (ORR, CR). These comparative efficacy benefits came with a greater likelihood of Grade ≥3 AEs, but similar rates of treatment discontinuation as a consequence of AEs.

Base-case Bayesian NMA results for OS and PFS outcomes within the overall and intermediate/poor risk populations are presented below. Results for the Bayesian NMA in other subgroups and using a FP approach NMA are presented in Appendix D.

[a] Each trial comprised an independent body which reviewed PFS independently from the investigator. This was equivalent to the independent imaging review conducted by a central core laboratory in CLEAR

[b] PFS according to FDA censoring criteria included: progression date assigned to the earliest date when any RECIST 1.1-defined disease progression is observed without missing more than one adequate radiologic assessment (FDA, 2018)

[c] PFS according to EMA censoring criteria included: using the actual reported date of progression by independent imaging review or death to define PFS regardless of missing assessments, or use of new anti-cancer therapy (EMA, 2019).

4.7.2.1. OS

Bayesian NMAs were feasible for OS for the following scenarios:

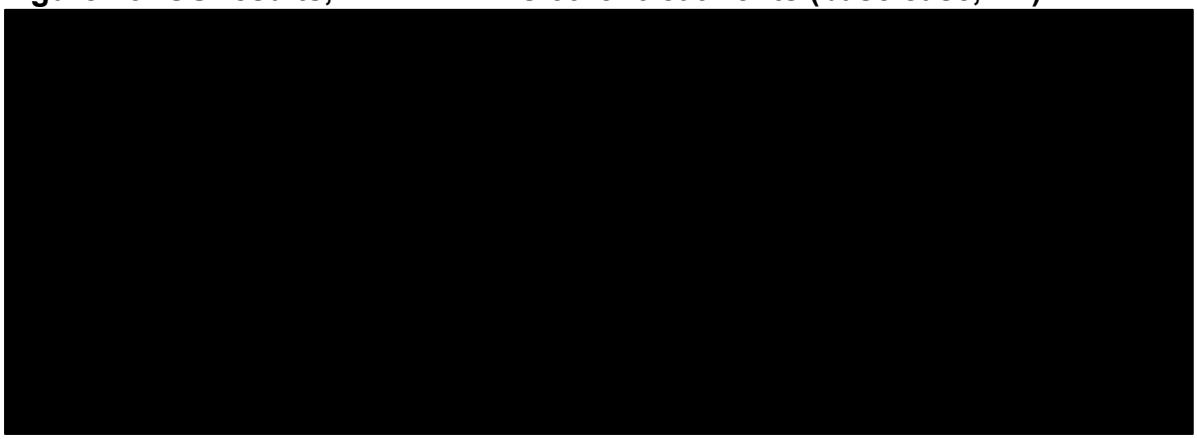
- base case
- assuming equivalence between sunitinib, pazopanib, and tivozanib (Appendix D)
- assuming equivalence between IMDC and MSKCC risk definitions for all risk subgroups (Appendix D)
- using only IMDC definitions for the intermediate/poor risk subgroup.

Three trials (SWITCH, SWITCH II, and CROSS-J-RCC) used sequential cross-over designs without reporting cross-over adjusted OS and were therefore excluded from the OS network. TIVO-1 enrolled a mixed population of first-line and second-line patients. Only subgroup data from first-line patients were included in the Bayesian NMA. Note that tivozanib is not included within this analysis; it could not be linked to the rest of the network because of the three aforementioned trials that use a sequential cross-over design. In addition, Escudier et al, 2009 did not report OS. Fixed effects (FE) models were used for all OS analyses across all scenarios and risk subgroups because the sparse networks, with no more than four comparators in total, one trial per comparison, no loops, meant that no statistically meaningful network heterogeneity or inconsistency between studies was expected.

Overall population

LEN+PEM provided a statistically significant OS benefit over sunitinib (Figure 13). A numerical, but not statistically significant improvement was observed for LEN+PEM vs pazopanib [redacted], however similar efficacy was assumed between sunitinib and pazopanib, in line with committee opinion in prior appraisals in first-line RCC (21, 89, 90, 92, 141).

Figure 13: OS results, LEN+PEM vs other treatments (base case, FE)



Note: IFNα-2a is not a comparator of interest within the scope; its inclusion in the network allowed an indirect comparison to be made between LEN+PEM and tivozanib.
Abbreviations: Crl, credible interval; FE, fixed effects; IFN, interferon; LEN, lenvatinib; PAZ, pazopanib; PEM, pembrolizumab; SUN, sunitinib.

Intermediate/poor risk population

The intermediate/poor risk network included three comparators (LEN+PEM, sunitinib, and cabozantinib), with evidence from two trials (CLEAR and CABOSUN) supporting the NMA analysis. Sunitinib is not a comparator of interest for the intermediate/poor risk population; its inclusion in the network allowed an indirect comparison to be made between LEN+PEM and cabozantinib.

Figure 14 shows that LEN+PEM provided an advantage in OS compared with the two other comparators in the intermediate/poor-risk network. A numerical, but non-significant advantage for LEN+PEM was observed vs cabozantinib [redacted].

Figure 14: OS Results, LEN+PEM vs other treatments (IMDC [=MSKCC] Intermediate/Poor Risk, FE)

Note: Sunitinib is not a comparator of interest for the intermediate/poor risk population; its inclusion in the network allowed an indirect comparison to be made between LEN+PEM and cabozantinib.
Abbreviations: CABO, cabozantinib; Crl, credible interval; LEN, lenvatinib; PEM, pembrolizumab; SUN, sunitinib.

4.7.2.2. PFS: FDA censoring

Overall population

A random effects (RE) model was selected over an FE model because:

- The deviance information criterion (DIC) for the RE model was slightly lower than the FE model although not meaningfully so ([redacted])
- Between-study heterogeneity in the sunitinib vs sorafenib comparison was low (I^2 = 0%). However, the network contained both loop #1 and loop #2, and statistically significant inconsistency was noted between studies providing direct and indirect comparisons between sorafenib and sunitinib ([redacted])
- A comparison of study results with Bucher ITC results for sorafenib vs IFN α-2a showed a difference in directionality of the effect ([redacted]). This difference in loop #2 was not statistically significant.

LEN+PEM provided a statistically significant PFS benefit over sunitinib, pazopanib, and tivozanib (Figure 15). Please note, IFNα-2a and sorafenib are not comparators of interest within the scope; the inclusion of both treatments within the network allowed an indirect comparison to be made between LEN+PEM and tivozanib.

Figure 15: PFS (FDA censoring) results, LEN+PEM vs other treatments (base case, RE)

[redacted]

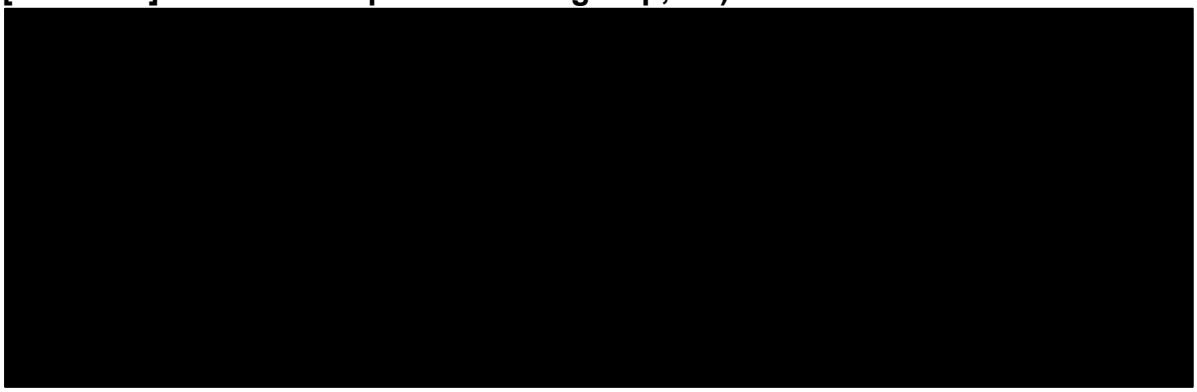
Note: IFNα-2a and sorafenib are not comparators of interest within the scope; the inclusion of both treatments within the network allowed an indirect comparison to be made between LEN+PEM and tivozanib.
Abbreviations: CrI, credible interval; IFN, interferon; LEN, lenvatinib; PAZ, pazopanib; PEM, pembrolizumab; SOR, sorafenib; SUN, sunitinib; TIV, tivozanib.

Intermediate/poor risk population

The intermediate/poor risk network included only three comparators (LEN+PEM, cabozantinib, and sunitinib), with evidence from two trials (CLEAR and CABOSUN) supporting the NMA analysis. Sunitinib is not a comparator of interest for the intermediate/poor risk population; its inclusion in the network allowed an indirect comparison to be made between LEN+PEM and cabozantinib.

Figure 16 shows that LEN+PEM provided a significant advantage in PFS vs sunitinib ([redacted]). A numerical, but not significant advantage was observed for LEN+PEM vs cabozantinib ([redacted]).

Figure 16: PFS (FDA censoring) Results, LEN+PEM vs other treatments (IMDC [=MSKCC] intermediate/poor risk subgroup, FE)



Note: Sunitinib is not a comparator of interest for the intermediate/poor risk population; its inclusion in the network allowed an indirect comparison to be made between LEN+PEM and cabozantinib.
Abbreviations: CAB, cabozantinib; Crl, credible interval; LEN, lenvatinib; PEM, pembrolizumab; SUN, sunitinib.

4.7.3. Uncertainties in the indirect and mixed treatment comparisons

Generally, statistical heterogeneity was low across the network for all outcomes, with the majority of individual comparisons having $I^2 < 30\%$; a variation generally thought of as indicating “low” heterogeneity (142). This is not surprising given the sparseness of the network for most outcomes and scenarios. I^2 values of >50% were uncommon, but consistently observed in select subgroup and scenario analyses for PFS, specifically in favourable risk patients for IMDC(=MSKCC) scenarios.

4.7.4. Conclusions from the NMA

The NMA showed that LEN+PEM generally provides significant and clinically meaningful improvements in OS, PFS, and response compared with current SoC

treatment options available in the England and Wales for treatment-naïve patients with aRCC. All feasible base-case comparisons for the efficacy outcomes were significant, with the exception of a numerical but not statistically significant advantage over pazopanib in the OS base-case network, and over cabozantinib in the PFS intermediate/poor risk network.

While LEN+PEM generally exhibited a qualitative, non-significant trend towards an increase in Grade ≥3 AEs over comparator treatments, it also showed a non-significant trend towards improvement in treatment discontinuation due to AEs in the majority of comparisons. Taken collectively, these results suggest LEN+PEM has a favourable efficacy profile and tolerable safety profile when used for the first-line treatment of aRCC.

4.8. Adverse reactions

The extent of exposure, and a summary of TEAEs, TEAEs by preferred term occurring in ≥10% patients, Grade ≥3 TEAEs and treatment-related TEAEs are presented in Sections 4.8.1–4.8.2.2. An overview of serious TEAEs, TEAEs of special interest, treatment discontinuation, TEAEs associated with dose modification, and deaths during the study are presented Appendix F.

4.8.1. Extent of exposure

The overall duration of treatment was defined as the duration between the start date of the first administration of the study drug and the end date of the last administration of the study drug medication. The median duration of treatment was 17 months in the LEN+PEM arm, compared with 7.84 months in the sunitinib arm (Table 17).

Table 17: Extent of exposure to study drug, safety analysis set

Extent of exposure	LEN+PEM N=355	Sunitinib N=340
Overall duration of treatment (months)† Mean (SD) Median Min, Max No. of patient months‡	[redacted] 17.00 [redacted]	[redacted] 7.84 [redacted]
Lenvatinib duration of treatment (months)† Mean (SD) Median Min, Max No. of patient months‡	[redacted]	NA

Extent of exposure	LEN+PEM N=355	Sunitinib N=340
Pembrolizumab/sunitinib duration of treatment (months)[†] Mean (SD) Median Min, Max No. of patient months[‡]	*Pembrolizumab*	*Sunitinib*

Data cut-off date: 28th August 2020.
[†]Duration of treatment (months) = (date of last dose of study drug – date of first dose of study drug + 1) / 30.4375. For overall duration of treatment, it is defined as the duration between the earliest first dose stare date of either medication and the latest last dose end date of either medication; [‡]Number of patient months = total duration of treatment (in days) across all patients in the relevant treatment arm / 30.4375.
Abbreviations: LEN, lenvatinib; Max, maximum; Min, minimum; NA, not applicable, PEM, pembrolizumab; SD, standard deviation.

4.8.2. Summary of AEs

Nearly all patients in both the LEN+PEM (n=351; 99.7%) and sunitinib (n=335; 98.5%) arms had at least one TEAE. Treatment duration was 2.5-times longer in the LEN+PEM arm compared with sunitinib. Longer treatment duration in the combination arm means these subjects are more likely to report AEs.

[d], while the proportion of patients with a TEAE leading to discontinuation of LEN+PEM was 13.4% compared with 14.4% of patients in the sunitinib arm (Table 18). The percentage risk difference for adverse events, with an associated 95% CI, are also presented in Table 18.

Table 18: Overview of TEAEs and risk difference (95% CI), final PFS analysis (28th August 2020), safety analysis set

	LEN+PEM (N=352) n (%)	Sunitinib (N=340) n (%)	Relative Risk (95% CI)	Risk Difference % (95% CI)[†]
Any TEAE	351 (99.7)	335 (98.5)	n.c.	
Treatment-related TEAE	341 (96.9)	313 (92.1)	n.c.	
Serious TEAE	178 (50.6)	113 (33.2)	n.c.	
Serious treatment-related TEAEs	119 (33.8)	51 (15.0)	n.c.	

[d] A serious adverse event is any adverse event that results in death, is life threatening, requires or prolongs hospitalisation, causes persistent or significant disability or incapacity, or is another condition which investigators deem to represent significant hazards (NIA guidelines).

	LEN+PEM (N=352) n (%)	Sunitinib (N=340) n (%)	Relative Risk (95% CI)	Risk Difference % (95% CI)[†]
TEAE Leading to treatment interruption	276 (78.4)	183 (53.8)	n.c.	[redacted]
Interruption of lenvatinib	257 (73.0)	NA	n.c.	[redacted]
Interruption of pembrolizumab	194 (55.1)	NA	n.c.	[redacted]
Interruption of both lenvatinib and pembrolizumab	138 (39.2)	NA	n.c.	[redacted]
TEAE leading to dose reduction	242 (68.8)	171 (50.3)	n.c.	[redacted]
TEAEs leading to study drug discontinuation	131 (37.2)	49 (14.4)	n.c	[redacted]
Discontinuation of lenvatinib	90 (25.6)	N/A	n.c	[redacted]
Discontinuation of pembrolizumab	101 (28.7)	N/A	n.c	[redacted]
Discontinuation of both lenvatinib and pembrolizumab	47 (13.4)	N/A	n.c	[redacted]
Fatal TEAE	15 (4.3)	11 (3.2)	n.c.	[redacted]

Data cut-off date: 28th August 2020. For each category, patients with two or more TEAEs were only counted once. For serious TEAEs, the follow-up window is 120 days after the last dose date. AEs were graded using CTCAE version 4.03.

[†]based on Miettinen and Nurminen method.

Abbreviations: CI, confidence interval; LEN, lenvatinib; NA, not applicable; n.c, not computed; PEM, pembrolizumab; TEAE, treatment-emergent adverse events.

TEAEs were also analysed by patient incidence and number of episodes adjusted for patient-years (PY) of exposure to study treatment. The total number of PY of exposure, including dose interruptions, was [redacted]. The incidence of TEAEs adjusted for drug exposure was [redacted] 19). Adjusted by treatment exposure, the rate of Grade ≥3 TEAEs was comparable between treatment groups, at [redacted]. The overall incidence of serious TEAEs was [redacted], while the incidence of fatal TEAEs was similar and low across both treatment groups [redacted]

Table 19: Overview of TEAEs adjusted by drug exposure, safety analysis set

Category	LEN+PEM N=352 n (AE rate)	Sunitinib N=340 n (AE rate)
Total exposure (PY)	[redacted]	[redacted]
All TEAEs adjusted by PY	[redacted]	[redacted]
Treatment-related TEAEs adjusted by PY	[redacted]	[redacted]
Grade 3–5 TEAEs adjusted by PY	[redacted]	[redacted]
Serious TEAEs adjusted by PY	[redacted]	[redacted]
TEAEs with fatal outcome adjusted by PY	[redacted]	[redacted]
Non-fatal serious TEAEs adjusted by PY	[redacted]	[redacted]

Data cut-off date: 28th August 2020. Treatment-related TEAEs include TEAEs which were considered by the investigator o be related to study treatment or TEAEs with a missing causality. MedDRA preferred terms “neoplasm progression”, “malignant neoplasm progression” and “disease progression” which were unrelated to study treatment were excluded. Total exposure: sum of drug exposure for all patients in each treatment arm (including dose interruption). Drug exposure: 9the earlier of last dose date + 30 or the database cut-off date – the first dose date + 1)/365.25 in years. AE rate: (episodes/patient-years) = total number of TEAE episodes (n) / total exposure in each treatment group.
Abbreviations: LEN, lenvatinib; MedDRA, Medical Dictionary for Regulatory Activities; n, number of TEAE records; PEM, pembrolizumab; PY, patient-year; TEAE, treatment-emergent adverse event.

4.8.2.1. TEAEs and Grade ≥3 TEAEs by system organ class and preferred term

The most commonly reported TEAEs occurring in either treatment arm (Table 20) were diarrhoea (LEN+PEM: 61.4% vs sunitinib: 49.4%), hypertension (55.4% vs 41.5%), hypothyroidism (47.2% vs 26.5%), decreased appetite (40.3% vs 30.9%), fatigue (40.1% vs 36.8%), nausea (35.8% vs 33.2%) and stomatitis (34.7% vs 38.5%).

The overall incidence of severe TEAEs (Grade ≥3) was higher in the LEN+PEM arm than the sunitinib arm (82.4% vs 71.8%). [redacted]. The most common Grade ≥3 TEAEs (≥5% of patients in either arm) were hypertension (LEN+PEM: 27.6% vs sunitinib: 18.8%), increase in lipase (12.8% vs 8.8%), diarrhoea (9.7% vs 5.3%), increase in amylase (9.1% vs 2.9%), decreased weight (8.0% vs 0.3%), proteinuria (7.7% vs 2.9%), and asthenia (5.4% vs 4.4%).

The percentage risk difference for adverse events, with an associated 95% CI, are also presented in Table 20.

Table 20: Frequency and gravity of TEAEs of any CTCAE Grade in ≥10% of patients and of CTCAE Grade ≥3 in ≥1% of patients by system organ class and preferred term, safety analysis set

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[+]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Blood and lymphatic system disorders	69 (19.6)	14 (4.0)	130 (38.2)	55 (16.2)	n.c.	n.c.	[redacted]	[redacted]
Anaemia	43 (12.2)	7 (2.0)	66 (19.4)	18 (5.3)	n.c.	n.c.	[redacted]	[redacted]
Leukopenia	5 (1.4)	0 (0.0)	24 (7.1)	9 (2.6)	n.c.	n.c.	[redacted]	[redacted]
Lymphopenia	7 (2.0)	1 (0.3)	9 (2.6)	4 (1.2)	n.c.	n.c.	[redacted]	[redacted]
Neutropenia	9 (2.6)	2 (0.6)	46 (13.5)	20 (5.9)	n.c.	n.c.	[redacted]	[redacted]
Thrombocytopenia	15 (4.3)	2 (0.6)	53 (15.6)	19 (5.6)	n.c.	n.c.	[redacted]	[redacted]
Cardiac disorders	60 (17.0)	25 (7.1)	36 (10.6)	5 (1.5)	n.c.	n.c.	[redacted]	[redacted]
Acute myocardial infarction	6 (1.7)	6 (1.7)	0 (0.0)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Myocardial infarction	6 (1.7)	6 (1.7)	1 (0.3)	1 (0.3)	n.c.	n.c.	[redacted]	[redacted]
Endocrine disorders	180 (51.1)	10 (2.8)	100 (29.4)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Adrenal insufficiency	17 (4.8)	4 (1.1)	0 (0.0)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Hypothyroidism	166 (47.2)	5 (1.4)	90 (26.5)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Gastrointestinal disorders	305 (86.6)	74 (21.0)	286 (84.1)	50 (14.7)	n.c.	n.c.	[redacted]	[redacted]
Abdominal pain	74 (21.0)	7 (2.0)	28 (8.2)	3 (0.9)	n.c.	n.c.	[redacted]	[redacted]
Constipation	89 (25.3)	3 (0.9)	64 (18.8)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Diarrhoea	216 (61.4)	34 (9.7)	168 (49.4)	18 (5.3)	n.c.	n.c.	[redacted]	[redacted]
Dry mouth	36 (10.2)	0 (0.0)	11 (3.2)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Dyspepsia	39 (11.1)	0 (0.0)	55 (16.2)	1 (0.3)	n.c.	n.c.	[redacted]	[redacted]
Nausea	126 (35.8)	9 (2.6)	113 (33.2)	2 (0.6)	n.c.	n.c.	[redacted]	[redacted]
Pancreatitis	9 (2.6)	5 (1.4)	0 (0.0)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Stomatitis	122 (34.7)	6 (1.7)	131 (38.5)	7 (2.1)	n.c.	n.c.	[redacted]	[redacted]
Vomiting	92 (26.1)	12 (3.4)	68 (20.0)	5 (1.5)	n.c.	n.c.	[redacted]	[redacted]
General disorders and administration site conditions	261 (74.1)	39 (11.1)	235 (69.1)	34 (10.0)	n.c.	n.c.	[redacted]	[redacted]
Asthenia	78 (22.2)	19 (5.4)	61 (17.9)	15 (4.4)	n.c.	n.c.	[redacted]	[redacted]

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Fatigue	141 (40.1)	15 (4.3)	125 (36.8)	15 (4.4)	n.c.	n.c.	[redacted]	[redacted]
Oedema peripheral	42 (11.9)	1 (0.3)	35 (10.3)	1 (0.3)	n.c.	n.c.	[redacted]	[redacted]
Pyrexia	54 (15.3)	2 (0.6)	44 (12.9)	1 (0.3)	n.c.	n.c.	[redacted]	[redacted]
Hepatobiliary disorders	34 (9.7)	14 (4.0)	28 (8.2)	4 (1.2)	n.c.	n.c.	[redacted]	[redacted]
Immune-mediated hepatitis	4 (1.1)	4 (1.1)	0 (0.0)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Infections and infestations	197 (56.0)	45 (12.8)	148 (43.5)	23 (6.8)	n.c.	n.c.	[redacted]	[redacted]
Nasopharyngitis	40 (11.4)	1 (0.3)	25 (7.4)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Pneumonia	13 (3.7)	7 (2.0)	13 (3.8)	6 (1.8)	n.c.	n.c.	[redacted]	[redacted]
Sepsis	3 (0.9)	3 (0.9)	4 (1.2)	4 (1.2)	n.c.	n.c.	[redacted]	[redacted]
Investigations	254 (72.2)	128 (36.4)	207 (60.9)	99 (29.1)	n.c.	n.c.	[redacted]	[redacted]
Alanine aminotransferase increased	42 (11.9)	15 (4.3)	35 (10.3)	8 (2.4)	n.c.	n.c.	[redacted]	[redacted]
Amylase increased	63 (17.9)	32 (9.1)	28 (8.2)	10 (2.9)	n.c.	n.c.	[redacted]	[redacted]

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Aspartate aminotransferase increased	39 (11.1)	11 (3.1)	37 (10.9)	3 (0.9)	n.c.	n.c.	[redacted]	[redacted]
Blood bilirubin increased	14 (4.0)	4 (1.1)	15 (4.4)	2 (0.6)	n.c.	n.c.	[redacted]	[redacted]
Blood cholesterol increased	24 (6.8)	4 (1.1)	14 (4.1)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Blood creatine phosphokinase increased	14 (4.0)	4 (1.1)	17 (5.0)	7 (2.1)	n.c.	n.c.	[redacted]	[redacted]
Blood creatinine increased	48 (13.6)	4 (1.1)	34 (10.0)	2 (0.6)	n.c.	n.c.	[redacted]	[redacted]
Blood thyroid stimulating hormone increased	39 (11.1)	0 (0.0)	21 (6.2)	0 (0.0)	n.c.	n.c.	[redacted]	[redacted]
Blood triglycerides increased	22 (6.3)	4 (1.1)	15 (4.4)	4 (1.2)	n.c.	n.c.	[redacted]	[redacted]
Electrocardiogram QT prolonged	22 (6.3)	10 (2.8)	13 (3.8)	4 (1.2)	n.c.	n.c.	[redacted]	[redacted]
Gamma-glutamyltransferase increased	12 (3.4)	4 (1.1)	5 (1.5)	2 (0.6)	n.c.	n.c.	[redacted]	[redacted]
Lipase increased	64 (18.2)	45 (12.8)	44 (12.9)	30 (8.8)	n.c.	n.c.	[redacted]	[redacted]
Lymphocyte count decreased	7 (2.0)	4 (1.1)	7 (2.1)	2 (0.6)	n.c.	n.c.	[redacted]	[redacted]

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Neutrophil count decreased	8 (2.3)	6 (1.7)	40 (11.8)	19 (5.6)	n.c.	n.c.		
Platelet count decreased	22 (6.3)	4 (1.1)	61 (17.9)	21 (6.2)	n.c.	n.c.		
Weight decreased	105 (29.8)	28 (8.0)	31 (9.1)	1 (0.3)	n.c.	n.c.		
White blood cell count decreased	10 (2.8)	1 (0.3)	33 (9.7)	6 (1.8)	n.c.	n.c.		
Metabolism and nutrition disorders	237 (67.3)	85 (24.1)	188 (55.3)	64 (18.8)	n.c.	n.c.		
Decreased appetite	142 (40.3)	14 (4.0)	105 (30.9)	5 (1.5)	n.c.	n.c.		
Dehydration	15 (4.3)	3 (0.9)	17 (5.0)	4 (1.2)	n.c.	n.c.		
Hypercholesterolaemia	31 (8.8)	5 (1.4)	7 (2.1)	1 (0.3)	n.c.	n.c.		
Hyperglycaemia	25 (7.1)	7 (2.0)	18 (5.3)	3 (0.9)	n.c.	n.c.		
Hyperkalaemia	28 (8.0)	12 (3.4)	18 (5.3)	7 (2.1)	n.c.	n.c.		
Hyperlipasaemia	7 (2.0)	5 (1.4)	0 (0.0)	0 (0.0)	n.c.	n.c.		
Hypertriglyceridaemia	42 (11.9)	17 (4.8)	41 (12.1)	22 (6.5)	n.c.	n.c.		
Hypokalaemia	22 (6.3)	4 (1.1)	11 (3.2)	1 (0.3)	n.c.	n.c.		

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Hypomagnesaemia	27 (7.7)	3 (0.9)	13 (3.8)	5 (1.5)	n.c.	n.c.		
Hyponatraemia	27 (7.7)	17 (4.8)	21 (6.2)	17 (5.0)	n.c.	n.c.		
Hypophosphataemia	22 (6.3)	8 (2.3)	15 (4.4)	8 (2.4)	n.c.	n.c.		
Musculoskeletal and connective tissue disorders	228 (64.8)	22 (6.3)	156 (45.9)	11 (3.2)	n.c.	n.c.		
Arthralgia	99 (28.1)	5 (1.4)	52 (15.3)	1 (0.3)	n.c.	n.c.		
Back pain	59 (16.8)	4 (1.1)	52 (15.3)	7 (2.1)	n.c.	n.c.		
Musculoskeletal pain	48 (13.6)	0 (0.0)	21 (6.2)	0 (0.0)	n.c.	n.c.		
Myalgia	56 (15.9)	3 (0.9)	12 (3.5)	0 (0.0)	n.c.	n.c.		
Pain in extremity	41 (11.6)	3 (0.9)	33 (9.7)	1 (0.3)	n.c.	n.c.		
Nervous system disorders	170 (48.3)	22 (6.3)	185 (54.4)	16 (4.7)	n.c.	n.c.		
Dysgeusia	43 (12.2)	1 (0.3)	95 (27.9)	1 (0.3)	n.c.	n.c.		
Headache	80 (22.7)	2 (0.6)	55 (16.2)	3 (0.9)	n.c.	n.c.		

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Syncope	5 (1.4)	4 (1.1)	5 (1.5)	5 (1.5)	n.c.	n.c.		
Psychiatric disorders	74 (21.0)	8 (2.3)	46 (13.5)	2 (0.6)	n.c.	n.c.		
Insomnia	38 (10.8)	0 (0.0)	21 (6.2)	0 (0.0)	n.c.	n.c.		
Mental status changes	5 (1.4)	4 (1.1)	0 (0.0)	0 (0.0)	n.c.	n.c.		
Renal and urinary disorders	153 (43.5)	46 (13.1)	83 (24.4)	21 (6.2)	n.c.	n.c.		
Acute kidney injury	13 (3.7)	8 (2.3)	14 (4.1)	5 (1.5)	n.c.	n.c.		
Haematuria	17 (4.8)	0 (0.0)	21 (6.2)	4 (1.2)	n.c.	n.c.		
Proteinuria	104 (29.5)	27 (7.7)	43 (12.6)	10 (2.9)	n.c.	n.c.		
Renal failure	10 (2.8)	5 (1.4)	8 (2.4)	1 (0.3)	n.c.	n.c.		
Respiratory, thoracic and mediastinal disorders	214 (60.8)	30 (8.5)	133 (39.1)	20 (5.9)	n.c.	n.c.		
Cough	70 (19.9)	0 (0.0)	53 (15.6)	1 (0.3)	n.c.	n.c.		
Dysphonia	105 (29.8)	0 (0.0)	14 (4.1)	0 (0.0)	n.c.	n.c.		

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Dyspnoea	54 (15.3)	9 (2.6)	34 (10.0)	8 (2.4)	n.c.	n.c.		
Epistaxis	25 (7.1)	0 (0.0)	37 (10.9)	0 (0.0)	n.c.	n.c.		
Pleural effusion	9 (2.6)	3 (0.9)	5 (1.5)	4 (1.2)	n.c.	n.c.		
Pneumonitis	18 (5.1)	7 (2.0)	0 (0.0)	0 (0.0)	n.c.	n.c.		
Pulmonary embolism	7 (2.0)	6 (1.7)	6 (1.8)	5 (1.5)	n.c.	n.c.		
Skin and subcutaneous tissue disorders	237 (67.3)	40 (11.4)	214 (62.9)	18 (5.3)	n.c.	n.c.		
Palmar-plantar erythrodysaesthesia syndrome	101 (28.7)	14 (4.0)	127 (37.4)	13 (3.8)	n.c.	n.c.		
Pruritus	58 (16.5)	1 (0.3)	26 (7.6)	1 (0.3)	n.c.	n.c.		
Rash	96 (27.3)	13 (3.7)	47 (13.8)	2 (0.6)	n.c.	n.c.		
Rash maculo-papular	29 (8.2)	4 (1.1)	7 (2.1)	0 (0.0)	n.c.	n.c.		

	LEN+PEM (N=352)		Sunitinib (N=340)		Relative risk (95% CI)		Risk diff % (95% CI)[†]	
Classification SOC/PT	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade n (%)**	**Grade ≥3 n (%)**	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Vascular disorders	214 (60.8)	103 (29.3)	156 (45.9)	68 (20.0)	n.c.	n.c.	[redacted]	[redacted]
Hypertension	195 (55.4)	97 (27.6)	141 (41.5)	64 (18.8)	n.c.	n.c.	[redacted]	[redacted]

Data cut-off: 28th August 2020 (final PFS analysis; 28th August 2020).

[†]based on Miettinen and Nurminen method.

Abbreviations: CI, confidence interval; LEN, lenvatinib; NA, not applicable; n.c, not computed; PEM, pembrolizumab; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse events.

4.8.2.2. Treatment-related AEs

Overall, treatment-related TEAEs were reported for 96.9% of patients in the LEN+PEM arm and 92.1% of patients in the sunitinib arm (Table 21). The most common treatment-related TEAEs (≥30% of patients) in the LEN+PEM and sunitinib treatment arms were diarrhoea (54.5% vs 44.4%), hypertension (52.3% vs 39.1%), hypothyroidism (42.6% vs 23.2%), stomatitis (32.1% vs 37.4%), decreased appetite (34.9% vs 24.7%), fatigue (32.1% vs 32.1%), and palmar-plantar erythrodysaesthesia syndrome (PPE; 28.1% vs 35.9%).

Table 21: Treatment-related TEAEs occurring in ≥10% of patients in any treatment arm by preferred term, safety analysis set

Preferred term, n (%)	LEN+PEM N=352	Sunitinib N=340
Patients with any treatment-related TEAE	**341 (96.9)**	**313 (92.1)**
Hypertension	184 (52.3)	133 (39.1)
Hypothyroidism	150 (42.6)	79 (23.2)
Diarrhoea	192 (54.5)	151 (44.4)
Stomatitis	113 (32.1)	127 (37.4)
Decreased appetite	123 (34.9)	84 (24.7)
Fatigue	113 (32.1)	109 (32.1)
PPE	99 (28.1)	122 (35.9)
Proteinuria	97 (27.6)	41 (12.1)
Nausea	94 (26.7)	94 (27.6)
Dysphonia	87 (24.7)	9 (2.6)
Rash	77 (21.9)	37 (10.9)
Asthenia	71 (20.2)	54 (15.9)
Decreased weight	70 (19.9)	19 (5.6)
Arthralgia	60 (17.0)	22 (6.5)
Vomiting	56 (15.9)	45 (13.2)
Increased amylase	53 (15.1)	26 (7.6)
Lipase increased	50 (14.2)	34 (10.0)
Pruritus	47 (13.4)	19 (5.6)
Abdominal pain	39 (11.1)	12 (3.5)
Dysgeusia	38 (10.8)	88 (25.9)
Headache	38 (10.8)	28 (8.2)
Blood thyroid stimulating hormone increased	38 (10.8)	17 (5.0)
Myalgia	38 (10.8)	8 (2.4)
Dyspepsia	26 (7.4)	42 (12.4)
Decreased platelet count	20 (5.7)	57 (16.8)
Anaemia	20 (5.7)	44 (12.9)
Thrombocytopenia	13 (3.7)	51 (15.0)

Preferred term, n (%)	LEN+PEM N=352	Sunitinib N=340
Neutropenia	8 (2.3)	42 (12.4)
Neutrophil count decreased	8 (2.3)	39 (11.5)

Data cut-off: 28th August 2020 (final PFS analysis; 28th August 2020). Display is in decreasing order of frequency of TEAEs in the LEN+PEM treatment arm. Patients with ≥2 TEAEs reported in the same preferred term were only counted once.
Abbreviations: LEN, lenvatinib; n, number of patients; PEM, pembrolizumab; PPE, palmar-plantar erythrodysaesthesia; TEAE, treatment-emergent adverse event.

4.8.2.3. Subgroup analysis of AEs

Analyses of MSKCC and IMDC subgroups indicated that the occurrence of TEAEs was relatively comparable between groups and to the overall patient population. Results are presented in Appendix F.

4.9. Ongoing studies

The extension phase of CLEAR is ongoing. A final OS update will be performed at the approximate timing of the pre-specified final analysis of OS (Table 98; Appendix L) per regulatory agency's request (143). Although the timing of this update is event driven, the final OS analysis is estimated to occur in Q3 2022.

There are no other ongoing studies which will report within 12 months of this submission.

4.10. Interpretation of clinical effectiveness and safety evidence

The CLEAR study demonstrated that LEN+PEM is an effective first-line treatment for aRCC, with statistically significant and clinically meaningful improvements in PFS and OS vs sunitinib, and a numerical improvement in ORR vs sunitinib. Median PFS was 23.9 months in the LEN+PEM arm compared with 9.2 months in the sunitinib arm (HR: 0.39, p<0.001), demonstrating a 2.5-fold increase in PFS, and a 61% reduction in the risk of disease progression with LEN+PEM compared with sunitinib.

Improvements in OS were also statistically significant with LEN+PEM compared with sunitinib. At the time of the final PFS analysis (data cut-off: 28th August 2020), median OS was not reached in either treatment arm, however a HR of 0.66, p=0.005 represents a 34% reduction in the risk of death with LEN+PEM treatment compared with sunitinib. The Kaplan-Meier curves for OS demonstrated a clear, early

separation, indicating an OS benefit in the LEN+PEM arm vs the sunitinib arm. The 18-month OS rate was [redacted] for LEN+PEM and [redacted] for sunitinib.

An updated OS analysis was performed when patients receiving LEN+PEM or sunitinib had a median follow-up of 33.7 and 33.4 months, respectively, and demonstrated that the OS benefit for LEN+PEM was maintained. At the time of this analysis, the HR in the study population was 0.72 (95% CI: 0.55, 0.93) with 105/355 (29.6%) events in the LEN+PEM arm and 122/357 (34.2%) events in the sunitinib arm. [redacted] The OS hazard ratios for the MSKCC favourable, intermediate, and poor risk groups were 1.00 (95% CI: 0.51, 1.96), 0.71 (95% CI: 0.52, 0.97), and 0.50 (95% CI: 0.25, 1.02), respectively.

The primary OS analysis was not adjusted to account for subsequent therapies. a higher proportion of patients in the sunitinib arm ([redacted]) received subsequent anti-cancer medication during survival follow-up compared with the LEN+PEM arm ([redacted]) (Table 15). An imbalance in the use of subsequent anti-cancer medication may lead to underestimation of the benefit of LEN+PEM. Therefore, the two-stage estimation method was applied to evaluate the impact of subsequent anti-cancer medication on the OS comparison. A decrease in the OS HR compared with the HR based on the overall population analysis was observed; two-stage estimation without and with re-censoring [redacted] The post-hoc analyses indicated that subsequent anti-cancer medication impacted the OS analysis in the overall population, underestimating the reduction in the risk of death for patients treated with LEN+PEM vs sunitinib.

With regard to ORR, LEN+PEM provided a statistically significant and clinically meaningful improvement in ORR compared with sunitinib; resulting in a confirmed ORR of 71.0% vs 36.1% for sunitinib [redacted]. In total, 16.1% of patients

achieved a confirmed CR and 54.9% achieved confirmed PR with LEN+PEM, compared with 4.2% CR and 31.9% PR with sunitinib, respectively. Responses were durable, with a median duration of response (DOR) in the LEN+PEM arm of 25.8 months (95% CI: 22.1, 27.9) vs 14.6 months (95% CI: 9.4, 16.7) in the sunitinib arm.

Prespecified subgroup analyses (Appendix F) showed that the PFS, OS, and ORR benefit observed with LEN+PEM vs sunitinib was generally maintained across subgroups, including MSKCC risk groups (favourable, intermediate, poor), IMDC risk groups (favourable, intermediate, poor), and PD-L1 status (combined positive score [CPS] ≥1, CPS <1 HR).

Treatment with LEN+PEM led to improved HRQoL (Appendix M), improving physical functioning, fatigue, dyspnoea, and constipation scores compared with sunitinib.

[redacted]

LEN+PEM is generally well-tolerated in patients with aRCC. The median duration of exposure was approximately 2.2-fold longer for LEN+PEM (17.0 months) than sunitinib (7.84 months). The most common TEAEs in the LEN+PEM arm were diarrhoea, hypertension, hypothyroidism, decreased appetite, fatigue, nausea, and stomatitis. Grade ≥3 TEAEs occurred in 82.4% of patients in the LEN+PEM arm vs 71.8% in the sunitinib arm. [redacted]

Discontinuation of all study treatments due to TEAEs was comparable in both treatment arms (13.4% and 14.4% for LEN+PEM and sunitinib, respectively). Clinically significant AEs for lenvatinib occurred in 94.0% of patients in the LEN+PEM arm and 85.0% of patients in the sunitinib arm, and are consistent with

the known safety profile of each drug, except for an increased incidence of hypothyroidism, which was primarily low-grade.

Furthermore, indirect treatment comparisons demonstrated that LEN+PEM generally outperformed all comparators relevant in England and Wales (sunitinib, pazopanib, and cabozantinib [intermediate/poor risk only]) on survival endpoints (OS, PFS) and response endpoints (ORR, CR).

4.10.1. Strengths and limitations of the evidence base

4.10.1.1. Strengths

The efficacy of LEN+PEM was investigated in CLEAR, a large and robust Phase 3, randomised, international, multicentre, open-label, active-controlled trial. CLEAR enrolled 1069 patients with aRCC who had no prior treatment with systemic therapy. Patients had a histological or cytological confirmation of RCC with a clear-cell component, which may have also included other histological features, such as sarcomatoid and papillary.

The CLEAR study included patients from eight centres in the UK (26 patients), with 358 (33.5%) patients being from Western Europe. Overall, 533 patients (LEN+PEM and sunitinib arms; 74.9%) in the CLEAR study were white, while 0.7% were black or African American and 20.0% were Asian, which generally aligns with that expected in England and Wales (144).

CLEAR collected data on a variety of clinically-relevant endpoints which are also important to patients. The efficacy of LEN+PEM was demonstrated consistently across all the clinically relevant endpoints, including PFS, OS and ORR which were directly referenced in the scope for this appraisal. Furthermore, these efficacy endpoints are consistent with that used in studies of other therapeutic interventions in the population of aRCC (145, 146). The definition of progression when evaluating PFS in CLEAR followed an established response evaluation criteria (RECIST 1.1), in line with EMA guidance (147).

HRQoL was investigated as a secondary endpoint during CLEAR, with changes from baseline in patients treated with LEN+PEM compared with sunitinib recorded using the NICE reference case preferred EQ-5D-3L, alongside the cancer-specific EORTC QLQ-C30, and kidney cancer-specific FKSI-DRS.

4.10.1.2. Limitations

CLEAR was an open-label study due to different routes of administration (lenvatinib: oral; pembrolizumab: IV). However, the study attempted to minimise bias by utilising IIR of primary endpoints. The updated OS data remain immature; median OS has not yet been achieved in either treatment arm. Another limitation of CLEAR was the utilisation of the MSKCC prognostic classification system to stratify patients into favourable, intermediate or poor risk. Although relevant, its successor, the IMDC system, is primarily applied in UK clinical practice.

4.10.2. End-of-life criteria

Median OS for patients treated with LEN+PEM or sunitinib has not yet been reached in the CLEAR study (as of 31st March 2021), however, based on the statistically significant improvements in PFS and OS, median OS for patients treated with IO-TKI combination therapy is expected to be greater than those patients treated with TKIs alone. In pivotal trials of the current NICE-recommended first-line monotherapies for aRCC (sunitinib, pazopanib, tivozanib, cabozantinib), median OS ranged from 21.8 to 30.3 months (23-28). Eisai does not consider LEN+PEM to meet end-of-life criteria in the overall aRCC patient population.

5. Cost effectiveness

LEN+PEM has the potential to be cost-effective as a first-line therapy in patients with aRCC

- A cost-utility analysis with a 40-year time horizon was conducted to evaluate the cost-effectiveness of LEN+PEM vs current comparators in England and Wales
    - In the base-case (list price) analysis of all patients with aRCC, LEN+PEM was associated with the following results:
    - vs sunitinib: 1.02 QALYs gained, £120,410 incremental costs, ICER £118,286 per QALY gained
    - vs pazopanib: 1.02 QALYs gained, £117,374 incremental costs, ICER £115,303 per QALY gained

- vs tivozanib: 1.02 QALYs gained, £130,982 incremental costs, ICER £128,671 per QALY gained

- In subgroup (list price) analyses of intermediate and poor risk patients with aRCC, LEN+PEM compared with cabozantinib was associated with 0.78 QALYs gained, £93,050 incremental costs, and an ICER of £118,571 per QALY gained.

5.1. Published cost-effectiveness studies

A broad SLR was conducted to identify cost-effectiveness studies from the published literature. The initial search was run on the 27th March 2019, with updates on 1st September 2020, and 5th January 2021. A complete description of the search methodology, a PRISMA flow diagram, and a summary of studies identified are presented in Appendix G. In total, 32 publications (relating to 28 cost utility and four budget impact analyses studies) were identified by the SLR. When these studies were narrowed to those relevant to the NICE decision problem (LEN+PEM, sunitinib, tivozanib, pazopanib, and cabozantinib), three studies; 13 publications were applicable.

5.2. Economic analysis

No existing economic evaluations of LEN+PEM vs sunitinib were identified in the cost-effectiveness SLR, therefore a de-novo cost-effectiveness model was developed.

5.2.1. Patient population

The economic analysis considered patients with untreated aRCC, in line with the patient population defined in CLEAR (118). Patient characteristics of the modelled cohort matched those of the CLEAR trial, with a mean age of 61.2, and 74.5% male.

5.2.2. Subgroups

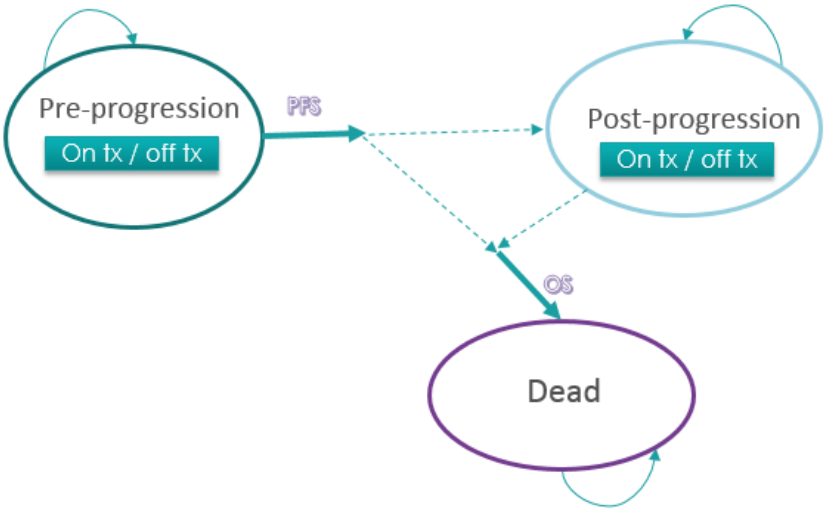
The model also included separate consideration for the IMDC intermediate and poor risk subgroup, which included an additional comparison with cabozantinib.

5.2.3. Model structure

The cost-effectiveness model was developed in Microsoft® Excel, and was structured as a partitioned survival model with three health states; pre-progression, post-progression, and death. The model schematic is presented in Figure 17. The cycle length considered was 7 days, aligned with most NICE technology appraisals (TAs) in RCC (21, 90-92, 141).

All patients enter the model progression-free, in the “pre-progression” state where they receive either LEN+PEM or comparator treatments. Patients can discontinue treatments but remain progression-free, or they can experience disease progression and transition to the post-progression state. Patients can transition to the ‘Dead’ state from any state in the model; this is an absorbing state.

Figure 17: Model schematic



Note: dashed lines indicate transitions that implied (but not explicitly modelled) while solid lines indicate explicit model transitions.
Abbreviations: OS, overall survival; PFS, progression-free survival; Tx, treatment.

To estimate the percentage of patients in each health state at each model cycle, survival distributions for PFS and OS were used. This enabled the estimation of treatment costs, disease state costs, and health state utility values to accrue quality-adjusted life years (QALY) and costs over the model time horizon. At each cycle, the PFS distribution was used to calculate the percentage of patients remaining in the pre-progression state, while the OS distribution was used to calculate the percentage of patients who died. The percentage of patients in the post-progression state was inferred from the percentage difference between OS and PFS.

Patients on-treatment, patients off-treatment, the number of incident patients progressed, incident dead and incident treatment discontinuers were calculated for

tracking purposes and to assign costs; they are not standalone health states. Progression-free, progressed, dead, patients on and off-treatment were half-cycle corrected. However, incident patients were not half-cycle corrected so that the number of new patients was captured at each cycle as opposed to the average number of new patients between cycles.

5.2.4. Features of the economic analysis

Key features of the economic analysis are outlined in Table 22.

Table 22: Features of the economic analysis

Setting	Base case	Justification
Time horizon	40 years	Lifetime horizon for the defined population, in line with time horizons used in NICE technology appraisals for NIVO+IPI, AVE+AXI and PEM+AXI (148-150)
Discount rate for health outcomes and cost outcomes	3.5%	In line with current NICE guidance (20)
Model population/ subgroup	Overall population Subgroup: IMDC Intermediate and poor risk sub-population	To reflect full expected indicated population (118, 134) In line with the recommendation for cabozantinib (92)
Perspective	NHS and personal social services	In line with current NICE guidance (20)
First-line comparators included in analysis	• Sunitinib • Pazopanib • Tivozanib • Cabozantinib	Based on recommended first-line treatments; cabozantinib to be evaluated for the intermediate and poor risk group only (92)
Subsequent treatments included in analysis	• Sunitinib • Pazopanib • Nivolumab • Everolimus • Cabozantinib • Axitinib • LEN+EVE	Based on commonly used subsequent treatment, as recommended by NICE pathways (151)
Stopping rule of pembrolizumab	Applied for 2 years	In line with KEYNOTE-426 protocol, NICE TA650 (149)

Abbreviations: AE, adverse event; AVE, avelumab; AXI, axitinib; CABO, cabozantinib; ERG, evidence review group; EVE, everolimus; FDA, Food and Drug Administration; HR, hazard ratio; IPI, ipilimumab; LEN, lenvatinib; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; NMA, network meta-analysis; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; TTD, time-to-treatment discontinuation; UK, United Kingdom.

5.2.5. Intervention technology and comparators

5.2.5.1. Intervention

The intervention considered is a combination of lenvatinib 20 mg, once daily (QD), every 21-day cycle, plus pembrolizumab 200 mg administered every 3 weeks (Q3W). This is aligned with the dosing schedule used in CLEAR (Section 4.2).

5.2.5.2. Comparators

Comparators within each population were selected based on current NICE recommendations (151). Therapies that are recommended for use within the Cancer Drugs Fund are not included as comparators as per current NICE guidance (152).

Overall population:

- Sunitinib
- Pazopanib
- Tivozanib.

Intermediate and poor risk population (as defined in the IMDC criteria):

- Cabozantinib.

5.3. Clinical parameters and variables

The principal source of data used to inform the analysis was the CLEAR trial (Section 4.6). Patient level data were used to inform the following outcomes for LEN+PEM, and sunitinib:

- Extrapolation of TTD
- Extrapolation of PFS
- Extrapolation of OS
- AE durations and frequencies
- Utility values

Survival analyses were conducted by fitting a series of distributions to the LEN+PEM and sunitinib data from CLEAR (153), using parametric survival techniques consistent with NICE DSU TSD 14 (154). All statistical models used in the base case

are presented in Appendix N. These distributions were: exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma. Single stratified fits and joint fits (with treatment as predictor) were fitted to the data. These parametric models were fitted to the OS, PFS and TTD data (joint fits were not fitted for the TTD data, but TTD was fitted separately for lenvatinib, pembrolizumab, and sunitinib).

The FDA PFS censoring rule was used in the base case, as this forms the primary endpoint from CLEAR. A scenario using the EMA censoring criteria is included as a scenario analysis. All analyses were completed using SAS (version 9.4).

The intermediate and poor risk subgroup was defined in accordance with the IMDC prognostic model. This is the risk classification system most commonly used in UK clinical practice.

In accordance with the DSU recommendations (155), proportional hazard (PH) assumptions were first tested though visual inspection of the log-cumulative hazard plot to assess if the LEN+PEM and sunitinib treatment curves cross for PFS and OS.

In addition, formal testing through the Schoenfeld residuals test was performed where a p-value less than 0.05 suggests the assumption of proportional hazards is rejected and that independent parametric fits may be more suitable. Subsequently, the statistical fits for LEN+PEM and sunitinib for PFS and OS, and for lenvatinib, pembrolizumab, and sunitinib for TTD were assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC) criteria, with the distribution producing the lowest AIC and BIC indicated as being the best fitting distribution. Similar to the approach adopted by the evidence review group (ERG) in NICE TA640 (156), survival models were categorised in terms of statistic fit using modified Burnham (157) or Anderson and Raftery (158) rules of thumb to highlight the appropriateness of the remaining distributions relative to the model(s) with the best statistical fits. The modified rules of thumb for goodness-of-fit are summarised in Table 23, and are based on the AIC and BIC point differences relative to the models with the lowest AIC and BIC.

Table 23: AIC and BIC rule of thumb for goodness-of-fit

Difference in points from model with lowest AIC and BIC	AIC rule of thumb category	BIC rule of thumb category
0–4 points	Good	Acceptable
4–7 points	Reasonable	
7–10 points	Acceptable	

Difference in points from model with lowest AIC and BIC	AIC rule of thumb category	BIC rule of thumb category
>10 points	Poor	Poor

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Furthermore, the proportion of patients expected to be alive and progression-free at Years 2, 5, and 10, as informed from the output of each distribution, were extracted and these predictions were compared with long-term survival data found in external publications.

Clinical validation of extrapolations was also conducted at an advisory board in July 2021 with three clinicians and three health economists (data on file). A subsequent advisory board also took place in September 2021 with four clinicians and two health economists, which informed resource use and other clinical assumptions, for the cost-effectiveness model (data on file).

5.3.1. Extrapolation of OS

5.3.1.1. LEN+PEM and sunitinib, from the CLEAR study

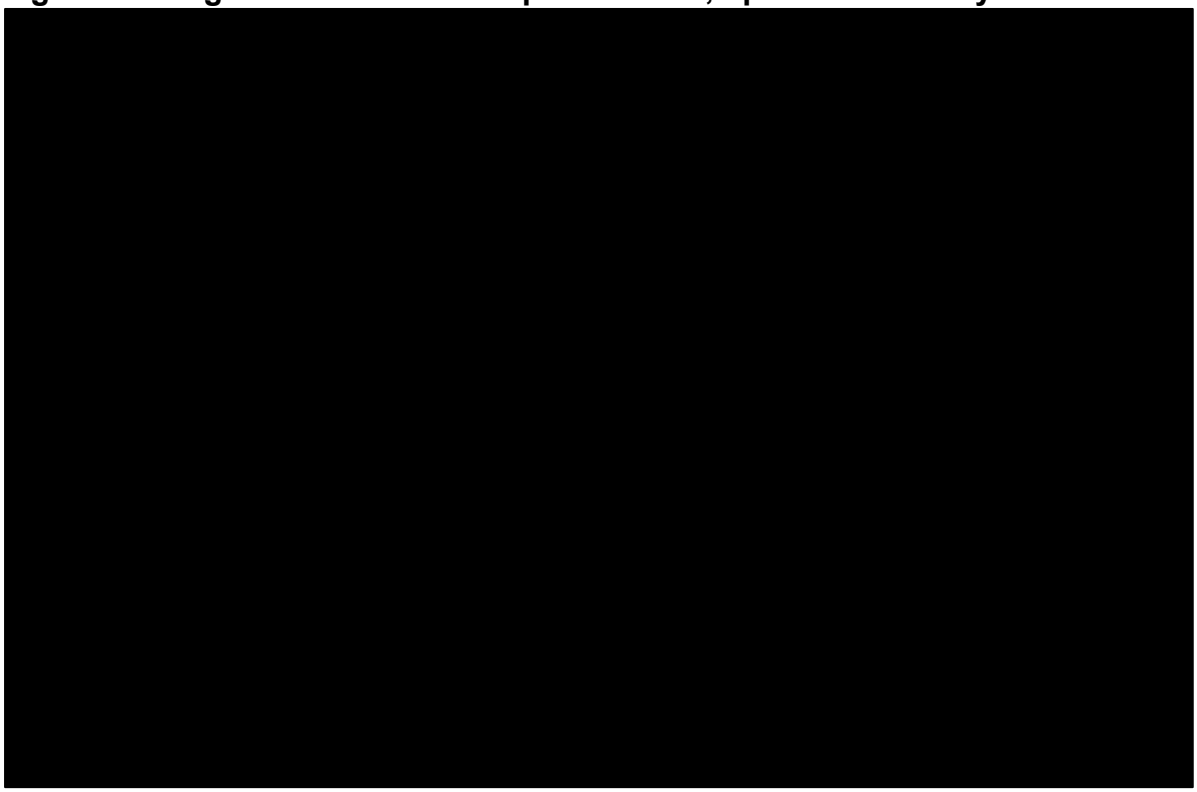
- Data from the CLEAR trial showed a convergence of OS between LEN+PEM and sunitinib
- The log-cumulative hazard plot and Schoenfeld residual test (p=0.014) indicated that a proportional hazards approach may not be appropriate and therefore independent fits were considered. All independent extrapolations of LEN+PEM and sunitinib crossed (resulting in long-term OS for LEN+PEM falling below that of sunitinib) except exponential and log-normal distributions
- Clinical opinion was that long-term OS for LEN+PEM would not be expected to fall below sunitinib, and therefore scenarios in which this occurred during extrapolation were considered clinically implausible
- Independent exponential distributions were used for LEN+PEM and sunitinib, as these were the most conservative OS extrapolations, and also coincided better with long-term predictions of survival from clinical experts

Based on the latest updated OS analysis (data cut-off 31st March 2021), the OS curves for LEN+PEM and sunitinib converged and appeared to cross at approximately 188 weeks. Log cumulative hazard plots for the LEN+PEM and

sunitinib treatment arms (Figure 18) were non-parallel, suggesting that the proportional hazards assumption did not hold and that joint parametric distributions were not suitable for modelling of OS.

While LEN+PEM showed improved OS in the short term, convergence and crossing occurred between the KM curves, as the risk of death for LEN+PEM appeared to increase and exceed the risk of mortality of sunitinib. However, it is important to note that there was a small number of patients at risk at the point at which the curves converge. Clinical experts at the July 2021 and September 2021 advisory boards indicated that while convergence may be expected at a point, long-term OS for LEN+PEM would not be expected to fall below that of sunitinib.

Figure 18: Log-cumulative hazard plots for OS, updated OS analysis



Abbreviations: LENVAT+PEMBRO, lenvatinib plus pembrolizumab.

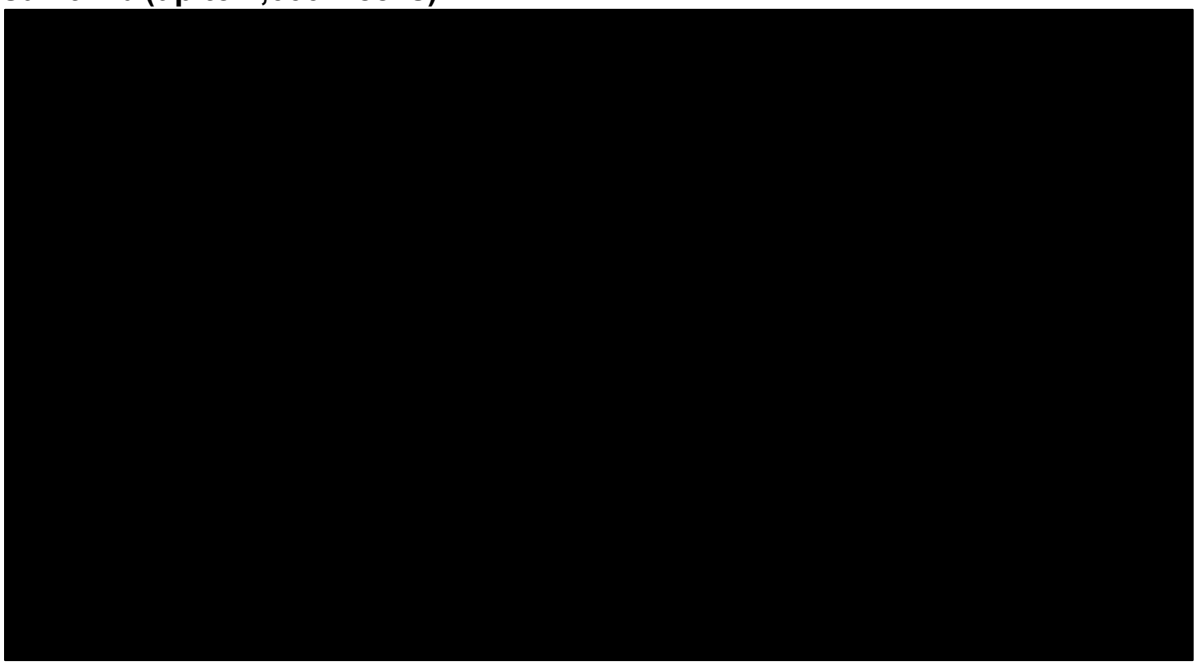
The NICE Decision Support Unit (DSU) TSD14 (154) recommends that the same type of parametric model be applied unless sufficient justification is provided to warrant the use of separate types of parametric models based on “clinical expert judgement, biological plausibility and robust statistical analysis.” Based on comments from clinical experts at the July and September 2021 advisory boards about the implausibility of the curves crossing, only parametric distributions that did not result in crossing of the curves for LEN+PEM and sunitinib (i.e. exponential and log-

normal) were considered for the extrapolation of long-term OS. Of these, the exponential distribution provided the most plausible set of extrapolations because it resulted in long-term OS estimates that are consistent with clinician expectations for the existing treatment landscape for aRCC (<20% at 10 years). The log-normal distribution resulted in more optimistic long-term OS with (>20% at 10 years for sunitinib) and was therefore tested in a sensitivity analysis.

Given the convergence of OS KM curves observed in the CLEAR trial and potential uncertainty around long-term extrapolations for OS, additional approaches were also considered for OS as part of scenario analyses to explore the impact of different OS extrapolation assumptions. These are described further in Appendix O and summarised in Table 24. Further information on the 2-stage adjustment is outlined in section 4.6.3

Figure 19 shows the selected distributions for LEN+PEM and sunitinib. More detailed discussion on statistical fits, long-terms OS estimates obtained and how the selected distribution was selected is presented in Appendix O.

Figure 19: Long-term single parametric OS predictions for LEN+PEM and sunitinib (up to 2,000 weeks)



Abbreviations: KM, Kaplan-Meier; LEN+PEM, lenvatinib plus pembrolizumab; OS, overall survival.

Table 24: Options for modelling OS for the overall population

Scenario		LEN+PEM	Sunitinib
1 (base case)	Single parametric fits	Single exponential distribution	Single exponential distribution

Scenario		LEN+PEM	Sunitinib
2	Joint parametric fits	Joint Weibull distribution	Joint Weibull distribution
3	Two-stage adjustment	0% of patients on subsequent treatment using single exponential distribution	0% of patients on subsequent treatment using single exponential distribution
4	Two-stage adjustment	Patients on subsequent treatment as per KOL recommendation using single exponential distribution	Patients on subsequent treatment as per KOL recommendation using single exponential distribution

Abbreviations: HR, hazard ratio; KOL, key opinion leader; KM, Kaplan-Meier; LEN+PEM, lenvatinib plus pembrolizumab; NMA, network meta-analysis.

5.3.1.2. Non-CLEAR comparators

An NMA was undertaken to inform comparisons against comparators not included within the CLEAR trial (Section 4.7 and Appendix D). This included pazopanib, tivozanib, and cabozantinib (cabozantinib only being relevant for the intermediate and poor risk subgroup). However, for the base-case model, the NMA was not utilised because equivalence in efficacy was assumed between sunitinib, pazopanib, and tivozanib, in line with committee opinion in prior appraisals in first-line RCC (21, 89, 90, 92, 141). Equivalence between sunitinib and pazopanib is widely accepted, and it is also acknowledged that tivozanib is expected to be 'at best' similar to sunitinib or pazopanib in TA512 (100). This assumption was confirmed by clinical experts at the September 2021 advisory board (Section 5.3).

5.3.1.3. Intermediate/poor risk subgroup

The selection of base-case OS distribution for LEN+PEM for the intermediate and poor risk subgroup was conducted using the same approach as the overall population.

External validation during the July 2021 advisory board suggested that in the current clinical landscape, for an overall first-line aRCC population, patients starting treatment would likely have 5-year OS of around 50%, and 10-year OS below 20%. These expectations relate to the overall population; it was assumed that the intermediate and poor risk group would have lower OS than the overall population. Using sunitinib as an example, this assumption is supported by the results of the KEYNOTE-426 (159) and CheckMate 214 (160) trials. In KEYNOTE-426, 1 and 2-year OS for sunitinib was 6.9% and 9.7% lower for the IMDC intermediate and poor risk subgroup compared with the overall population (sunitinib 1 year OS rate: 72% vs

78.9%; 2 year OS rate 55.8% vs 65.5%). Similarly, CheckMate 214 showed 7.5% lower OS for the IMDC intermediate and poor risk subgroup compared with the overall population at Year 4 (35.8% vs 43.3%).

Assuming a similar OS decrement would be present at 10 years for LEN+PEM, the most plausible long-term extrapolation based on the CLEAR trial data was the exponential distribution (Table 25) therefore, this was used in the base-case. Other distributions where curves did not cross were Weibull, log-normal, and log-logistic. The log-normal and log-logistic distributions produced overly optimistic extrapolations for an intermediate and poor risk group population, therefore the Weibull distribution was tested in a sensitivity analysis.

Table 25: Expected OS per distribution with LEN+PEM using updated OS analysis (31st March 2021), intermediate and poor risk group (IMDC) vs overall population

Distribution for LEN+PEM	2-year OS prediction	5-year OS prediction	10-year OS prediction	40-year OS prediction
IMDC intermediate and poor population				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Overall population				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab.

The Bayesian NMA was utilised to estimate relative effectiveness of cabozantinib compared with LEN+PEM. More information on the NMA and its results are presented in Appendix D, but results for OS of cabozantinib are summarised in Table 26.

Table 26: OS HR of comparator vs LEN+PEM for the intermediate and poor risk population (IMDC)*

Treatment	HR comparator vs LEN+ PEM	Lower 95% limit (LEN+PEM)	Upper 95% limit (LEN+PEM)	Comments
OS				
Cabozantinib	[redacted]	[redacted]	[redacted]	NMA output

*NMA results as of 31 March 2021.
Abbreviations: HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; LEN+PEM, lenvatinib plus pembrolizumab; NMA, network meta-analysis; OS, overall survival.

5.3.2. Extrapolation of PFS

PFS in the base case was assessed according to the US FDA censoring criteria in line with the primary endpoint from CLEAR.

5.3.2.1. CLEAR comparators (LEN+PEM and sunitinib)

- Assessment of the PH assumption via the Schoenfeld residuals test resulted in a p-value of 0.35, suggesting that the proportional hazard assumption holds (p>0.05), and that joint parametric fits for LEN+PEM and sunitinib were suitable
- The log-normal joint parametric distribution was selected, based on having the best statistical fit according to both AIC and BIC, the best visual fit to the tails of both LEN+PEM and sunitinib, and also was the distribution that produced estimates most similar to the published literature at 2 years

As depicted in Figure 20, the log-cumulative hazard plots for LEN+PEM and sunitinib converged very early on, however, after approximately 8 weeks, the curves maintained their separation and were broadly parallel until the end of follow-up. Formal assessment of the PH assumption via the Schoenfeld residuals test resulted in a p-value of 0.35, suggesting that the proportional hazard assumption holds (p>0.05), and that joint parametric fits for LEN+PEM and sunitinib were suitable.

Figure 20: Log-cumulative hazard plots for PFS, FDA censoring rule

*Please note that the log-cumulative hazard plot is based on the diagnostic plot for the Weibull distribution hence why Weibull is shown in the title.

The log-normal joint parametric distribution was selected for PFS, based on having the best statistical fit according to both AIC and BIC, as well as the best visual fit to the tail for LEN+PEM and the best visual fit to the tail for sunitinib. In addition, the log-normal distribution produced estimates most similar to the published literature at 2 years, followed by the log-logistic distribution. The selected distributions are presented in Figure 21. The next best fitting distribution, generalised gamma, was tested in a scenario analysis.

Figure 21: Long-term single parametric PFS predictions for LEN+PEM and sunitinib (up to 2,000 weeks)

Abbreviations: KM, Kaplan-Meier; LEN+PEM, lenvatinib plus pembrolizumab; OS, overall survival.

5.3.2.2. Non-CLEAR comparators

Pazopanib and tivozanib were assumed to have equivalent PFS to sunitinib, which has been accepted by the committee in previous appraisals (21, 89, 90, 92, 141). Equivalence between sunitinib and pazopanib is widely accepted, and it is also acknowledged that tivozanib is expected to be 'at best' similar to sunitinib or pazopanib in TA512 (100).

5.3.2.3. Intermediate/poor risk subgroup

The selection of base-case PFS distribution for LEN+PEM for the intermediate and poor risk subgroup was selected using the same approach of distribution selection for the overall population. As sunitinib is not considered under this population, a single fit model was applied to LEN+PEM.

The exponential distribution was selected for LEN+PEM, as this had the best statistical fit on both AIC and BIC, and also visually had a good fit to the tail of the Kaplan-Meier curve. The Weibull was the next best fitting distribution and was tested in a sensitivity analysis.

The Bayesian NMA was utilised to estimate relative effectiveness of cabozantinib compared with LEN+PEM. More detail on the NMA methodology and results are

presented in Appendix D, however, results for PFS of cabozantinib from the NMA are summarised in Table 27.

Table 27: PFS HR of comparator vs LEN+PEM for the intermediate and poor risk population (IMDC)*

Treatment	HR comparator vs LEN+ PEM	Lower 95% limit (LEN+PEM)	Upper 95% limit (LEN+PEM)	Comments
PFS				
Cabozantinib	[redacted]	[redacted]	[redacted]	NMA output

*NMA results as of 31 March 2021.
Abbreviations: HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; LEN+PEM, lenvatinib plus pembrolizumab; NMA, network meta-analysis; PFS, progression-free survival.

5.3.3. Extrapolation of TTD

5.3.3.1. CLEAR comparators (LEN+PEM and sunitinib)

- TTD curves were generated separately for LEN and PEM because they are administered separately and PEM has a fixed time on treatment duration of 2 years. Given the different stopping rules for PEM compared with LEN and sunitinib, independent models were fitted for each treatment
- For PEM, although the generalised gamma was the best fitting curve, considerable uncertainty was observed around its parameters. The exponential, Weibull and Gompertz models all produced similar visual fits to the generalised gamma distribution. Of these, the Weibull distribution had the best statistical fit and was used in the base case
- The generalised gamma distribution generated good statistical and good visual fits to the tails for both LEN and sunitinib, and hence was used for the base case analysis

TTD curves were generated separately for lenvatinib and pembrolizumab as the treatments are administered separately, and pembrolizumab has a fixed time on treatment duration of 2 years (149). Given the different stopping rules for pembrolizumab compared with lenvatinib and sunitinib, independent models were fitted for each treatment. Further, the hazards for each treatment were expected to be sufficiently different to justify the use of different types of parametric model for each treatment.

For pembrolizumab, the generalised gamma distribution produced the best statistical and visual fit to the TTD KM curve for pembrolizumab. However, it is important to note that the poor relative statistical and visual fits of other distributions compared with the generalised gamma distribution are due to the sharp drop in the tail of the KM curve associated with the 2-year stopping rule for pembrolizumab. Therefore, these may produce unreliable indications of the most appropriate parametric distribution for pembrolizumab TTD. Furthermore, considerable uncertainty was observed around the generalised gamma parameters, with the standard errors being larger than the parameter values themselves, and a 95% CI around the median survival time of 1.30×10^{-141} to 4.04×10^{144} weeks. The exponential, Weibull and Gompertz models all produced similar visual fits to the generalised gamma distribution up until the sharp drop in the tail (at approximately 100 weeks). Of these, the Weibull distribution had the best statistical fit and was therefore selected for use in the base-case analysis.

Compared with pembrolizumab, lenvatinib and sunitinib have different treatment stopping rules (treatment until progression or unacceptable toxicity) and mechanisms of action. Therefore it was considered reasonable to apply different types of parametric survival models to these treatments compared with pembrolizumab. The generalised gamma distribution generated good statistical and good visual fits to the tails for both lenvatinib and sunitinib, and hence was used for the base-case analysis.

5.3.3.2. Non-CLEAR comparators

For comparators outside the CLEAR trial (pazopanib and tivozanib) TTD was assumed equivalent to sunitinib, based on equivalence assumptions previously explained (Section 5.3.1.2).

5.3.3.3. Intermediate/poor risk subgroup

The selection of base-case TTD distributions for lenvatinib and pembrolizumab for the subgroup was based on statistical and visual fit to the data.

For lenvatinib, only the generalised gamma model produced a good statistical and visual fit, and hence this distribution was used. For pembrolizumab, while the generalised gamma distribution clearly produced the best statistical fit and one of the better visual fits to the tail, there was considerable uncertainty around the parameter

estimates for this distribution (similar to the overall population). Aside from the generalised gamma distribution, the Weibull and exponential distributions appeared to also produce reasonable fits to the tail, with the Weibull distribution selected over the exponential distribution on the basis of statistical fit.

The generalised gamma distribution was chosen to model TTD for cabozantinib. Although it did not have the best statistical fit, it was deemed appropriate because cabozantinib has a similar mechanism of action and stopping rules to lenvatinib. Additionally, the NICE DSU recommends that the same type of parametric model be selected across comparators. The generalised gamma distribution generated a relatively good statistical fit to the data compared with the distribution with the lowest AIC and BIC (as well as a reasonable visual fit). More detail on curve selection is presented in Appendix O.

Table 28 presents the base-case TTD distributions selected for lenvatinib, pembrolizumab and cabozantinib. Further information on curve selection for cabozantinib is presented in Appendix O.

Table 28: Base case TTD distributions for Intermediate and poor risk subgroup

Subgroup	Lenvatinib Distribution	Pembrolizumab Distribution	Cabozantinib
Intermediate and poor risk	Single generalised gamma	Single Weibull	Generalised gamma distribution

Abbreviations: TTD, time to treatment discontinuation.

5.3.4. Adverse events

The model includes Grade ≥3 AEs occurring in ≥5% of patients. This is a commonly accepted approach as Grade ≥3 AEs reflect events that are likely to require hospitalisation; therefore, assumed to have the greatest burden on resources and quality of life. Rates of AEs were taken from the CLEAR trial for LEN+PEM and sunitinib (118). Probabilities of experiencing AEs for all other comparators were extracted from their respective clinical trial publications (97, 99, 161). For comparators used in subsequent treatment, TEAEs were reported in the clinical trial publication for pazopanib (rate of AEs with pazopanib and sunitinib as subsequent line were assumed to be the same as first-line) only, while sources other than the clinical trial publication were used for all other subsequent treatments (162-165).

Frequencies of AE events are listed in Table 29 for first-line treatments (representing frequencies for pre-progression patients) and in Table 30 for subsequent treatments (representing frequencies for progressed patients). AE frequencies were assumed to be the same in the overall population and the intermediate and poor risk subgroup.

Table 29: Frequency of patients experiencing Grade ≥3 AEs by first-line treatment (pre-progression) occurring in ≥5% of patients

AE	LEN+PEM	Sunitinib	Pazopanib	Cabozantinib	Tivozanib
Anaemia	[redacted]	[redacted]	0.000	0.000	0.000
Asthenia	[redacted]	[redacted]	0.000	0.000	0.000
Decreased appetite	[redacted]	[redacted]	0.000	0.051	0.000
Diarrhoea	[redacted]	[redacted]	0.088	0.103	0.000
Dyspnoea	[redacted]	[redacted]	0.000	0.000	0.000
Fatigue	[redacted]	[redacted]	0.106	0.064	0.054
Hyperglycaemia	[redacted]	[redacted]	0.051	0.000	0.000
Hypertension	[redacted]	[redacted]	0.148	0.282	0.270
Hypertriglyceridemia	[redacted]	[redacted]	0.000	0.000	0.000
Increased ALT	[redacted]	[redacted]	0.176	0.051	0.000
Increased amylase	[redacted]	[redacted]	0.000	0.000	0.000
Increased AST	[redacted]	[redacted]	0.126	0.000	0.000
Increased lipase	[redacted]	[redacted]	0.000	0.000	0.000
Lymphocytopenia	[redacted]	[redacted]	0.053	0.000	0.000
Nausea	[redacted]	[redacted]	0.000	0.000	0.000
Neutropenia	[redacted]	[redacted]	0.000	0.000	0.000
Palmar-plantar syndrome	[redacted]	[redacted]	0.058	0.077	0.000
Platelet count decrease	[redacted]	[redacted]	0.000	0.000	0.000
Proteinuria	[redacted]	[redacted]	0.000	0.000	0.000
Stomatitis	[redacted]	[redacted]	0.000	0.051	0.000
Weight decreased	[redacted]	[redacted]	0.000	0.000	0.000

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; LEN+PEM, lenvatinib plus pembrolizumab.

Table 30: Frequency of patients experiencing Grade ≥3 AEs by subsequent treatment (post-progression) occurring in ≥5% patients

AE	Sunitinib	Pazopanib	Nivolumab	Everolimus	Cabozantinib	Axitinib	LEN+EVE
Anaemia	[redacted]	0.000	0.000	0.165	0.057	0.000	0.078
Asthenia	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Decreased appetite	[redacted]	0.000	0.000	0.000	0.000	0.000	0.059
Diarrhoea	[redacted]	0.088	0.000	0.000	0.130	0.111	0.196
Dyspnoea	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Fatigue	[redacted]	0.106	0.000	0.075	0.109	0.103	0.137
Hyperglycaemia	[redacted]	0.051	0.000	0.000	0.000	0.000	0.000
Hypertension	[redacted]	0.148	0.000	0.000	0.148	0.167	0.137
Hypertriglyceridemia	[redacted]	0.000	0.000	0.000	0.000	0.000	0.078
Increased ALT	[redacted]	0.176	0.000	0.000	0.000	0.000	0.000
Increased amylase	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Increased AST	[redacted]	0.126	0.000	0.000	0.000	0.000	0.000
Increased lipase	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Lymphocytopenia	[redacted]	0.053	0.000	0.000	0.000	0.000	0.000
Nausea	[redacted]	0.000	0.000	0.000	0.000	0.000	0.059
Neutropenia	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Palmar-plantar syndrome	[redacted]	0.058	0.000	0.000	0.082	0.056	0.000
Platelet count decrease	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Proteinuria	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Stomatitis	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Weight decreased	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; LEN+EVE, lenvatinib plus everolimus.

5.4. Measurement and valuation of health effects

5.4.1. HRQoL data from clinical trials

HRQoL data were collected in the CLEAR trial using the FKSI-DRS, EORTC QLQ-C30, and EQ-5D-3L instruments. These assessments were conducted at baseline and on Day 1 of every treatment cycle, starting with Cycle 2.

Completion rates per cycle for EQ-5D are presented in Table 31.

Table 31: EQ-5D completion rates per cycle

	LEN+PEM (N=355)				Sunitinib (N=357)			
	Completion	**≥1 item completed**	**All items complete**	**All items missing**	**Completion**	**≥1 item completed**	**All items complete**	**All items missing**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	LEN+PEM (N=355)				Sunitinib (N=357)			
	Completion	≥1 item completed	All items complete	All items missing	Completion	≥1 item completed	All items complete	All items missing
Cycle 17	[redacted]							
Cycle 18								
Cycle 19								
Cycle 20								
Cycle 21								
Cycle 22								
Cycle 23								
Cycle 24								
Cycle 25								
Cycle 26								
Cycle 27								
Cycle 28								
Cycle 29								
Cycle 30								
Cycle 31								
Cycle 32								
Cycle 33								
Cycle 34								
Cycle 35								
Cycle 36								
Cycle 37								
Cycle 38								
Cycle 39								
Cycle 40								
Cycle 41								

	LEN+PEM (N=355)				Sunitinib (N=357)			
	Completion	≥1 item completed	All items complete	All items missing	Completion	≥1 item completed	All items complete	All items missing
Cycle 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 54	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off: 28th August 2020 (final PFS analysis).
Abbreviations: LEN, lenvatinib; OTV, off-treatment visit; PEM, pembrolizumab.

Observed EQ-5D index values were classified into three groups based on the time of assessment and disease progression status as follows: baseline, before progression, and after progression.

The mean EQ-5D index values for the treatment arms were similar ([redacted] for LEN+PEM, and [redacted] for sunitinib) at baseline. The means decreased only very slightly during treatment before disease progression, with the mean index value for sunitinib declining to [redacted] For LEN+PEM, the mean index value before progression was [redacted] and the difference was statistically significant [redacted]. For participants who discontinued treatment due to disease progression, the mean index value at the off-treatment visit was [redacted] in the LEN+PEM arm, and also [redacted] in the sunitinib arm. The differences between the LEN+PEM arm and the sunitinib arm were not significant.

5.4.2. Mapping

Utilities were evaluated using EQ-5D-3L directly from patients from the CLEAR trial, which is consistent with the NICE reference case methods (20). Therefore, no mapping was conducted.

5.4.3. HRQoL studies

An SLR was conducted to identify health state utility value (HSUV) studies relevant to the decision problem from the published literature. A complete description of the search strategy and identified studies is presented in Appendix H. The SLR identified 24 studies that met the pre-defined inclusion criteria.

5.4.4. Adverse event disutilities

Disutility estimates and duration were taken from sunitinib arm of the NICE NIVO+IPI submission TA581 (148) and were assumed to be the same for all treatments and subgroups in the model. The total disutility decrement associated with each treatment was calculated as the sum product of the disutility associated with each AE, the duration of the disutility and the rate of experiencing an AE. Disutility due to AEs was not considered for subsequent treatments. Disutilities and duration per AE are presented in Table 32. AE disutility was not included in the base case as it was assumed that AE

disutility is included in utilities by health states, following a similar assumption in avelumab plus axitinib NICE TA645 (150) but they were explored in scenario analyses.

Table 32: AE disutilities and durations (Grade 3/4)

AEs	Grade 3/4 disutility	Disutility duration (weeks)	Comments
Anaemia	0.081	3.14	Median disutility duration based on sunitinib
Asthenia	0.204	3.14	Median disutility duration based on sunitinib
Decreased appetite	0.038	3.42	Median disutility duration based on sunitinib
Diarrhoea	0.261	3.42	Median disutility duration based on sunitinib
Dyspnoea	0.204	15.43	Assumed same as fatigue
Fatigue	0.204	15.43	Median disutility duration based on sunitinib
Hyperglycaemia	0.081	3.14	Assumed same as increased lipase
Hypertension	0.015	3.14	Median disutility duration based on sunitinib
Hypertriglyceridemia	0.081	3.14	Assumed same as increased lipase
Increased ALT	0.081	3.14	Assumed same as increased lipase
Increased amylase	0.081	3.14	Assumed same as increased lipase
Increased AST	0.081	3.14	Assumed same as increased lipase
Increased lipase	0.081	3.14	Median disutility duration based on sunitinib and assumed to be same as anaemia
Lymphocytopenia	0.081	3.14	Assumed same as platelet count decrease
Nausea	0.255	3.42	Median disutility duration based on sunitinib
Neutropenia	0.081	3.14	Assumed same as platelet count decrease
Palmar-plantar syndrome	0.040	15.00	Median disutility duration based on sunitinib
Platelet count decrease	0.081	3.14	Median disutility duration based on sunitinib and assumed to be same as anaemia
Proteinuria	0.081	3.14	Assumed same as increased lipase
Stomatitis	0.040	15.00	Median disutility duration based on sunitinib
Weight decreased	0.038	3.42	Assumed same as decreased appetite

Source: NIVO+IPI submission, NICE TA581 (21)
Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase.

5.4.5. HRQoL data used in the cost-effectiveness analysis

Treatment-specific utility values from CLEAR were used for the progression-free health state in the model. Progression-free utility for non-CLEAR comparators of pazopanib and tivozanib (and cabozantinib in the intermediate and poor risk population) was assumed to be equivalent to that of sunitinib.

Post-progression utility is not treatment-specific and was therefore applied to all progressed patients. The utility values from the CLEAR trial used in the analysis are presented in Table 33, for both the overall population and the intermediate and poor risk population. Pooled (i.e. non treatment-specific) utilities by progression status (pre- and post-progression) are presented in Table 34, and were used in a scenario analysis.

Table 33: Summary of utility values for cost-effectiveness analysis, CLEAR treatment-specific

Health state	Treatment	Mean	SE	Source
	Overall population			
Progression-free	LEN+PEM	[redacted]	[redacted]	CLEAR, EQ-5D UK tariff values
	Sunitinib	[redacted]	[redacted]	
	Pazopanib	[redacted]	[redacted]	Assumed equal to sunitinib
	Tivozanib			
Post progression	All	[redacted]	[redacted]	CLEAR, EQ-5D UK tariff values
	Intermediate and poor risk population (IMDC)			
Progression-free	LEN+PEM	[redacted]	[redacted]	CLEAR, EQ-5D UK tariff values
	Sunitinib	[redacted]	[redacted]	
	Pazopanib	[redacted]	[redacted]	Assumed equal to sunitinib
	Tivozanib			
	Cabozantinib			
Post progression	All	[redacted]	[redacted]	CLEAR, EQ-5D UK tariff values

Abbreviations: IMDC, International Metastatic RCC Database Consortium; LEN, lenvatinib; PEM, pembrolizumab; SE, standard error.

Table 34: Utility values from CLEAR, non-treatment specific (used in scenario)

Health state	Mean	SE	Source
	Overall population		
Progression-free	[redacted]	[redacted]	CLEAR, EQ-5D UK tariff values
Post progression	[redacted]	[redacted]	

Abbreviations: IMDC, International Metastatic RCC Database Consortium; SE, standard error.

5.4.5.1. General population utility

In the base case, no age adjustment was applied to the progression-free or post-progression utilities. In a scenario analysis, the regression model from Ara and Brazier, 2010 (166) was applied to adjust utilities for age and sex using a multiplicative approach whereby a multiplier was applied based on the ratio between the general population utility values for current age and starting age (Table 35).

Table 35: Age and sex-adjusted utility regression model coefficients

	Ara and Brazier (2010) (166)
Parameter	**Regression coefficient**
Constant	0.950857
Sex (male)	0.021213
Age	–0.000259
Age squared	–0.000033

Abbreviations: SE, standard error.

The calculated reference general population utility is presented in Table 36. The reference age (61 years) and the percentage of the male population (74.5%) from the CLEAR trial were used for both the overall population and intermediate and poor risk subgroup.

Table 36: Calculated reference general population utility

Utility calculation source	Utility
Ara & Brazier, 2010 (166)	0.8273

5.5. Cost and healthcare resource use identification, measurement and valuation

5.5.1. Intervention and comparator costs and resource use

5.5.1.1. Drug acquisition costs

Unit costs for each first-line drug component were extracted from the British National Formulary (BNF) (167). Where multiple formulations of the same drug component exist, the cheapest formulation per mg/unit was calculated as the pack price of each drug component divided by the product of the strength per unit of the drug component multiplied by the number of units per pack.

This was applicable to the following drugs:

- lenvatinib (available as 4 mg and 10 mg capsules)
- sunitinib (available as 12.5 mg, 25 mg and 50 mg capsules)
- pazopanib (available as 200 mg and 400 mg tablets)
- cabozantinib (available as 20 mg, 40 mg and 60 mg tablets)
- tivozanib (available as 0.89 mg and 1.34 mg capsules).

Only single preparations and form of pembrolizumab are listed in the BNF (167).

The drug acquisition cost for lenvatinib was calculated using a weighted cost per mg based on the average dose of lenvatinib patients received in the CLEAR trial. This accounted for usage of the 4 mg and 10 mg tablets based on cumulative days on the doses used in CLEAR (i.e. 0 mg, 4 mg, 8 mg, 10 mg, 14 mg, 20 mg, 28 mg, and 40 mg). The cumulative days on each dose as a percentage of the sum of all cumulative days was multiplied by the number of 4 mg and 10 mg tablets required for each dose to obtain the average number of 4 mg and 10 mg tablets used within CLEAR. This was then multiplied by the cost per tablet to obtain a weighted average cost per mg of lenvatinib used within the trial.

The cost per cycle for each drug component was calculated based on the dosing regimens of each drug component and dose intensity taken from CLEAR for lenvatinib, pembrolizumab, and sunitinib. The regimens for pazopanib, cabozantinib, and tivozanib were obtained from the relevant NICE technology appraisals (89, 90, 92). Table 37 presents the dosages, Table 38 presents the relative dose intensities, and Table 39 presents the acquisition costs for each treatment. Drug acquisition costs were assumed to be equivalent across the intermediate and poor subgroup.

Table 37: Dosing schedule for first-line treatment

Treatment		Route	Maintenance posology	Source
LEN+PEM	Lenvatinib	Oral	20 mg once daily	CLEAR
	Pembrolizumab	IV	200 mg Q3W	CLEAR
Sunitinib		Oral	50 mg once daily for 4 weeks followed by 2 weeks off treatment	CLEAR

Treatment	Route	Maintenance posology	Source
Pazopanib	Oral	800 mg once daily	NICE TA215 (89)
Cabozantinib	Oral	60 mg once daily	NICE TA542 (92)
Tivozanib	Oral	1.34 mg once daily for 21 days, followed by a 7-day rest period	NICE TA512 (90)

Abbreviations: IV, intravenous; LEN, lenvatinib; NICE, National Institute for Health and Care Excellence; PEM, pembrolizumab; Q3W, every 3 weeks.

Table 38: Relative dose intensity

Treatment	Drug	Relative dose intensity	Source	Assumptions
LEN+PEM	Lenvatinib	[redacted][†]	CLEAR	-
	Pembrolizumab	[redacted][‡]	CLEAR	CLEAR did not allow dose reductions for patients treated with PEM, however the estimate shown here reflects delays in drug administration
Sunitinib		[redacted]	CLEAR	-
Pazopanib		86%	NICE TA215 (89)	-
Cabozantinib		94%	NICE TA542 (92)	-
Tivozanib		94%	NICE TA512 (90)	-

[†]Dose intensity was calculated based on the cumulative days that patients received lenvatinib in CLEAR; [‡]In CLEAR, dose reductions for pembrolizumab were not permitted, however dose delays and interruptions could occur. An administration intensity was therefore calculated to represent these delays defined as the mean number of administrations received divided by the mean number of administrations expected during the time the patient was considered to be on pembrolizumab
Abbreviations: LEN, lenvatinib; NICE, National Institute for Health and Care Excellence; PEM, pembrolizumab.

Table 39: Drug acquisition costs (list price)

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

First-line drug acquisition costs were applied to the proportion of patients in each treatment arm remaining on first-line treatment in each model cycle within the model time horizon based on their respective TTD curves. Pembrolizumab has a maximum

time on treatment of 2 years (141). Table 40 shows the per cycle drug acquisition costs of first-line treatment and the total combined per cycle for each combination first-line treatment.

A scenario analysis considers alternative dosing frequency for pembrolizumab of 400 mg every 6 weeks. Drug acquisition costs would be the same however drug administration costs would be reduced due to less frequent dosing.

Table 40: Calculated first-line drug acquisition costs per model cycle

Treatment	Drug	Cost per model cycle	Total per cycle cost
LEN+PEM	Lenvatinib	[redacted]	[redacted]
	Pembrolizumab	[redacted]	
Sunitinib		[redacted]	[redacted]
Pazopanib		£450	£450
Cabozantinib		£1,132	£1,132
Tivozanib		£482	£482

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab.

5.5.1.2. Administration costs

Unit costs of drug administration were sourced from the National Schedule of NHS Costs 2019/20 (168) and are presented in Table 41. Drug administration costs were considered based on respective route of administration and dosing schedule as detailed in Table 37. Administration costs for oral drugs are assumed to be zero. Drug administration costs were assumed to be equivalent across the intermediate and poor subgroup. The per cycle drug administration costs of first-line treatment by each drug component of first-line intervention, and the total combined per cycle cost for each combination first-line treatment is shown in Table 42.

Table 41: NHS drug administration costs

Mode of administration	Unit cost	Source	HRG code
Exclusively oral chemotherapy	£0.00	Not applicable	Assumption
Simple parenteral chemotherapy at first attendance	£221.35	National Schedule of NHS Costs 2019/20 (168)	SB12Z
Subsequent oral chemotherapy or subsequent IV chemotherapy delivered on the same day	£0.00	Not applicable	Assumption

Abbreviations: HRG, healthcare resource group; IV, intravenous; NHS, National Health Service.

Table 42: Drug administration costs per model cycle for first-line treatments

Treatment	Administration type	Cost per model cycle	Total per cycle cost
LEN+PEM Lenvatinib	Subsequent oral chemotherapy or subsequent IV chemotherapy delivered on the same day	£0	
Pembrolizumab	Simple parenteral chemotherapy at first attendance	£74	£74
Sunitinib	Exclusively oral chemotherapy	£0	£0
Pazopanib		£0	£0
Cabozantinib		£0	£0
Tivozanib		£0	£0

Abbreviations: IV, intravenous; LEN, lenvatinib; PEM, pembrolizumab.

The per cycle drug administration costs were applied to the proportion of patients remaining on treatment in each model cycle within the model time horizon.

5.5.1.3. Subsequent treatment costs

Unit costs for each subsequent drug component were extracted from the BNF (167). Where multiple formulations of the same drug component exist, the cheapest formulation per mg was calculated and then selected for use in the model. Subsequent treatment unit costs are presented in Table 43. Dosing schedules for subsequent treatments are presented in Table 44.

Table 43: Subsequent treatment acquisition costs (list price)

Treatment	mg per unit	Pack size	Cost per pack
Lenvatinib	10 mg	30	£1,437.00
Lenvatinib	4 mg	30	£1,437.00
Sunitinib	12.5 mg	28	£784.70
Pazopanib	200 mg	30	£560.50
Nivolumab	10 mg/ml	10 ml	£1,097.00
Everolimus	10 mg	30	£2,673.00
Cabozantinib	60 mg	30	£5,143.00
Axitinib	1 mg	56	£703.40

Table 44: Dosing schedule for subsequent treatments

Treatment	Route	Maintenance posology	Relative dose intensity	Source	Assumptions
Sunitinib	Oral	50 mg once daily for 4 weeks followed by 2 weeks off treatment	[redacted]	Assumed same as first-line, CLEAR	Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity assumed to be 100%
Pazopanib	Oral	800 mg once daily	86%	Assumed same as first-line and TA650 (149)	Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity taken from NICE TA650
Nivolumab	Oral	480 mg Q4W	92%	Assumed same as first-line and TA650 (149)	Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity taken from NICE TA650
Everolimus	Oral	10 mg once daily	100%	EMA EPAR Afinitor (169)	100% dose intensity assumed
Cabozantinib	Oral	60 mg once daily	100%	Assumed same as first-line and TA650 (149)	Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity taken from NICE TA650
Axitinib	Oral	5 mg twice daily	102%	Assumed same as first-line and TA650 (149)	Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity taken from NICE TA650
LEN+EVE Lenvatinib	Oral	18 mg once daily	68%	Motzer et al., 2019 (161) and TA650 (149)	Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity taken from NICE TA650
Everolimus	Oral	5 mg once daily	85%		Dependency, dose, number of administrations per treatment cycle, number of weeks per treatment cycle all assumed same as first-line. Dose intensity taken from NICE TA650

Abbreviations: EMA, European Medicines Agency; EPAR, European public assessment report; IV, intravenous; LEN+EVE, lenvatinib plus everolimus; NICE, National Institute for Health and Care Excellence; Q4W, every 4 weeks.

The proportion of patients who receive subsequent treatment and the distribution of subsequent treatments received are presented in Table 45. These are based on a survey of two KOLs from the September 2021 advisory board (data on file). Clinicians highlighted that on average, patients go on to receive more than one line of subsequent treatment, therefore the distributions across treatments sum to more than 100%

Duration of subsequent treatments in weeks is presented in Table 46, and were based on data from the CLEAR trial for LEN+PEM and sunitinib, while for pazopanib, cabozantinib and tivozanib it was assumed to be equivalent to sunitinib, as these are also TKI treatments.

A scenario analysis using the distribution of subsequent treatments and proportion receiving subsequent treatments, from the CLEAR trial for LEN+PEM and sunitinib, and values from the PEM+AXI submission (TA650) for the non-CLEAR comparators (141) (Table 47) was conducted.

Table 45: Distribution of subsequent treatments as per first-line treatment received

First-line treatment	% of patients continuing to receive subsequent treatment	SUN	PAZO	NIVO	EVE	CABO	AXI	LEN+ EVE	Source
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	KOL responses, September 2021 UK advisory board (data on file)
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: AXI, axitinib; CABO, cabozantinib; EVE, everolimus; LEN, lenvatinib; NIVO, nivolumab; PAZO, pazopanib; PEM, pembrolizumab; SUN, sunitinib.

Table 46: Duration of subsequent treatments (weeks)

First-line treatment	SUN	PAZO	NIVO	EVE	CABO	AXI	LEN+EVE	Source
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CLEAR
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CLEAR
Pazopanib Cabozantinib Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to SUN

Abbreviations: AXI, axitinib; CABO, cabozantinib; EVE, everolimus; LEN, lenvatinib; NIVO, nivolumab; PAZO, pazopanib; PEM, pembrolizumab; SUN, sunitinib.

Table 47: Scenario analysis - Distribution of subsequent treatments as per first-line treatment received

First-line treatment	% of patients continuing to receive subsequent treatment	SUN	PAZO	NIVO	EVE	CABO	AXI	LEN+ EVE	Source
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CLEAR trial
SUN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PAZO	50%	0.0%	0.0%	60.0%	0.0%	25.0%	15.0%	0.0%	

First-line treatment	% of patients continuing to receive subsequent treatment	SUN	PAZO	NIVO	EVE	CABO	AXI	LEN+ EVE	Source
CABO	50%	0.0%	0.0%	60.0%	0.0%	0.0%	15.0%	25.0%	ERG base case. Re-weighted to sum to 100% (141)
TIVO	50%	0.0%	0.0%	60.0%	0.0%	25.0%	15.0%	0.0%	

Abbreviations: AXI, axitinib; CABO, cabozantinib; ERG, evidence review group; EVE, everolimus; LEN, lenvatinib; NIVO, nivolumab; PAZO, pazopanib; PEM, pembrolizumab; SUN, sunitinib; TIVO, tivozanib.

Subsequent treatment costs as per first-line treatment were calculated as the product of the per cycle drug acquisition and drug administration costs for each subsequent treatment, proportion of patients eligible to receive subsequent treatments by first-line treatment arm, the proportions receiving each subsequent treatment by first-line treatment arm, and the duration of each subsequent treatment. The subsequent treatment costs as per first-line treatment are presented in Table 48.

Table 48: Subsequent treatments costs based on first-line treatment received

Treatment	One-off cost
LEN+PEM	£20,494
Sunitinib	£39,307
Pazopanib	£39,307
Cabozantinib	£35,989
Tivozanib	£17,226

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab.

The total subsequent treatment cost for each first-line treatment was calculated as the sum of incident progressed patients within the model time horizon, multiplied by its one-off subsequent treatment cost. Subsequent treatment estimates were assumed as equivalent across the intermediate and poor subgroup due to a lack of subgroup population data.

5.5.2. Health-state unit costs and resource use

Medical resource use frequencies for each health state were based on frequencies detailed within the PEM+AXI NICE technology appraisal TA650 (141). Unit costs for medical resource use were taken from NHS Schedule of Reference Costs 2019/20 (168) (Table 49). The frequencies of resource use for progression-free patients and progressed were assumed to be the same for all treatments presented in Table 50.

Table 49: Medical resource use unit costs for routine disease management

Resource	Outpatient consultation medical oncology		Blood test	CT scan
	(first visit)	(follow-up)		
Unit cost	£253.20	£200.20	£2.53	£120.55
Source	National Schedule of NHS Costs 2019/20			
Source code	370	370	DAPS05	RD22Z

Abbreviations: CT, computed tomography; NHS, National Health Service.

Table 50: Per cycle medical resource use frequencies for routine disease management

Health state	Outpatient consultation medical oncology		Blood test	CT scan	Source	Comments
	(first visit)	(follow-up)				
Progression-free, all treatments	1.00[†]	0.25	0.25	0.08	NICE TA650 (149)	Assumed same resource use as in PEM+AXI submission
Progressed, all treatments	0.00	0.25	0.25	0.08	NICE TA650 (149)	Assumed same resource use as in PEM+AXI submission

[†]Applied only in the first cycle.
Abbreviations: CT, computed tomography; PEM + AXI, pembrolizumab plus axitinib.

The per cycle cost of disease management is presented in Table 51. A one-off cost for patients attending an outpatient consultation medical oncology (first visit) was applied in the first cycle only for progression-free patients. Resource use frequencies and unit costs for disease management were assumed equivalent across the intermediate and poor subgroup.

Table 51: Progression-free and progressed per cycle disease management costs

Health state	First cycle only costs	All cycles cost
Progression-free, all treatments	£253.20	£60.33
Progressed, all treatments	£0.00	£60.33

In addition, a one-off terminal care cost of £7,015.24 which was sourced from the PEM+AXI NICE TA650 (149) and inflated to 2020 estimates was applied for deaths in each cycle and assumed to be the same for all treatments. Furthermore, the model assumed no additional best supportive costs for patients who progress after first-line treatment but do not receive any subsequent treatment, in line with the PEM+AXI (149) and AVE+AXI (91) NICE technology appraisal submissions.

5.5.3. Adverse event unit costs and resource use

AE management costs were calculated based on the per event unit costs shown in Table 52, and the rate of AEs for each comparator (Section 5.3.4) and were applied as a one-off cost for each comparator. The cost assumptions associated with the management of AEs were informed by NICE technology appraisal TA551 (21) and

unit costs were derived from NHS Schedule of Reference Costs 2019/20 (168). AE management costs were assumed to be equivalent across the intermediate and poor subgroup. AEs costs were considered for first-line treatments (representing costs of progression-free patients) and for subsequent treatments (representing costs for progressed patients). The total AE costs by treatment are presented in Table 53.

Table 52: Adverse event costs per event

AE	Cost per event	Notes
Anaemia	£650	NHS Reference Costs 2019/20. Weighted average cost SA04G-L. Iron Deficiency Anaemia (£607.95) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Asthenia	£1,076	NHS Reference Costs 2019/20. Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay (£1034.43) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Decreased appetite	£1,068	NHS Reference Costs 2019/20. Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay (£1034.43) + PSSRU 2020 - dietitians/speech and language therapists - cost per working hour, Band 4 (£34)
Diarrhoea	£829	NHS Reference Costs 2019/20. FD10K Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10 – non-elective short-stay. Based on TA551 costing assumptions.
Dyspnoea	£1,076	NHS Reference Costs 2019/20. Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay (£1034.43) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Fatigue	£1,076	NHS Reference Costs 2019/20. Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay (£1034.43) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Hyperglycaemia	£657	NHS Reference Costs 2019/20. Weighted average SA08G-J. Other Haematological or Splenic Disorders. Non-elective short stay (£614.78) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.

AE	Cost per event	Notes
Hypertension	£671	NHS Reference Costs 2019/20. EB04Z. Hypertension. Non-elective short stay (£392.87) + NHS Reference Costs 2019/20. WF01A. Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (medical oncology) (£200.20) + 2 x PSSRU 2020 – General practitioner – cost per surgery consultation lasting 9.22 minutes – including direct care staff costs, with qualification costs (£39 x 2). Based on TA551 costing assumptions.
Hypertriglyceridaemia	£657	NHS Reference Costs 2019/20. Weighted average SA08G-J. Other Haematological or Splenic Disorders. Non-elective short stay (£614.78) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Increased ALT	£947	NHS Reference Costs 2019/20. Weighted average of GC17G-K. Non-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions (£651.31) + NHS Reference Costs 2019/20. WF01A. Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (medical oncology) (£200.20) + Average of computerised tomography currency codes (adult only; one area only) weighted by activity (RD20A, RD21A, RD22Z) (£95.37). Based on TA551 costing assumptions.
Increased amylase	£693	NHS Reference Costs 2019/20. Weighted average of GC17G-K. on-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions (£651.31) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Increased AST	£693	NHS Reference Costs 2019/20. Weighted average of GC17G-K. on-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions (£651.31) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Increased lipase	£693	NHS Reference Costs 2019/20. Weighted average of GC17G-K. on-Malignant, Hepatobiliary or Pancreatic Disorders, without Interventions (£651.31) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Lymphocytopenia	£748	NHS Reference Costs 2019/20. Weighted average of SA35A-E Agranulocytosis. Non-elective short stay (£705.82) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.

AE	Cost per event	Notes
Nausea	£829	NHS Reference Costs 2019/20. FD10K Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10 – non-elective short-stay. Based on TA551 costing assumptions.
Neutropenia	£748	NHS Reference Costs 2019/20. Weighted average of SA35A-E Agranulocytosis. Non-elective short stay (£705.82) + PSSRU 2020 - nurse (GP practice) cost per hour inc. qualifications (£42). Based on TA551 costing assumptions.
Palmar-plantar syndrome	£473	NHS Reference Costs 2019/20 – JD07J Skin Disorders without Interventions, with CC score 2-5 – non-elective short stay. Based on TA551 costing assumptions.
Platelet count decrease	£805	NHS Reference Costs 2019/20. Weighted average SA12G-K. Thrombocytopenia. Based on TA551 costing assumptions.
Proteinuria	£751	NHS Reference Costs 2019/20. Weighted average cost of LA09M-Q. General Renal Disorders without Interventions (£550.88) + NHS Reference Costs 2019/20. WF01A. Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (medical oncology) (£200.20). Based on TA551 costing assumptions.
Stomatitis	£1,076	NHS Reference Costs 2019/20. Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay. Based on TA551 costing assumptions.
Weight decreased	£801	NHS Reference Costs 2019/20. HRG codes FD04A-E.

*Source: NHS Reference Costs 2019/20 (168)
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CC, complications and comorbidities; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 53: Total adverse events costs by treatment

Treatment	Progression-free: AE one-off cost	Progressed: AE one-off cost
LEN+PEM	£459.44	£305.40
Sunitinib	£251.53	£229.81
Pazopanib	£641.04	£229.81
Cabozantinib	£538.26	£188.18
Tivozanib	£239.55	£85.69

Abbreviations: AE, adverse event ; LEN, lenvatinib; PEM, pembrolizumab.

The total progression-free AE management cost associated with each first-line comparator was applied at the start of the model. For each first-line comparator, the total progressed AE management cost was calculated by summing the number of

incident patients who progress within the model time horizon and multiplying them by the corresponding progressed AE management one-off cost for that comparator.

5.6. Summary of base-case analysis inputs and assumptions

5.6.1. Base-case analysis inputs

A summary of base-case analysis inputs is provided in Table 54. Full information on survival models is presented in Appendix N.

Table 54: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Mean age	61.7	Gamma (61.08, 62.32)	Section 5.2.1
Proportion male	74.5%	Beta (72%, 77%)	Section 5.2.1
Time-to-event estimates			
OS, PFS, and TTD regression model parameters LEN+PEM and sunitinib (and cabozantinib TTD)	Multiple	Cholesky decomposition	Sections 5.3.1–5.3.3
Pazopanib	Assumed same as sunitinib	N/A	Section 5.3.1
Tivozanib	Assumed same as sunitinib	N/A	Section 5.3.1
Cabozantinib HR, OS	[redacted]	Log-normal [redacted]	Section 5.3.1
Cabozantinib HR, PFS	[redacted]	Log-normal: [redacted]	Section 5.3.3
Drug costs			
Lenvatinib maintenance cost per model cycle	[redacted]	Gamma [redacted]	Section 5.5.1
Pembrolizumab maintenance cost per model cycle	[redacted]	Gamma [redacted]	Section 5.5.1
Sunitinib maintenance cost per model cycle	[redacted]	Gamma [redacted]	Section 5.5.1
Pazopanib maintenance cost per model cycle	£450	Gamma (£291, £643)	Section 5.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Cabozantinib maintenance cost per model cycle	£1,132	Gamma (£732, £1,616)	Section 5.5.1
Tivozanib maintenance cost per model cycle	£482	Gamma (£312, £688)	Section 5.5.1
Administration cost LEN+PEM per model cycle	£74	Gamma (£48, £105)	Section 5.5.1
Subsequent treatment costs			
Subsequent treatment drug cost: LEN+PEM	£20,494.04	Gamma (£13,263, £29,274)	Section 5.5.1.3
Subsequent treatment drug cost: Sunitinib	£39,307.38	Gamma (£25,438, £56,147)	Section 5.5.1.3
Subsequent treatment drug cost: Pazopanib	£39,307.38	Gamma (£25,438, £56,147)	Section 5.5.1.3
Subsequent treatment drug cost: Cabozantinib	£35,988.64	Gamma (£23,290, £51,406)	Section 5.5.1.3
Subsequent treatment drug cost: Tivozanib	£17,226.21	Gamma (£11,148, £24,606)	Section 5.5.1.3
Subsequent treatment			
% receiving subsequent treatment after LEN+PEM	[redacted]	Beta [redacted]	Section 5.5.1.3
% receiving subsequent treatment after sunitinib	[redacted]	Beta [redacted]	Section 5.5.1.3
% receiving subsequent treatment after pazopanib	[redacted]	Beta [redacted]	Section 5.5.1.3
% receiving subsequent treatment after tivozanib	[redacted]	Beta [redacted]	Section 5.5.1.3
% receiving subsequent treatment after cabozantinib	[redacted]	Beta [redacted]	Section 5.5.1.3
AE management costs			
AE management progression-free cost: LEN+PEM	£459.44	Gamma (£297, £656)	Section 5.5.3
AE management progression-free cost: Sunitinib	£251.53	Gamma (£163, £359)	Section 5.5.3
AE management progression-free cost: Pazopanib	£641.04	Gamma (£415, £916)	Section 5.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
AE management progression-free cost: Cabozantinib	£538.26	Gamma (£348, £769)	Section 5.5.3
AE management progression-free cost: Tivozanib	£239.55	Gamma (£155, £342)	Section 5.5.3
AE management progressed cost: LEN+PEM	£305.40	Gamma (£198, £436)	Section 5.5.3
AE management progressed cost: Sunitinib	£229.81	Gamma (£149, £328)	Section 5.5.3
AE management progressed cost: Pazopanib	£229.81	Gamma (£149, £328)	Section 5.5.3
AE management progressed cost: Cabozantinib	£188.18	Gamma (£122, £269)	Section 5.5.3
AE management progressed cost: Tivozanib	£85.69	Gamma (£55, £122)	Section 5.5.3
Disease management costs			
Disease management progressed cost - Progression-free one-off cost: all treatments	£253.20	Gamma (£164, £362)	Section 5.5.2
Disease management cost, Progression-free cycle cost: all treatments	£60.33	Gamma (£39, £86)	Section 5.5.2
Disease management cost, Progressed one-off cost: all treatments	£0	NA	Section 5.5.2
Disease management cost, Progressed cycle cost: all treatments	£60.33	Gamma (£39, £86)	Section 5.5.2
BSC for progression after first-line	£0	NA	Section 5.5.2
Disease management cost, One-off cost of mortality	£7,015.24	Gamma (£4,540, £10,021)	Section 5.5.2
Utility			
Treatment-specific utility (overall population) progression-free: LEN+PEM	[redacted]	Beta [redacted]	Section 5.4.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Treatment-specific utility (overall population) progression-free: sunitinib, pazopanib, tivozanib	[redacted]	Beta [redacted]	Section 5.4.5
Treatment-specific utility (intermediate and poor population) progression-free: LEN+PEM	[redacted]	Beta [redacted]	Section 5.4.5
Treatment-specific utility (intermediate and poor population) progression-free: sunitinib, pazopanib, tivozanib	[redacted]	Beta [redacted]	Section 5.4.5
Post-progression utility (all treatments) overall population	[redacted]	Beta [redacted]	Section 5.4.5
Post-progression utility (all treatments) intermediate and poor population	[redacted]	Beta [redacted]	Section 5.4.5

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; AXI, axitinib; CABO, cabozantinib; CI, confidence interval; EVE, everolimus; HR, hazard ratio; LEN, lenvatinib; NMA, network meta-analysis; N/A, not applicable; PEM, pembrolizumab; SE, standard error.

5.6.2. Modelling assumptions

A summary of assumptions made during model development are provided in Table 55, with justification provided if necessary.

Table 55: Modelling assumptions

Input	Assumption
Treatment efficacy	• OS, PFS and TTD of PAZO and TIVO are assumed to be clinically equivalent to SUN as per: o The assumptions used by the ERG in assuming PAZO efficacy is equivalent with SUN's in NICE TA542 (92) for CABO, TA512 for TIVO (90) and TA581 for NIVO+IPI (21) o The recommendations of the NICE committee in their appraisal for TIVO TA512 (90) where they acknowledged that tivozanib is expected to be 'at best' similar to sunitinib or pazopanib in TA512 (100). • If PFS or OS are estimated by applying a constant HR, it is assumed that Cox proportionality holds to the selected reference arm • Standard error (SE) for median treatment duration was assumed to vary by 10% from the median treatment duration estimate

Input	Assumption
Subsequent treatment	• Patients are assumed to be eligible for subsequent treatment upon progression. This assumption was informed by clinical guidelines on RCC such as guidance from ESMO (170) and NHS Pathway (91) • Subsequent treatments are not modelled as individual line of therapies but represent an aggregated line of subsequent therapies due to lack of data for each subsequent treatment. In addition, this assumption has been made in previous RCC HTA assessments such as TA650 for PEM+AXI and TA645 for AVE+AXI (91, 141) • The treatment duration of each individual subsequent treatment for patients who received a non-CLEAR treatment as first-line, were assumed the same as sunitinib, and are assumed the same for the intermediate and poor risk subgroup in the model • Where equivalence is assumed in efficacy between SUN, PAZO, and TIVO, then equivalence in the subsequent treatment durations is also assumed.
Utilities	• Utility values are distinguished for patients who are progression-free or post-progression and are reported by subgroup. The base case uses treatment specific progression-free utilities • For treatment specific utilities, the progression-free utility of sunitinib was assumed to be the for same all remaining monotherapies • In the base case no age-adjustment is applied to the utility estimates
AEs	• Only Grade ≥3 TEAEs occurring in ≥5% of patients in any of the included treatments are included in the model. Use of a 5% threshold has also been used in previous RCC HTA assessments: TA650 and TA645 (91, 141) • AEs costs are calculated separately for progression-free and progressed patients and are applied as one-off costs. • AE frequencies for subsequent treatments: SUN, PAZO and LEN+PEM were assumed the same as AE frequencies as in first-line use with these treatments due to a lack of data • AE rates and AE unit costs are assumed equivalent for the intermediate and poor risk subgroup due to a lack of subgroup specific estimates

Disutilities	• Disutilities are not captured in the model base case as it is assumed that AE disutility is included in the utilities by health states, following a similar assumption taken by AVE+AXI NICE TA645 (91)
	• AE disutility data reported for SUN were taken from NIVO+IPI NICE TA581 and used to inform the disutility estimates and duration of disutility in this model
	• Where data were missing for certain AEs, the following assumptions were made for disutility from NICE TA581 (21):
	  ○ Disutility for dyspnoea assumed same as fatigue
	  ○ Disutility for hyperglycaemia, hypertriglyceridaemia, increased alanine transaminase, increased amylase, increased aspartate aminotransferase and proteinuria assumed same as increased lipase

Input	Assumption
	○ Disutility for lymphocytopenia and neutropenia assumed same as platelet count decrease ○ Disutility for weight decreased assumed the same as decreased appetite • Disutility data is assumed the same for the intermediate and poor risk subgroup due to a lack of subgroup specific estimates
Drug acquisition costs	• Treatment dosing is subject to an observed estimate of dose intensity, for LEN this was calculated based on the cumulative days per LEN dose from CLEAR • For subsequent treatments, dose intensity is based on assumption used in TA650 (141) to ensure consistency with the data source used to obtain the duration and distribution of each subsequent treatment • Drug acquisition costs are assumed to be equivalent for the intermediate and poor risk subgroup
Drug administration costs	• No drug administration cost was assumed for drugs taken orally • Drug administration costs for subsequent oral chemotherapy or subsequent IV chemotherapy drugs delivered on the same day were assumed to not incur any further cost i.e. if two components of a combination therapy were delivered on the same day, only one drug would incur the administration cost, if applicable • Drug administration costs are assumed to be equivalent for the intermediate and poor risk subgroup
AE management costs	• AE management costs are assumed to be equivalent across for the intermediate and poor risk subgroup • Unit cost per event for AEs were based on costing assumptions used in NICE TA551 (171)
Disease management costs	• Disease management costs are applied by health state and assumed to be equivalent across for the intermediate and poor risk subgroup • BSC costs are applied per cycle to patients who progress on first-line treatment but do not receive any subsequent treatment. The model assumes this cost is £0 in the base case following the approach adopted in NICE TA650 and TA645 (91, 141) • One-off event cost for mortality apply to patients who die as has been used within NICE TA650, TA645 and TA542 for CABO (91, 92, 141)
Other	• To conduct the sensitivity analysis, in the absence of published ranges, higher and lower values were assumed to be ±10% around the mean/median base-case value, with costs varied by ±20% of the mean/median base-case value

Abbreviations: AE, adverse event; AVE, avelumab; AXI, axitinib; BSC, best supportive care; HR, hazard ratio; HTA, health technology assessment; LEN, lenvatinib; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; NIVO+IPI, nivolumab + ipilimumab; NMA, Network meta-analysis; OS, overall survival; PAZO, pazopanib; PEM, pembrolizumab; PFS, progression-free survival; RCC, renal cell carcinoma; SE, standard error; TEAE, treatment-emergent adverse event; TIVO, tivozanib; TTD, time to discontinuation.

5.6.3. Scenarios

A summary of settings used in the scenario analyses is provided in Table 56.

Table 56: Scenarios included in the model

	Scenario	Base case setting	Scenario setting
OS	Alternative OS parametric distributions, using single parametric fits	Single exponential distribution for LEN+PEM OS, and sunitinib OS	Single log-normal distributions for LEN+PEM OS and sunitinib OS
	Alternative OS fits, using joint parametric distributions		Joint Weibull parametric distribution for LEN+PEM OS and sunitinib OS (Appendix P)
	Alternative OS fits, using March 2021 data cut and adjusting OS for subsequent treatment		Use 2-stage adjustment for OS assuming 0% of patients receive subsequent therapy (Appendix P)
			Use 2-stage adjustment for OS assuming patients receive subsequent therapy as per KOL responses (Appendix P)
PFS	Alternative PFS distributions	PFS modelled as joint log-normal distribution for LEN+PEM and sunitinib	Joint generalised gamma distribution for LEN+PEM PFS and sunitinib PFS
	Alternative censoring rules for PFS	FDA rule	EMA rule
Discounting	Discounting of health outcomes and costs at 1.5%	Health outcomes and costs at 3.5%	Health outcomes and costs at 1.5%
Utilities	No treatment-specific utility (CLEAR)	CLEAR trial utility using treatment-specific values (pazopanib and tivozanib assumed equal to sunitinib)	Non-treatment specific utility from CLEAR
	General population utilities age adjustment	No adjustment	Ara & Brazier 2010
	AE disutility	Excluded	Included
Subsequent treatment	Alternative estimates for those receiving subsequent treatment and distribution of subsequent treatments	Based on KOL responses	Based on CLEAR trial for LEN+PEM and sunitinib, and PEM + AXI NICE submission ERG base case for remaining comparators

	Scenario	Base case setting	Scenario setting
Dosing frequency of PEM	Alternative dosing frequency	200mg every 3 weeks	400mg every 6 weeks.

Abbreviations: AE, adverse event; EMA, European Medicines Agency; ERG, Evidence Review Group; FDA, Food and Drug Administration; HR, hazard ratio; LEN+PEM, lenvatinib + pembrolizumab; OS, overall survival; PEM+AXI, pembrolizumab + axitinib; PFS, progression-free survival; TTD, time to discontinuation.

5.7. Base-case results

Pairwise cost-effectiveness results of LEN+PEM vs each comparator are presented in Table 57, while fully incremental results are presented in Table 58.

Pazopanib and tivozanib were assumed to be equal to sunitinib in terms of efficacy therefore, they produced the same total QALYs as sunitinib. However tivozanib provided the lowest cost and was therefore, dominant over sunitinib and pazopanib. LEN+PEM compared with the only non-dominated comparator (tivozanib) provided incremental costs of £130,982, and incremental QALYs of 1.02, resulting in an ICER of £128,671 per QALY gained. Disaggregated results are presented in Appendix J.

5.7.1. Base-case cost-effectiveness analysis results

Table 57: Base-case pairwise cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, LEN+PEM vs comparator			ICER (LEN+PEM vs) (£/QALY)
				Costs (£)	LYG	QALYs	
LEN+PEM vs sunitinib							
Sunitinib	[redacted]	4.86	[redacted]	–	–	–	–
LEN+PEM	[redacted]	6.07	[redacted]	£120,410	1.21	1.02	£118,286
LEN+PEM vs pazopanib							
Pazopanib	[redacted]	4.86	[redacted]	–	–	–	–
LEN+PEM	[redacted]	6.07	[redacted]	£117,374	1.21	1.02	£115,303
LEN+PEM vs tivozanib							
Tivozanib	[redacted]	4.86	[redacted]	–	–	–	–
LEN+PEM	[redacted]	6.07	[redacted]	£130,982	1.21	1.02	£128,671

Abbreviations: ICER, incremental cost-effectiveness ratio; LEN+PEM, lenvatinib + pembrolizumab; LYG, life years gained; QALYs, quality-adjusted life years.

Table 58: Base-case fully incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, LEN+PEM vs comparator			ICER versus baseline (£/QALY)	ICER (LEN+PEM vs) (£/QALY)
				Costs (£)	LYG	QALYs		
Tivozanib	[redacted]	4.86	[redacted]	–	–	–	–	–
Sunitinib	[redacted]	4.86	[redacted]	£10,571	0.00	0.00	Dominated	Dominated
Pazopanib	[redacted]	4.86	[redacted]	£3,037	0.00	0.00	Dominated	Dominated
LEN+PEM	[redacted]	6.07	[redacted]	£117,374	1.21	1.02	£128,671	£128,671

Abbreviations: ICER, incremental cost-effectiveness ratio; LEN+PEM, lenvatinib + pembrolizumab; LYG, life years gained; QALYs, quality-adjusted life years.

5.8. Sensitivity analyses

5.8.1. Probabilistic sensitivity analysis (PSA)

Pairwise PSA cost-effectiveness results of LEN+PEM vs each comparator are presented in Table 59, while fully incremental PSA results are presented in Table 60. Results were plotted on a cost-effectiveness plane (CEP) in Figure 22 and a cost-effectiveness acceptability curve (CEAC) was generated as shown in Figure 23.

Exploratory convergence testing suggested that any number of simulations above 4,000 would result in a change to the outcomes of less than 1% and so the number of simulations chosen for the PSA was 4,000 iterations.

LEN+PEM compared with the only non-dominated comparator (tivozanib) provided incremental costs of £131,578, and incremental QALYs of 1.02, resulting in an ICER of £129,181 per QALY gained. This is highly congruent with deterministic changes in costs of £130,982 and QALYs of 1.02, respectively. LEN+PEM had 0% probability of being cost-effective at both thresholds of £20,000 and £30,000 per QALY.

Table 59: PSA pairwise results, overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, LEN+PEM vs comparator			ICER (LEN+PEM vs) (£/QALY)
				Costs (£)	LYG	QALYs	
LEN+PEM vs sunitinib							
Sunitinib	[redacted]	4.87	[redacted]	–	–	–	–
LEN+PEM	[redacted]	6.08	[redacted]	£121,254	1.21	1.02	£119,044
LEN+PEM vs pazopanib							
Pazopanib	[redacted]	4.87	[redacted]	–	–	–	–
LEN+PEM	[redacted]	6.08	[redacted]	£117,926	1.21	1.02	£115,783
LEN+PEM vs tivozanib							
Tivozanib	[redacted]	4.87	[redacted]	–	–	–	–
LEN+PEM	[redacted]	6.08	[redacted]	£131,578	1.21	1.02	£129,181

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

Table 60: PSA fully incremental results, overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, LEN+PEM vs comparator			ICER versus baseline (£/QALY)[†]	ICER (LEN+PEM vs) (£/QALY)
				Costs (£)	LYG	QALYs		
Tivozanib	[redacted]	4.87	[redacted]	–	–	–	–	–
Sunitinib	[redacted]	4.87	[redacted]	£10,323.9	0.00	0.00	Dominated	Dominated
Pazopanib	[redacted]	4.87	[redacted]	£3,328.1	0.00	0.00	£287,814,116	Ext. Dominated
LEN+PEM	[redacted]	6.08	[redacted]	£117,926.1	1.21	1.02	£129,181	£129,181

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

[†]pazopanib and tivozanib were assumed to have similar efficacy to sunitinib, with respect to survival curves and also inputs such as treatment specific utilities, therefore the QALYs produced in the deterministic analysis were the same for sunitinib, pazopanib and tivozanib. In the probabilistic analysis however, the inputs for each treatment which were assumed equivalent (sunitinib, pazopanib, and tivozanib) could vary independently, and therefore small differences in total QALY between those three treatments could occur. Consequently pazopanib has a very high ICER versus tivozanib, due to it having higher costs but also slightly higher QALYs.

Figure 22: Cost-effectiveness plane of LEN+PEM vs all comparators

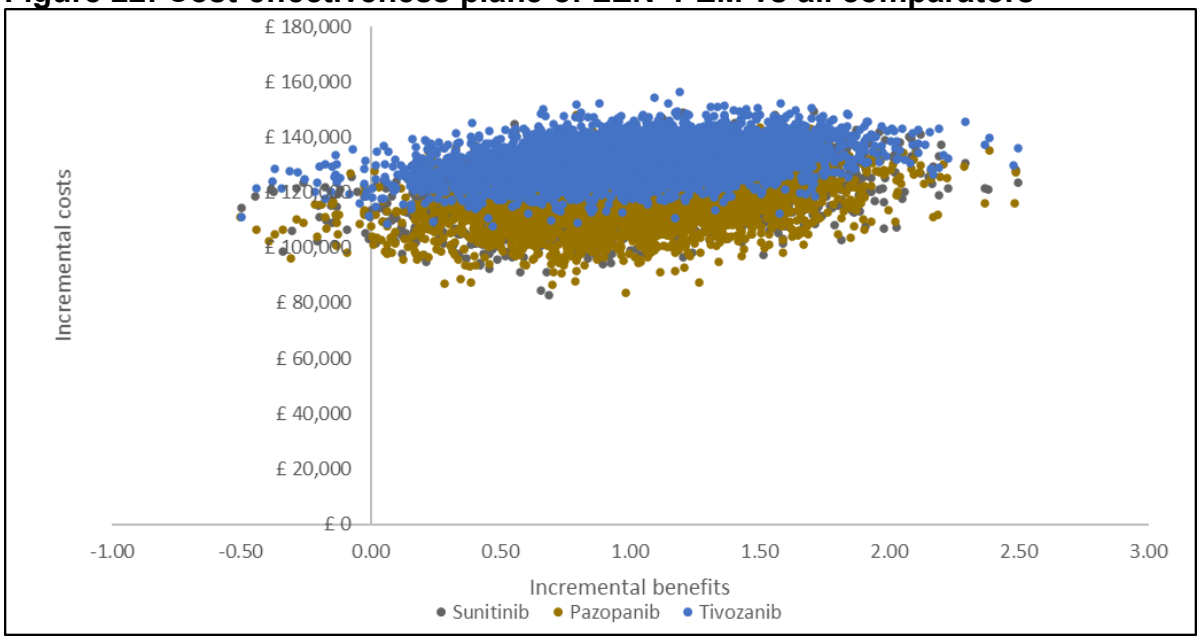
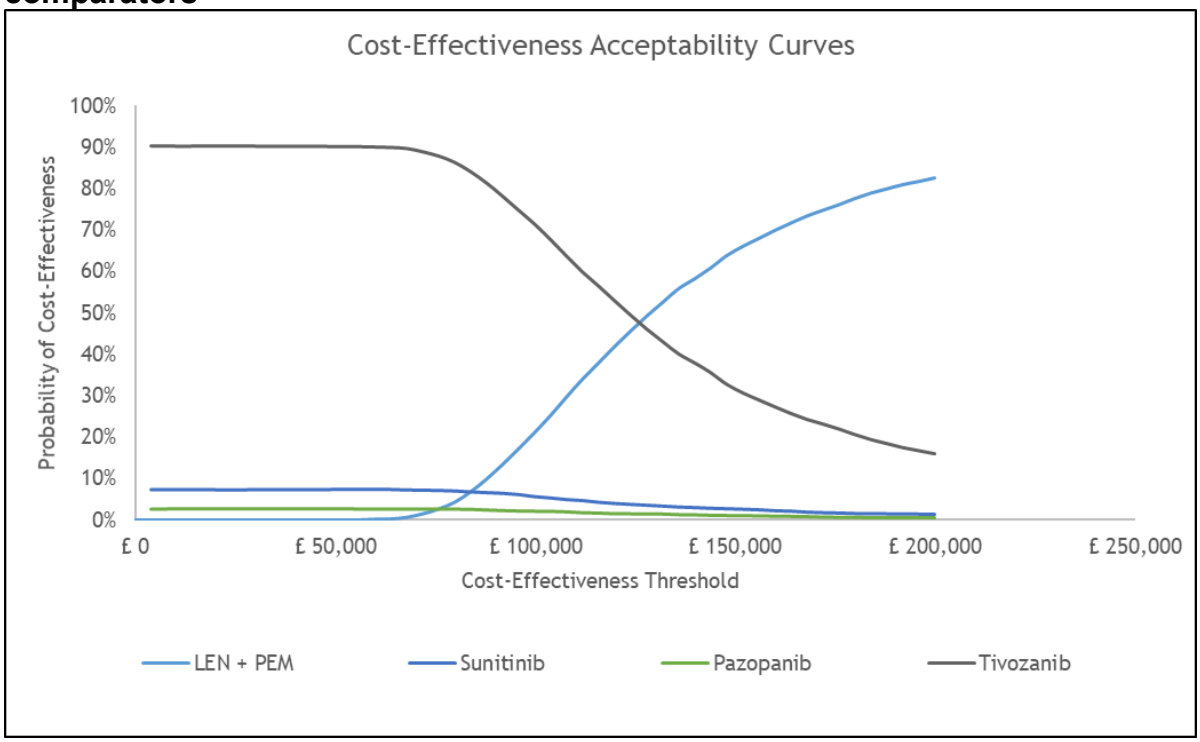


Figure 23: Cost-effectiveness acceptability curve (CEAC) of LEN+PEM vs all comparators



5.8.2. Deterministic one-way sensitivity analysis (OWSA)

Results for the comparison between LEN+PEM and sunitinib were most sensitive to drug costs, treatment discontinuation, and PFS. Results for the 20 most influential

parameters for LEN+PEM against sunitinib are presented in Table 61 and Figure 24. Results vs the remaining comparators are presented in Appendix P.

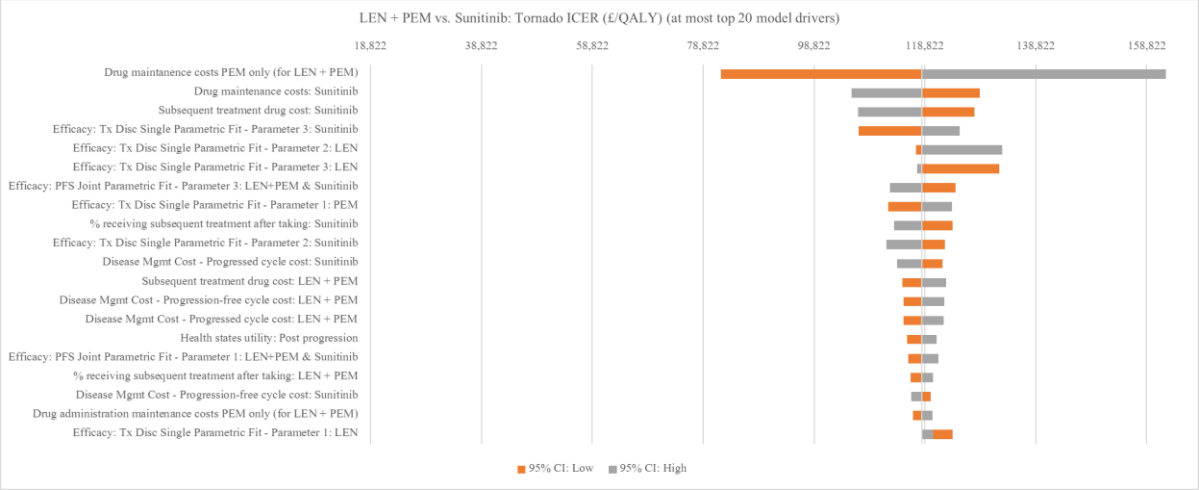
5.8.2.1. LEN+PEM vs sunitinib

Table 61: OWSA results, LEN+PEM vs sunitinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Drug maintenance costs PEM only (for LEN+PEM)	£82,057	£162,273
Drug maintenance costs: Sunitinib	£128,706	£105,635
Subsequent treatment drug cost: Sunitinib	£127,800	£106,735
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: Sunitinib	£106,838	£125,085
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: LEN	£117,245	£132,761
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: LEN	£132,227	£117,429
Efficacy: PFS Joint Parametric Fit - Parameter 3: LEN+PEM & Sunitinib	£124,311	£112,543
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: PEM	£112,232	£123,704
% receiving subsequent treatment after taking: Sunitinib	£123,854	£113,283
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: Sunitinib	£122,473	£111,904
Disease management cost - Progressed cycle cost: Sunitinib	£121,985	£113,795
Subsequent treatment drug cost: LEN+PEM	£114,736	£122,596
Disease management cost - Progression-free cycle cost: LEN+PEM	£114,934	£122,355
Disease management cost - Progressed cycle cost: LEN+PEM	£115,019	£122,252
Health states utility: Post progression	£115,570	£120,976
Efficacy: PFS Joint Parametric Fit - Parameter 1: LEN+PEM & Sunitinib	£115,836	£121,229
% receiving subsequent treatment after taking: LEN+PEM	£116,269	£120,260
Disease management cost - Progression-free cycle cost: Sunitinib	£119,889	£116,339
Drug administration maintenance costs PEM only (for LEN+PEM)	£116,688	£120,226
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: LEN	£123,765	£120,270

Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; OWSA, one-way sensitivity analysis; PEM, pembrolizumab; PFS, progression-free survival; Tx, treatment.

Figure 24: Tornado diagram for ICER of LEN+PEM vs sunitinib



Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; mgmt, management; PEM, pembrolizumab; PFS, progression-free survival; QALY, quality-adjusted life year; Tx, treatment.

5.8.3. Scenario analysis

Scenario analyses conducted are summarised in Section 5.6.3.

5.8.3.1. LEN+PEM vs sunitinib

Results from scenario analyses of LEN+PEM vs sunitinib are presented in Table 62. Results vs the remaining comparators are presented in Appendix P. Discounting costs and outcomes at 1.5% led to a reduction in the ICER vs sunitinib of more than 10%. All other scenarios led to an increase in the ICER, however the magnitude of the increase was less than 10%.

Table 62: Scenario analyses results for LEN+PEM vs sunitinib

Scenario	Incremental costs	Incremental QALYs	ICER/QALY	% Change from base case ICER/QALY
Base case result	£120,410	1.02	£118,286	–
Alternative OS fits, using single parametric fits (single lognormal)	£120,716	0.99	£121,640	2.84%
Alternative PFS fits, using joint generalised gamma	£119,822	1.01	£118,579	0.25%
Alternative censoring rule for PFS	£120,499	1.00	£120,217	1.63%
Discounting of health outcomes and costs at 1.5%	£123,312	1.24	£99,421	–15.95%
No treatment-specific utility (CLEAR)	£120,410	0.99	£121,802	2.97%

Scenario	Incremental costs	Incremental QALYs	ICER/QALY	% Change from base case ICER/QALY
Age-adjusted utilities (using Ara & Brazier 2010)	£120,410	0.96	£125,444	6.05%
AE disutility	£120,410	0.99	£121,562	2.77%
Alternative estimates for those receiving subsequent treatment and distribution of subsequent treatments	£125,664	1.02	£123,447	4.36%
Alternative dosing frequency for PEM	£118,105	1.02	£116,021	–1.91%

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; QALY, quality-adjusted life year.

5.8.4. Summary of sensitivity analyses results

Probabilistic sensitivity analysis showed that the results are not sensitive to parameter uncertainty, with the PSA results being very similar to the deterministic results.

In a one-way sensitivity analysis, results vs sunitinib were sensitive to the drug cost of PEM, and PFS and TTD parameters. All the scenarios explored had little impact on the ICER, except for discounting which led to a 15.95% reduction in the ICER for LEN+PEM vs. sunitinib.

5.9. Subgroup analysis

5.9.1. Intermediate and poor risk population, cost-effectiveness analysis results

Cost-effectiveness results of LEN+PEM vs each comparator are presented in Table 63. LEN+PEM compared with cabozantinib provided incremental costs of £97,597, incremental QALYs of 0.78 with an ICER of £118,571 per QALY gained. Disaggregated results are presented in Appendix J.

Table 63: Intermediate and poor risk subgroup cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, LEN+PEM vs comparator			ICER (LEN+PEM vs) (£/QALY)
				Costs (£)	LYG	QALYs	
LEN+PEM vs cabozantinib							
Cabozantinib	[redacted]	4.25	[redacted]	–	–	–	–
LEN+PEM	[redacted]	5.29	[redacted]	£93,050	1.03	0.78	£118,571

Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; LYG, life-years gained; PEM, pembrolizumab; QALY; quality-adjusted life year.

5.9.2. Probabilistic sensitivity analysis

PSA cost-effectiveness results of LEN+PEM vs cabozantinib in the intermediate and poor population are presented in Table 64. Results were plotted on a cost-effectiveness plane (CEP) in Figure 25, and a cost-effectiveness acceptability curve (CEAC) was generated as presented in Figure 26. LEN+PEM had 0% probability of being cost-effective at both thresholds of £20,000 and £30,000 per QALY.

Table 64: PSA results, intermediate/poor risk population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental, LEN+PEM vs comparator			ICER (LEN+PEM vs) (£/QALY)
				Costs (£)	LYG	QALYs	
Cabozantinib	[redacted]	4.35	[redacted]	–	–	–	–
LEN+PEM	[redacted]	5.30	[redacted]	£95,191	0.95	0.73	£130,923

Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; LYG, life years gained; PEM, pembrolizumab; QALYs, quality-adjusted life years.

Figure 25: Cost-effectiveness plane of LEN+PEM vs cabozantinib

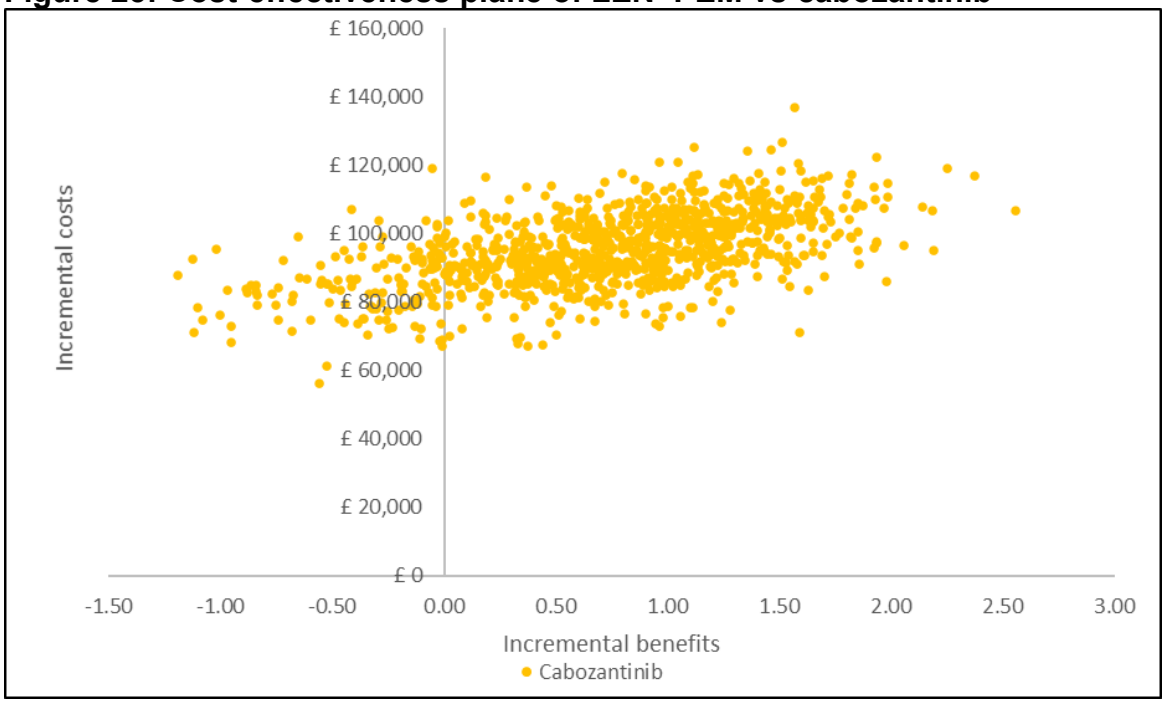
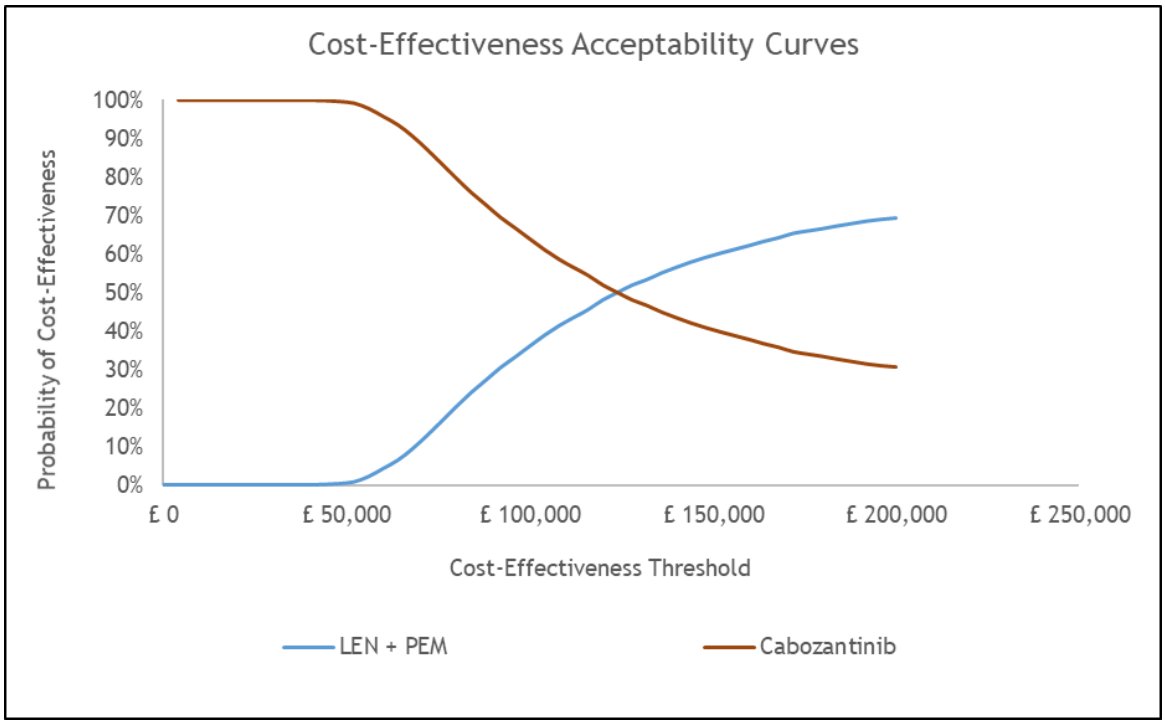


Figure 26: Cost-effectiveness acceptability curve (CEAC) of LEN+PEM vs cabozantinib



5.9.3. Deterministic sensitivity analysis

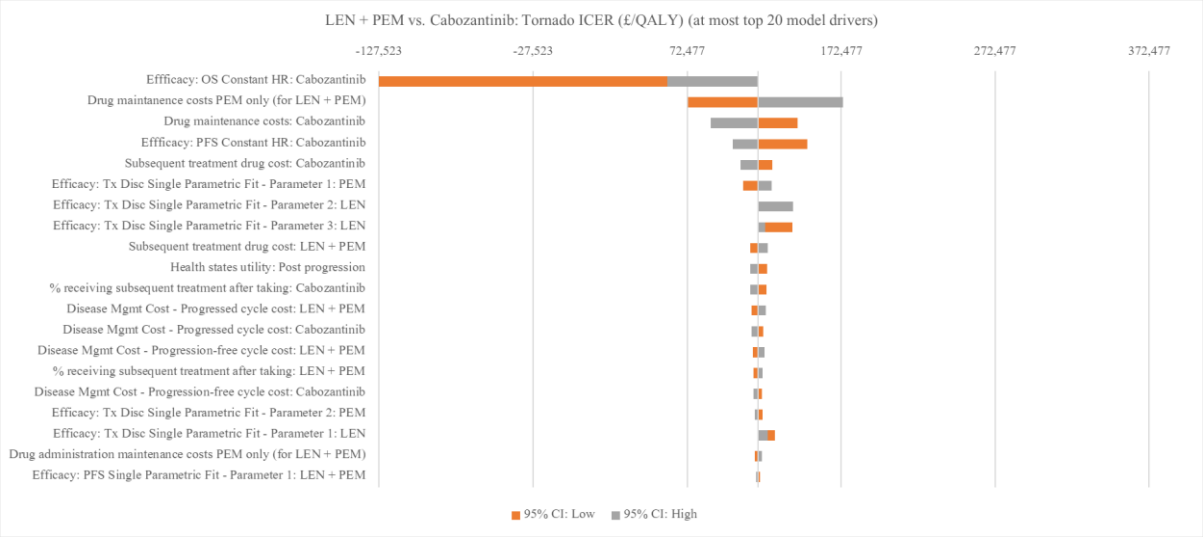
Results for the comparison between LEN+PEM and cabozantinib were most sensitive to the OS and PFS HRs for LEN+PEM vs cabozantinib, and drug costs. Results for the 20 most influential parameters for LEN+PEM vs cabozantinib are presented in Table 65 and Figure 27.

Table 65: OWSA results, LEN+PEM vs cabozantinib

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Efficacy: OS Constant HR: Cabozantinib	–£127,523	£59,644
Drug maintenance costs PEM only (for LEN+PEM)	£73,113	£173,761
Drug maintenance costs: Cabozantinib	£144,084	£87,594
Efficacy: PFS Constant HR: Cabozantinib	£150,683	£101,927
Subsequent treatment drug cost: Cabozantinib	£127,822	£107,338
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: PEM	£108,778	£127,333
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: LEN	£123,121	£141,266
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: LEN	£140,878	£122,984
Subsequent treatment drug cost: LEN+PEM	£113,495	£124,733
Health states utility: Post progression	£124,330	£113,580
% receiving subsequent treatment after taking: Cabozantinib	£123,930	£113,647
Disease management cost - Progressed cycle cost: LEN+PEM	£114,450	£123,574
Disease management cost - Progressed cycle cost: Cabozantinib	£122,017	£114,386
Disease management cost - Progression-free cycle cost: LEN+PEM	£115,210	£122,650
% receiving subsequent treatment after taking: LEN+PEM	£115,686	£121,393
Disease management cost - Progression-free cycle cost: Cabozantinib	£121,143	£115,447
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: PEM	£121,278	£116,238
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: LEN	£129,644	£124,905
Drug administration maintenance costs PEM only (for LEN+PEM)	£116,565	£121,005
Efficacy: PFS Single Parametric Fit - Parameter 1: LEN+PEM	£119,676	£117,396

Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; OWSA, one-way sensitivity analysis; PEM, pembrolizumab; PFS, progression-free survival; Tx, treatment.

Figure 27: Tornado diagram for ICER of LEN+PEM vs cabozantinib



Note: the OS constant HR for cabozantinib is placed on the left side of the tornado diagram as the ICER moves from dominated (a negative ICER) to a lower ICER than the base case.
Abbreviations: ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; mgmt, management; PEM, pembrolizumab; PFS, progression-free survival; QALY, quality-adjusted life year; Tx, treatment.

5.9.4. Scenario analysis

Scenario analyses for LEN+PEM vs cabozantinib in the intermediate and poor risk subgroup are reported in Table 66. Using a single Weibull distribution for the OS fit for LEN+PEM resulted in an increase in the ICER vs cabozantinib of more than 10%, while discounting costs and outcomes at 1.5% led to a reduction in the ICER vs cabozantinib of more than 10%. All other scenarios led to a change in the ICER, however the magnitude of the change was less than 10%.

Table 66: Scenario analyses results for LEN+PEM vs cabozantinib

Scenario	Incremental costs	Incremental QALYs	ICER/QALY	% change from base-case ICER/QALY
Base case result	£93,050	0.78	£118,571	–
Alternative OS fit for LEN+PEM (Weibull)	£91,853	0.58	£157,507	32.84%
Alternative PFS fit for LEN+PEM (Weibull)	£92,975	0.78	£119,757	1.00%
Alternative censoring rule for PFS	£93,355	0.77	£121,272	2.28%
Discounting of health outcomes and costs at 1.5%	£95,366	0.93	£102,003	-13.97%
No treatment-specific utility (CLEAR)	£93,050	0.75	£124,330	4.86%

Scenario	Incremental costs	Incremental QALYs	ICER/QALY	% change from base-case ICER/QALY
Age-adjusted utilities (using Ara & Brazier 2010)	£93,050	0.75	£124,860	5.30%
AE disutility	£93,050	0.74	£125,125	5.53%
Alternative estimates for those receiving subsequent treatment and distribution of subsequent treatments	£96,247	0.78	£122,643	3.43%
Alternative dosing frequency for PEM	£90,821	0.78	£115,729	-2.40%

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; QALY, quality-adjusted life year.

5.10. Validation

The model validation process followed the current guidelines from the International Society for Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) (172).

In order to assess the clinical validity of the extrapolations, parametric models were validated using available external data and KOL opinion from prior appraisals. Further information on the external information used to validate PFS and OS extrapolations is described in the relevant OS and PFS sections in Appendix O. A comparison of the data used for validation and model outcomes is summarised in Table 67. Whilst estimates of OS appear higher than historical sources, it is important to note that this is reflected in the sunitinib arms of the relevant studies and is not a consequence of the approach to economic modelling. The differences in OS may partly be attributed to the contemporary use of immunotherapy at later lines of therapy.

Table 67. External data and TA650 KOL opinion for sunitinib OS, and external data for PFS, compared with sunitinib base case

Data source	2 years	5 years	10 years
OS			
Gore et al, 2015 (173)	~41.3%	~25.9%	–
Pooled studies (99, 174, 175)	60.0%	~26.73%	–
COMPARZ trial (99)	~56%	–	–
KEYNOTE-426 trial (159)	65.5%	–	–
SEER data (176)	~39.0%	–	–

Data source	2 years	5 years	10 years
TA650 KOL opinion	–	20%–25%	10%–15%
Selected OS distribution for sunitinib (single exponential)	**71.1%**	**42.6%**	**18.1%**
PFS			
COMPARZ trial (99)	25%	–	–
KEYNOTE-426 trial (159)	26.5%	–	–
Selected PFS distribution for sunitinib (joint lognormal)	**21.9%**	**6.3%**	**1.8%**

Abbreviations: KOL, key opinion leader; OS, overall survival; PFS, progression-free survival; SEER, Surveillance Epidemiology and End Results.

As an additional validation exercise, undiscounted post-progression life years using each OS single fit distribution for LEN+PEM and sunitinib were explored. A large imbalance in subsequent treatments between the two arms which would impact post-progression survival was not expected (Section 5.3.1.1). Therefore, the purpose of this exercise was to explore which distribution would minimise differences in post-progression survival between the two treatments. The results presented in Table 68 show that the difference in post-progression survival was minimised with the exponential distribution, followed by the log-normal distribution. All other distributions, particularly Gompertz and generalised gamma, had much higher differences in post-progression life years between the two arms.

The exponential distribution was considered the most plausible option for the base case. The results in Table 68 supports its use as any other distribution would lead to much more of an imbalance in post-progression survival between arms, which contradicts clinical opinion that the OS curves of LEN+PEM and sunitinib were unlikely to cross.

Table 68: Undiscounted post-progression survival by OS single fit distributions

	LEN+PEM	Sunitinib	Pazopanib	Tivozanib	Difference
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab.

5.11. Interpretation and conclusions of economic evidence

The cost-effectiveness analysis illustrates the economic value of LEN+PEM as a treatment for patients with first-line aRCC compared with other first-line treatment options currently recommended by NICE. In the base case, LEN+PEM was associated with an ICER of £118,286 per QALY vs sunitinib, £115,303 vs pazopanib, and £128,671 vs tivozanib. In the intermediate and poor subgroup, LEN+PEM was associated with an ICER of £118,571 vs cabozantinib.

The benefits of LEN+PEM were driven by longer PFS, which led to high QALY gains in the pre-progression state; LEN+PEM had the highest QALY gain. However, in this analysis the costs associated with LEN+PEM were higher than other comparators, driven by treatment costs, which are high due to the longer treatment duration and the omission of confidential patient access schemes. Sensitivity analyses showed that the model was most sensitive to parameters associated with drug acquisition cost for PEM and sunitinib, and TTD curves for lenvatinib, pembrolizumab, and sunitinib. Scenario analyses around alternative OS assumptions, presented in Appendix P demonstrated that changing assumptions around OS had a large impact on results, with assuming a joint fit increasing the ICERs, and adjusting for subsequent treatment reducing the ICERs. The intermediate and poor risk population also had an impact on results, as incremental QALYs in particular were not as high for this group with 0.78 incremental QALYs compared with cabozantinib (compared with 1.02 for the comparators of the overall population).

The economic evaluation reflects patients assessed in CLEAR, and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem. No study assessing the cost-effectiveness of LEN+PEM for the target population specified above was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

5.11.1. Strengths and limitations

The cost-effectiveness model was designed after careful consideration of the clinical evidence and treatment pathways for patients with aRCC to ensure that key aspects of the disease and treatment practices were captured.

- The model structure was developed based on a review of published economic modelling approaches and available NICE HTA submission reports and is consistent with previous modelling approaches in RCC.
- The model design provided extensive flexibility on how to estimate clinical benefits associated with LEN+PEM.
- The analyses of clinical data used to parameterise the model were based on relevant statistical and health economic best practice guidelines.
- Further, the parameters and approaches used in the base case model were selected following careful consideration of statistical fit, and clinical plausibility based on clinical expert opinion.
- Extensive sensitivity and scenario analyses were conducted to address uncertainty and test the sensitivity of results to changes in assumptions. Most deterministic scenarios did not lead to a significant change in the results of the analysis, and results from the PSA were very similar to those of the deterministic base-case analysis.

A limitation of the analyses was the immaturity of OS from the CLEAR trial which led to uncertainty in the extrapolation of long-term estimates. The converging and crossing of KM curves late in the data collection period was unexpected, given the high ORR and PFS gain associated with LEN+PEM compared with sunitinib. This observation is likely due to the imbalance in subsequent anti-cancer therapy between the CLEAR study arms and patients receiving sunitinib being more likely to discontinue first-line treatment earlier and receive immunotherapy treatment in the second line. Additionally the small number of patients at risk at the point of crossing means there is a high level of uncertainty around the data. Additional data from the final analysis of CLEAR will provide longer term follow up of patients in the CLEAR trial which may address this uncertainty. However, cost-effectiveness estimates

based on data from the final analyses are expected to fall within the range of those observed in the scenario analyses around OS extrapolation currently included in the model.

5.11.2. Conclusions

In conclusion, LEN+PEM provides clinical benefit compared with all standard-of-care treatments and has the potential to be a cost-effective option for the first-line treatment of adults with aRCC when confidential discounts are applied.

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Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Pembrolizumab in combination with lenvatinib for treating advanced renal cell carcinoma ID3760

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
MSD Company evidence submission [ACIC]	**1.0**	**Yes**	**November 10 2021**

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ASaT	All subjects as treated
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BMI	Body mass index
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BP	Blood pressure
BV	Brentuximab vedotin
CBR	Clinical benefit rate
CDF	Cancer drug fund
cHL	Classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran- Mantel-Haenszel
CNS	Central nervous system
CPS	Combined positive score
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DIC	Deviance intervention criterion
DOR	Duration of response
DSU	Decision Support Unit
EAU	European Association of Urologists
ECOG	Eastern cooperative oncology group performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicine Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-3L	European Quality of Life Five Dimensions 3 Level
EPAR	European public assessment report
ERG	Evidence Review Group
FAS	Full Analysis Set
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index disease
FWER	Family wise error rate
HIV	Human Immunodeficiency Virus

HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRG	Health Resource Groups
HRQoL	Health related quality of life
HTA	Health technology assessment
IA	Interim analyses
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
IMDC	International Metastatic RCC Database Consortium
ITT	Intent-to-Treat
IV	Intravenous
IIR	Independent Radiologic Review
IxRS	Interactive voice and web response system
KM	Kaplan-Meier
KPS	Karnofsky performance status
LS	Least square
LY	Life year
LYG	Life year gained
MA	Marketing authorisation
Mg	milligram
MID	Minimal important difference
MMRM	Mixed model for repeated measures
MoM	Method of moments
mRCC	Metastatic Renal Cell Carcinoma
MSD	Merck Sharp & Dohme Ltd
MSKCC	Memorial Sloan-Kettering Cancer Centre
N	Number of patients per treatment group
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung carcinoma
NYHA	New York Heart Association
N/A	Not applicable
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PbR	Payment-by-results
PD	Progressive disease or disease progression
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	Progression free survival
PO	Orally

PP	Per Protocol
PPS	Post-progression state
PR	Partial response
PRO	Patient reported outcomes
PSA	Prostate specific antigen
PSSRU	Personal and Social Services Research Unit
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life years
QD	Once daily
RCC	Renal cell carcinoma
RCT	Randomised controlled trials
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
SA	Sensitivity analysis
SAE	Serious adverse event
SD	Standard deviation
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SY	Subject years
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TEAE	Treatment-emergent adverse events
ToT	Time on treatment
TOT	Time-on-treatment
TPS	Tumour proportion score
TTD	Time to discontinuation
TTO	Time trade-off
UK	United Kingdom
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VAS	Visual Analogue Scale

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.

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

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated advanced renal cell carcinoma	People with untreated advanced renal cell carcinoma	N/A
Intervention	Lenvatinib with pembrolizumab	Pembrolizumab (KEYTRUDA®) in combination with lenvatinib	N/A
Comparator(s)	Pazopanib Sunitinib Tivozanib Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) Nivolumab + ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) - subject to ongoing appraisal	Pazopanib Sunitinib Tivozanib Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria)	MSD considers nivolumab + ipilimumab to not be a relevant comparator because at the time of the submission to NICE nivolumab + ipilimumab combination was not recommended in the routine commissioning in England[1]
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	N/A
Subgroups to be considered	People with advanced RCC that is intermediate- or poor-risk as defined by IMDC criteria	People with untreated advanced renal cell carcinoma, with intermediate or poor risk disease as defined in the IMDC criteria	N/A

Abbreviations: RCC, renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

B.1.2 Description of the technology being appraised

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

Table 2. Technology being appraised

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

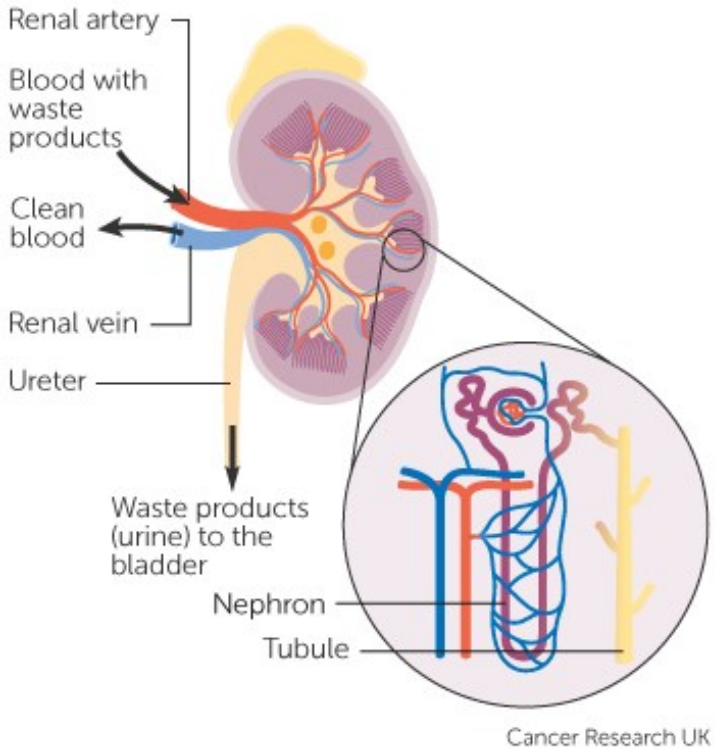
	brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10. Keytruda, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1. Keytruda, as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. Keytruda, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults. Keytruda as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults. Keytruda, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10. Keytruda, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication to which this submission relates: Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.
Method of administration and dosage	Pembrolizumab 200 mg every three weeks (Q3W); intravenous (IV) infusion (up to a maximum duration of 2 years). Pembrolizumab can be administered intravenously as 400mg every six weeks infusion. Lenvatinib 20 mg per day orally.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial, the cost of a single administration being £5,260.

Patient access scheme (if applicable)	A Patient Access Scheme (PAS) with a simple discount of [redacted], therefore 200 mg administration of pembrolizumab will cost [redacted]. Due to the highly confidential nature of this figure MSD requests that documentation from the Assessment Group does not include the PAS price and instead references back to this table

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

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

Figure 1. Kidney cross-section



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

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

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

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

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

Approximately 70% of patients with RCC live at least 1 year after diagnosis, and around 50% live at least 10 years after diagnosis[6]. Survival rates for RCC are linked to the stage of the cancer at diagnosis: for example, 95% of patients diagnosed with stage 1 kidney cancer survived their illness for at least one year, compared with only 37% of those diagnosed at stage IV[6]. In the UK, the 5-year relative survival rate ranges from approximately 83% at stage I to 6% at stage IV for patients diagnosed with RCC[6]; approximately 4,500 people die each year due to kidney cancer, and it is the 13th most common cause of cancer deaths in the UK[6].

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

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

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

Cabozantinib[11] is recommended, within its marketing authorisation, for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria. It is recommended only if the company provides cabozantinib according to the commercial arrangement.

Tivozanib[12] is recommended as an option for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment and the company provides tivozanib with the discount agreed in the patient access scheme.

Pazopanib[13] is recommended as a first-line treatment option for people with advanced renal cell carcinoma who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme.

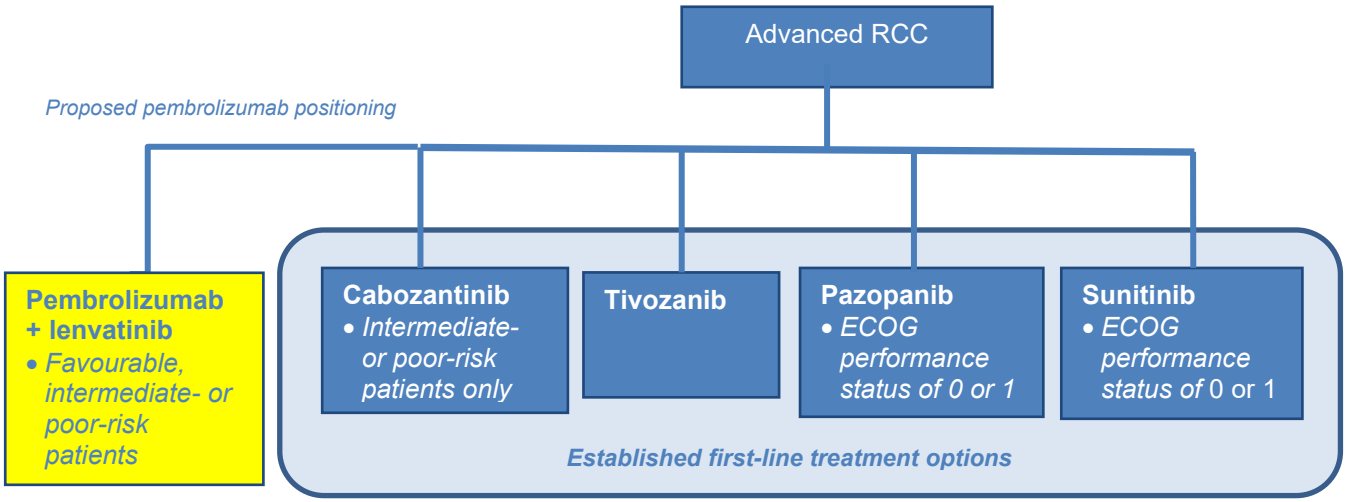
Sunitinib[14] is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an ECOG performance status of 0 or 1.

Nivolumab with ipilimumab[1] is recommended for use within the Cancer Drugs Fund as an option for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the IMDC criteria. It is recommended only if the conditions in the managed access agreement for nivolumab with ipilimumab are followed.

Avelumab with axitinib[15] is recommended for use within the Cancer Drugs Fund as an option for untreated advanced renal cell carcinoma in adults. It is recommended only if the conditions in the managed access agreement for avelumab with axitinib are followed.

The updated European Society for Medical Oncology (ESMO) and European Association of Urologists (EAU) guidelines[16] include recommendations on the below treatment options but also state that immune checkpoint inhibitors (pembrolizumab plus lenvatinib) are considered the new backbone in first-line treatment of metastatic clear-cell RCC[17,18]. Therefore, it is envisaged that pembrolizumab plus lenvatinib would offer an alternative first-line treatment option to the above listed therapies for patients with advanced RCC as shown in Figure 2.

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



B.1.4 Equality considerations

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

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

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

B.2.2 List of relevant clinical effectiveness evidence

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

The SLR was conducted on July 29, 2021. As the manufacturer of the technology being appraised, MSD is aware of all relevant RCTs for pembrolizumab in combination with lenvatinib in this indication.

In total, six RCTs were identified [19–24] six trials reporting evidence for the relevant comparators and one reporting evidence for pembrolizumab in combination with lenvatinib: KEYNOTE-581[25].

Please refer to Table 3 for a summary of the evidence coming from the pivotal clinical trial KEYNOTE-581[25].

Table 3. Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">Motzer et al Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med 2021;384:1289-300. DOI: 10.1056/NEJMoa2035716</td></tr>
<tr><td>Study design</td><td colspan="5">Multicentre, randomized, open-label, Phase 3 study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment in subjects with advanced RCC.</td></tr>
<tr><td>Population</td><td colspan="5">• Has histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features.
• Has locally advanced/metastatic disease (i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer) or has recurrent disease.
• Has measurable disease per Response Evaluation in Solid Tumours (RECIST) 1.1 as assessed by the investigator/site radiologist.
• Has received no prior systemic therapy for advanced RCC.
• Has Karnofsky performance status (KPS) ≥ 70% as assessed within 10 days prior to randomisation.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">• Lenvatinib 18 mg (orally, once daily) plus everolimus 5 mg (orally, once daily)
• Lenvatinib 20 mg (orally, once daily) plus pembrolizumab 200 mg (intravenously [IV], every 3 weeks [Q3W])</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Sunitinib 50 mg (orally, once daily) on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2)</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">KEYNOTE-581 is the pivotal clinical trial in this indication</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Overall survival (OS)
• Progression free survival (PFS)
• Objective response rate (ORR)
• Adverse effects (AEs) of treatment
• Health related quality of life (HRQoL)
Bolded outcomes are included in the economic model</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Time to discontinuation (TTD)
• Duration of response (DOR)
• Patient reported outcomes (PRO)
• Disease control rate (DCR)
Bolded outcomes are included in the economic models</td></tr>
</table>

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

2.3.1 KEYNOTE – 581 trial overview

Trial design

KEYNOTE – 581 is a phase III, multicentre, randomised, open-label study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment in subjects with advanced RCC[25] .

Approximately 1,050 eligible subjects were planned to be enrolled into the study. Eligible subjects were randomized to one of three treatment arms in a 1:1:1 ratio as follows:

- Arm A: lenvatinib 18 mg orally (PO) once daily (QD) plus everolimus 5 mg PO QD.
- Arm B: lenvatinib 20 mg PO QD plus pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W).
- Arm C: sunitinib 50 mg PO QD on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

Subjects were stratified by geographic region and Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic group.

The study consists of 3 phases: the pre-randomisation phase, randomisation phase, and the extension phase.

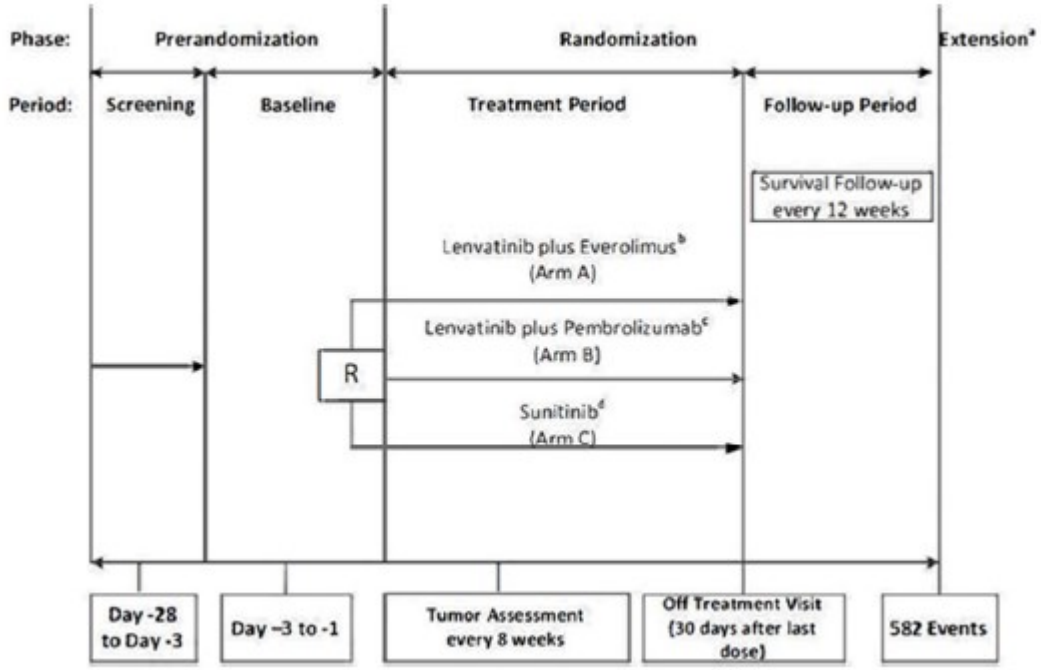
The pre-randomisation phase included a screening period to obtain informed consent and establish eligibility, and a baseline period to confirm eligibility and establish baseline disease characteristics.

The randomisation phase included a treatment period and a follow-up period. The randomisation phase began at the time of randomisation of the first subject and ended on 28 Aug 2020; the data cut-off date for the final analysis of PFS and second interim analysis of OS (IA3). The treatment period for each subject began at the time of randomisation and ended with the completion of the off-treatment visit, which occurred within 30 days of the final dose of study treatment. The follow-up period began the day after the off-treatment visit and continued as long as the subject was alive, unless the subject withdrew consent, was lost to follow-up, or in case the sponsor terminated the study. During the follow-up period, subjects were treated by the investigator according to the prevailing local standard of care. Subjects were followed every 12 weeks (±1 week) for PFS2, survival, and all subsequent anticancer treatments received.

There were 3 interim analyses (IA) conducted during the randomisation phase. The interim analysis for ORR and DOR (IA1) was planned to occur after a median follow-up of 12 months and a minimum DOR follow-up of 6 months. This included 89 subjects from the pembrolizumab with lenvatinib arm only. The interim analysis for PFS and OS (IA2) was planned to occur when approximately 310 PFS events (as determined by independent imaging review [IIR]) for each comparison had been observed. The final PFS analysis (and second interim analysis of OS; IA3) was planned to occur when approximately 388 PFS events (as determined by IIR) for each comparison had been observed. All subjects who were still on study treatment or in follow-up at the time of IA3 entered the extension phase. The subsequent additional OS follow up analysis was conducted for regulatory purposes in March 2021.

The extension phase consisted of a treatment period and a follow-up period. KEYNOTE-581 study design is summarised in Figure 3.

Figure 3. KEYNOTE – 581 study design



R = Randomisation
a: Extension Phase includes a Treatment and Follow-up Period. All subjects still on treatment at the end of the Randomisation Phase will enter the Extension Phase and continue to receive the same study treatment they received in the Randomisation Phase.
b: Lenvatinib 18 mg plus everolimus 5 mg given orally once daily.
c: Lenvatinib 20 mg once daily plus pembrolizumab 200 mg intravenously every 3 weeks.
d: Sunitinib 50 mg once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

Eligibility criteria

Male and female subjects (≥18 years) with locally advanced/metastatic RCC were enrolled in KEYNOTE-581[25]

Subject inclusion criteria

- Histological or cytological confirmation of RCC with a clear-cell component
- At least 1 measurable target lesion according to the RECIST 1.1 criteria
- (KPS of ≥70
- Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1 (C1/D1)
- Adequate organ function per blood work

Subject exclusion criteria

- Participants who have received any systemic anticancer therapy for RCC, including anti-vascular endothelial growth factor (VEGF) therapy, or any systemic investigational anticancer agent
- Participants with central nervous system (CNS) metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment
- Active malignancy (except for RCC, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix or bladder) within the past 24 months. Participants with history of localized & low risk prostate cancer are allowed in the study if they were treated with curative intent and there is no prostate specific antigen (PSA) recurrence within the past 5 years
- Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start
- Received a live vaccine within 30 days of planned start of study treatment
- Participants with urine protein ≥1 gram/24 hour

- Fasting total cholesterol >300 milligram per decilitre (mg/dL) (or >7.75 millimole per litre (mmol/L)) and/or fasting triglycerides level >2.5 x upper limit of normal (ULN).
- Uncontrolled diabetes as defined by fasting glucose >1.5 times the ULN.
- Prolongation of corrected QT (QTc) interval to >480 milliseconds (ms)
- Bleeding or thrombotic disorders or participants at risk for severe haemorrhage
- Clinically significant haemoptysis or tumour bleeding within 2 weeks prior to the first dose of study drug
- Significant cardiovascular impairment within 12 months of the first dose of study drug: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cerebrovascular accident, or cardiac arrhythmia associated with hemodynamic instability. The following is also excluded: left ventricular ejection fraction below the institutional normal range as determined by multiple-gated acquisition scan or echocardiogram
- Active infection (any infection requiring systemic treatment)
- Participants known to be positive for Human Immunodeficiency Virus (HIV).
- Known active Hepatitis B or Hepatitis C
- Known history of, or any evidence of, interstitial lung disease
- Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis
- Participants with a diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy (doses exceeding 10 mg/day of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) may be used during the study
- Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment
- Known intolerance to any of the study drugs (or any of the excipients)
- Participant has had an allogenic tissue/solid organ transplant

Settings and locations where data were collected

The study was conducted at 181 centres in North America (41), Europe (93) including 8 sites in the UK, Asia (41), and Australia (6).

Trial drugs and concomitant medication

Trial drugs

Combination lenvatinib plus everolimus arm (Arm A): lenvatinib 18 mg QD plus everolimus 5 mg QD was taken orally in each 21-day cycle.

Combination pembrolizumab with lenvatinib arm (Arm B): lenvatinib 20 mg QD was taken orally in each 21-day cycle. Pembrolizumab was administered at a dose of 200 mg IV over 30 minutes on Day 1 of each 21-day cycle.

Sunitinib arm (Arm C): sunitinib 50 mg once daily was administered orally for 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) in each 21-day cycle.

2.3.2 Comparative summary of the trial methodology

A summary of the trial methodology is present below in Table 4.

Table 4. Summary of trial methodology

Trial number (acronym)	**KEYNOTE-581**
Trial design	A Multicentre, Open-Label, Randomized, Phase 3 Trial to **c**ompare the efficacy and safety of **l**envatinib in combination with **e**verolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with **a**dvanced **r**enal cell carcinoma (**CLEAR**) Eligible subjects were randomized to 1 of 3 treatment arms in a 1:1:1 ratio as follows: • Arm A: lenvatinib 18 mg orally (PO) once daily (QD) plus everolimus 5 mg PO QD. • Arm B: lenvatinib 20 mg PO QD plus pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W). • Arm C: sunitinib 50 mg PO QD on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). Subjects were stratified by geographic region and Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic group.
Locations	Multicentre: 181 sites in North America (41), Europe (93), Asia (41), and Australia (6)
Eligibility criteria for participants	• Adults (≥18 years of age) with a histologically or cytologically confirmed diagnosis of RCC with a clear-cell component and documented evidence of advanced disease, who had not received any previous systemic anticancer therapy for RCC were eligible for enrolment. • Subjects had to have at least 1 measurable target lesion according to RECIST 1.1, adequate liver, bone marrow, blood coagulation, and renal function as defined in the protocol, KPS of ≥70, and adequately controlled BP with or without antihypertensive medications. • Subjects with central nervous system metastases were eligible if they had completed local therapy (e.g., whole brain radiation therapy, surgery, or

	radiosurgery) and had discontinued the use of corticosteroids for at least 4 weeks before starting treatment in this study.
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as out-patients.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) **Permitted and disallowed concomitant medication**	**Interventions:** • Lenvatinib 4 mg and 10 mg capsules. Lenvatinib 18 mg PO QD (Arm A) or 20 mg PO QD (Arm B) in each 21-day cycle • Everolimus (Arm A) n=357 5 mg tablets. Everolimus 5 mg PO QD in each 21-day cycle. • Pembrolizumab (Arm B) n=355 4 mL solution for IV infusion in a vial containing 100 mg pembrolizumab. Pembrolizumab 200 mg IV Q3W in each 21-day cycle **Comparator:** • Sunitinib malate (Arm C) n= 357 12.5 mg and 25 mg oral capsules. Dose: 50 mg PO QD on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). Duration of Treatment Subjects received study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. Subjects were permitted to continue study treatment beyond RECIST 1.1-defined disease progression if the investigator considered that the subject was tolerating study drug and had clinical benefit.
Primary outcomes (including scoring methods and timings of assessments)	PFS assessed by IIR, defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurred first) using RECIST 1.1
Other outcomes used in the economic model/specified in the scope	**Key secondary outcome:** OS, defined as the time from the date of randomization to the date of death from any cause. Subjects who were lost to follow-up and those who were alive at the data cut-off date were censored, either at the last date the subject was last known alive or at the data cut-off date, whichever occurred first.
Pre-planned subgroups	Exploratory analyses for PFS, OS, and ORR were conducted for the following subgroups: age, sex, race, geographic region, MSKCC and IMDC risk groups, number of metastatic sites per IIR, KPS group, baseline bone, liver, and lung metastasis status, PD-L1 status, prior nephrectomy, and clear cell histology with sarcomatoid features.

2.3.3. KEYNOTE-581: Participant baseline characteristics

Baseline demographics were generally balanced across the treatment arms. Most subjects were male, white, overweight with a KPS score ≥80 at study entry. Overall, the age of subjects ranged from 29 to 88 years, with a median age of 62.0 years (Table 5).

Table 5. Demographic and Baseline Characteristics – Full Analysis Set

Category	Lenvatinib + Everolimus (N=357)	Pembrolizumab + lenvatinib (N=355)	Sunitinib (N=357)	Total (N=1069)
Age (years)				
Mean (SD)	61.9 (10.86)	62.3 (10.23)	60.8 (9.96)	61.7 (10.36)
Median	62.0	64.0	61.0	62.0
Min, Max	32, 86	34, 88	29, 82	29, 88
Age Group, n (%)				
<65 years	201 (56.3)	194 (54.6)	225 (63.0)	620 (58.0)
≥65 years	156 (43.7)	161 (45.4)	132 (37.0)	449 (42.0)
Sex, n (%)				
Male	266 (74.5)	255 (71.8)	275 (77.0)	796 (74.5)
Female	91 (25.5)	100 (28.2)	82 (23.0)	273 (25.5)
Race, n (%)				
White	254 (71.1)	263 (74.1)	270 (75.6)	787 (73.6)
Black or African American	1 (0.3)	2 (0.6)	3 (0.8)	6 (0.6)
Asian	77 (21.6)	81 (22.8)	67 (18.8)	225 (21.0)
Japanese	44 (12.3)	42 (11.8)	31 (8.7)	117 (10.9)
Chinese	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)
Other Asian	33 (9.2)	37 (10.4)	36 (10.1)	106 (9.9)
American Indian or Alaskan Native	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Other	7 (2.0)	4 (1.1)	7 (2.0)	18 (1.7)
Missing	16 (4.5)	5 (1.4)	10 (2.8)	31 (2.9)
Ethnicity, n (%)				
Hispanic or Latino	23 (6.4)	12 (3.4)	20 (5.6)	55 (5.1)
Not Hispanic or Latino	328 (91.9)	339 (95.5)	334 (93.6)	1001 (93.6)
Missing	6 (1.7)	4 (1.1)	3 (0.8)	13 (1.2)
BMI (kg/m^2)				
Mean (SD)	27.48 (5.613)	27.48 (5.179)	28.29 (5.809)	27.75 (5.547)
Median	26.75	26.90	27.45	27.00
Min, Max	14.4, 50.2	16.0, 46.8	16.9, 62.8	14.4, 62.8

Category	Lenvatinib + Everolimus (N=357)	Pembrolizumab + lenvatinib (N=355)	Sunitinib (N=357)	Total (N=1069)
Geographic Region per IxRS, n(%)				
Western Europe and North America	200 (56.0)	198 (55.8)	199 (55.7)	597 (55.8)
Rest of World	157 (44.0)	157 (44.2)	158 (44.3)	472 (44.2)
KPS Score Group, n (%)				
100 – 90	286 (80.1)	295 (83.1)	294 (82.4)	875 (81.9)
80 – 70	70 (19.6)	60 (16.9)	62 (17.4)	192 (18.0)
Missing	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)

Data cut-off date: 28 Aug 2020.
Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.
Abbreviations: BMI, body mass index; IxRS, interactive voice and web response system; KPS, Karnofsky Performance Status; Max, maximum; Min, minimum; NA, not applicable; SD, standard deviation

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

This section reports the relevant statistical methodology of KEYNOTE-581[25].

B.2.4.1 Study Endpoints

Primary endpoint

The primary endpoint is PFS by independent review defined as the time from the date of randomization to the date of the first documentation of disease progression per RECIST 1.1 or death (whichever occurs first).

Secondary endpoints

The secondary endpoints are as follows:

- Objective response rate (ORR) was defined as the proportion of subjects who have best overall response of CR or PR as determined by IIR using RECIST 1.1.
- Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Subjects who were lost to follow-up and those who were alive at the date of data cut-off were censored at the date the subject was last known alive, or date of data cut-off, whichever occurs first.

- Safety was be assessed summarizing the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) together with all other safety parameters.
- Proportion of subjects who discontinued treatment due to toxicity is defined as the proportion of subjects who discontinue study treatment due to TEAEs.
- Time to treatment failure due to toxicity is defined as the time from the date of first dose to the date that a subject discontinues study treatment due to TEAEs.
- HRQoL were assessed using the Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQOL) EQ-5D-3L instruments.
- PFS on next-line of therapy (PFS2) is defined as the time from randomization to disease progression on next-line of treatment, or death from any cause, (whichever occurs first).
- PFS by investigator assessment is defined as the time from the date of randomization to the date of first documentation of disease progression based on the investigator assessment per RECIST v.1.1 or death (whichever occurs first).

Exploratory endpoints

The exploratory endpoints were as follows:

- Duration of response (DOR) is defined as the time from the date a response was first documented until the date of the first documentation of disease progression or date of death from any case.
- Disease control rate is the proportion of subjects who have best overall response of complete response (CR) or partial response (PR) or stable disease (SD). SD must be achieved at ≥ 7 weeks after randomization to be considered best overall response.
- Clinical benefit rate is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥ 23 weeks after randomization).
- Blood and tumour biomarkers were assessed for identifying potential correlation with clinical outcomes-related endpoints.

Definitions of Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT] Population) is the group of all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for all efficacy analyses which were based on the ITT principle.

The Per Protocol (PP) Analysis Set is the group of those subjects who received at least 1 dose of study drug, had no major protocol deviations and had both baseline and at least 1 postbaseline tumour assessments. Subjects for whom death occurred prior to the first postbaseline tumour assessment will also be included. The per protocol analysis set was the secondary analysis set for efficacy endpoints.

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug. This is the analyses population used for all safety analyses which was based on as-treated principle.

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the full analysis set was summarized for each treatment arm and for all treatment arms combined using descriptive statistics. Continuous demographic and baseline variables include age, body weight, and height; categorical variables include sex, age group, race, region, KPS, NYHA cardiac disease classification, MSKCC prognostic group, and AJCC staging at the time of diagnosis.

Efficacy Analyses

Primary efficacy analysis

Comparisons of PFS between lenvatinib + everolimus (Arm A) versus sunitinib (Arm C), and pembrolizumab plus lenvatinib (Arm B) versus sunitinib (Arm C) were performed. PFS was evaluated using Kaplan-Meier (KM) estimates and the statistical significance of the difference in PFS for the 2 primary comparisons were tested by stratified log rank test.

Geographic region and MSKCC prognostic groups were used as stratification factors for randomization. The hazard ratio (lenvatinib + everolimus relative to sunitinib and pembrolizumab plus lenvatinib relative to sunitinib) and the corresponding 95% confidence intervals (CIs) were estimated using the Cox regression model with Efron's method for handling tied results, stratified by the same stratification factors.

An interim and a final analysis of PFS were planned to be performed. Lan- DeMets spending function[26] with O'Brien-Fleming boundary[27] was used to control alpha levels between the

interim and final analysis of PFS. The interim analysis of PFS was performed when it is approximately 4 months after the last subject is randomized and an approximately 80% information fraction of PFS events (as determined by the IIR) in Arm B and Arm C. The final analysis of PFS was performed when approximately 388 PFS events, as determined by the IIR, were observed between each comparison. A graphical approach was used to control the family wise error rate (FWER, explained below) at the two-sided 0.0499 for multiple comparisons, including both PFS comparisons of Arm B vs Arm C and Arm A vs Arm C. For each comparison, a statistical significance can be claimed based on either interim or final analysis of PFS at specified alpha levels.

Progression date was assigned to the earliest date when any RECIST 1.1-defined disease progression was observed without missing more than one adequate radiologic assessment.

Censoring rules are described below in Table 6.

Table 6. Censoring Rules for Derivation of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or postbaseline tumour assessments	Date of randomization	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off	Date of last adequate radiologic assessment prior to or on date of data cut-off	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of newanticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment*	Date of death	Progressed
7	Death or progression after more than one missed visit/tumour assessment**	Date of last adequate radiologic assessment before missed tumour assessments	Censored

Abbreviations: *CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease*
**Adequate tumour assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators at regular interval as defined in the protocol. Any tumour assessments after new anticancer treatment starts will be removed in the definition of PFS.*
*** More than one missed visit/adequate tumour assessment is defined as having the duration between the last adequate tumour assessment and PD or death being longer than 16 weeks + 10 days (tumour assessment window) - 1 day, which is 121 days for subjects on the 8-weekly tumour assessment schedule in this study.*

The priority of the censoring rules was as follows:

1. If the subject had PD or death, the following sequence was applied:

2. If a subject did not have a baseline tumour assessment (No. 1), the subject was censored on the date of randomization. However, if the subject died within 121 days after randomization and did not receive a new anticancer treatment, it was counted as PFS event at the date of death. If a subject had new anticancer treatment before PD or death (No. 4), the subject was censored on the date of the last adequate tumour assessment prior to or on the date of new anticancer treatment.
3. If a subject missed two or more tumour assessments before PD or death (No. 7), the subject was censored on the date of the last adequate tumour assessment before PD or death. Note that if a subject was censored by both this criterion and the anticancer treatment criterion, the earliest censoring date was used.
4. Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date was used.
5. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).
6. Sensitivity analyses were performed using unstratified log rank tests for comparisons of PFS of lenvatinib + everolimus (Arm A) versus sunitinib alone (Arm C) and pembrolizumab plus lenvatinib (Arm B) versus sunitinib alone (Arm C), as well as unstratified Cox proportional hazards model with Efron's method for ties, including treatment arms as a single covariate for the estimation of the hazard ratio. In addition, the following sensitivity analyses were also performed:
   - Using the actual reported date of progression by IIR or death to define PFS regardless of missing assessments, or use of new anti-cancer therapy (per EMA guidance);
   - Using the radiologic assessment data as assessed by Investigator and death to define PFS;
   - Using the different derivation rule for the situation with more than one missed visit/tumour assessment: death or progression immediately after more than one missed visit/tumour assessment (i.e., if a subject missed two or more tumour assessments right before PD or death, the subject will be censored on the date of the last adequate tumour assessment before PD or death. Note that if a subject was censored by both this criterion and the anticancer treatment criterion, the earliest censoring date was used).

Secondary efficacy analyses

OS was compared between lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and pembrolizumab plus lenvatinib (Arm B) vs. sunitinib alone (Arm C) using the stratified

logrank test with geographic region (Western Europe and North America vs. Other) and MSKCC prognostic groups (favorable, intermediate and poor risk) as strata. The hazard ratio and its 95% CI comparing lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and pembrolizumab plus lenvatinib (Arm B) vs. sunitinib alone (Arm C) was estimated by a stratified Cox proportional hazards model with Efron's method for handling tied results, stratified by geographic region and MSKCC prognostic groups. Median OS with 2-sided 95% CIs were calculated using K-M product-limit estimates for each treatment arm and K-M estimates of OS were plotted over time. Lan-DeMets spending function[26] with Pocock boundary[28] was used to control alpha levels among the interim and final analysis of OS. The first two OS interim analyses were performed at the time of PFS interim and final analysis, corresponding to approximately 45% and 60% of information fractions of OS events. The third OS interim analysis was performed at approximately 80% information fraction of OS events. The final analysis of OS will be performed when 304 OS events are observed for each comparison. ORR was calculated with exact 95% confidence intervals using the method of Clopper and Pearson. The difference between treatment arms was tested using the Cochran- Mantel-Haenszel (CMH) test, stratified by geographic region and MSKCC prognostic groups. The p-value for hypothesis testing of ORR was based on the ORR data at the time of the PFS interim analysis. The ORR data available at the subsequent analysis time points was provided for supportive purposes.

PFS2 was calculated using the Kaplan-Meier (KM) product-limit estimates for each treatment group and presented with two-sided 95% CIs. The KM estimate of PFS2 was plotted over time for each treatment group. PFS by investigator assessment per RECIST v1.1 was analysed similarly as for the primary endpoint of PFS by IIR per RECIST v1.1.

Interim Analysis

Interim analyses of PFS, OS, and ORR were planned for this study. The timing of each analysis is summarized in Table 7. Type I error control for the efficacy analyses as well as efficacy boundaries are described in Appendix D1.4.

Table 7. Summary of Interim and Final Efficacy Analyses

No.	Analysis	Endpoint	Timing	Estimated Time after First Subject Randomized

1	Interim analysis of ORR and DOR (the first 88 subjects from Arm B)	ORR DOR	Median follow-up of 12 months and a minimum DOR follow-up of 6 months	~28 months
2	Interim analysis of PFS, Interim analysis of OS	PFS OS ORR*	Trigger: approximately 4 months afterthe last subject randomized and approximately 310 (80% IF) PFS events observed in Arms B and C (estimated to have ~140 (45% IF) deaths observed for each comparison)	~38 months
3	Final analysis of PFS, Interim analysis ofOS	PFS OS	Trigger: ~ 388 PFS events observed foreach comparison (estimated to have 182 (60% IF) deathsobserved for each comparison)	~45 months
4	Interim analysis of OS	OS	Trigger: ~243 (80% IF) deaths observed for each comparison	~57 months
5	Final analysis of OS	OS	Trigger: ~304 deaths observed for eachcomparison	~69 months

Abbreviations: DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; IF, information fraction
**: The p-value for hypothesis testing of ORR was based on the ORR data at the analysis No 2.*

Subgroup analyses

For efficacy endpoints, the hazard ratio and two-sided 95% confidence interval (CI) for comparing PFS as assessed by the IIR and investigator assessment of either Arm A versus Arm C or Arm B versus Arm C was presented in forest plots for the subgroups. Median PFS and 95% CIs was presented for all subgroups. Similar summary and plots were provided for OS. In addition, the odds ratio and two-sided 95% CIs for comparing ORR as assessed by IIR were summarised and presented in forest plots. If sample size of subgroup/strata is less than 18 (5% of sample size in the treatment group), the subgroup/strata may be considered to collapse to the closest subgroup/strata as appropriate.

- Age group (<65 years, ≥65 years)
- Sex (male, female)
- Race (White, Asian, all others)
- Geographic region per IxRS (West Europe and North America, Rest of World)
- MSKCC risk group per IxRS (favourable, intermediate, poor risk)
- IMDC risk group (favourable, intermediate, poor risk)
- Number of metastatic sites per IIR (0, 1, 2, ≥3)
- KPS score group (100-90, 80-70)
- Baseline bone metastasis (yes, no)
- Baseline liver metastasis (yes, no)

- Baseline lung metastasis (yes, no)
- PD-L1 status (CPS≥1, CPS<1, not available)
- Prior nephrectomy (yes, no)
- Histologic clear component featuring sarcomatoid (yes, no)

2.4.5 Participant flow in the relevant randomised controlled trials

Details of the participant flow in KEYNOTE-581 are provided in Appendix D.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

2.5.1 & 2 Summary of quality assessment

Quality assessment of KEYNOTE-581[25] was conducted using the Cochrane risk of bias tool[29]. Based on this analysis, the study was determined to be at 'low risk' across four of six key domains, with "unclear risk" in one domain and 'high risk' for the blinding bias domain, due to the open-label nature of this study and subsequent lack of blinding; nevertheless, it is important to note that this study included an element of blinding as independent central imaging review was performed without knowledge of the treatment group assignments of the participants. The complete quality assessment is included in Appendix D.

2.5.3. Consideration of UK clinical practice

Currently in the UK, there is no innovative immuno-oncology treatment available in the routine practice for the first-line treatment of patients with locally advanced or metastatic RCC. Data from KEYNOTE-581[25] show that pembrolizumab in combination with lenvatinib is a promising treatment option which has demonstrated efficacy, including significant survival benefits, in RCC patients and has an acceptable tolerability profile.

KEYNOTE-581[25] recruited 56% of its patients in Europe and baseline demographics suggest these patients were representative of those typically seen in UK clinical practice[5]. The control treatment in KEYNOTE-581 was sunitinib, which has been acknowledged to have equivalent efficacy with other TKIs available in UK clinical practice (tivozanib and pazopanib[12,13]). In contrast, the data from KEYNOTE-581[25] suggest that pembrolizumab in combination with lenvatinib could offer a significant step-change in benefit for these patients.

B.2.6 Clinical effectiveness results of the relevant trials

2.6.1 KEYNOTE-581 results

Results are presented from the KEYNOTE-581[25] study, based on the third interim analysis (IA3), which had a data cut-off date of 28 August 2020. The results for overall survival are based on the IA3 and the ad-hoc follow up analyses conducted for the regulatory purposes, data cut-off date 31 March 2021. The results for pembrolizumab plus lenvatinib and sunitinib arms of the KEYNOTE-581 trial are presented in the following sections.

Primary efficacy endpoint

Progression-free survival – IA3 data-cut (28 August 2020)

Pembrolizumab with lenvatinib treatment resulted in a statistically significant and clinically meaningful improvement in PFS compared with sunitinib. Median PFS was 23.9 months for pembrolizumab with lenvatinib and 9.2 months for sunitinib (HR=0.39, [95% CI: 0.32, 0.49], *P*<0.0001), presented in Table 8. The *P* value was less than the pre-specified *P* value boundary of 0.0411 and the null hypothesis was rejected. This demonstrates a 2.5-fold increase in PFS, and a 61% reduction in the risk of disease progression or death with pembrolizumab with lenvatinib compared with sunitinib (Table 9 and Figure 4). A similar pattern was seen with higher PFS rates at 6, 12, 18, and 24 months for pembrolizumab with lenvatinib compared with sunitinib, showing a continuous trend of superior PFS over time.

Table 8. Analysis of Progression-Free Survival by Independent Imaging Review Full Analysis Set

Study: KEYNOTE 581	Pembrolizumab + lenvatinib			Sunitinib			Pembrolizumab + lenvatinib vs. sunitinib	
Progression Free Survival	N[b]	Participants with Event n (%)	Median Time in Months [95 %-CI]	N[b]	Participants with Event n (%)	Median Time in Months [95 %-CI]	Hazard Ratio[d] [95 %-CI]	p-value [d,e]
Progression Free Survival per RECIST 1.1 (months)	355	160 (45.1)	23.9 [20.8; 27.7]	357	205 (57.4)	9.2 [6.0; 11.0]	0.39 [0.31; 0.49]	< 0.001

a: Database Cut-off Date: 28AUG2020
b: Number of participants: full analysis set
c: From product-limit (Kaplan-Meier) method
d: Based on Cox regression model with treatment as a covariate stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) in IxRS using Wald confidence interval
e: Two-sided p-value (Wald test)

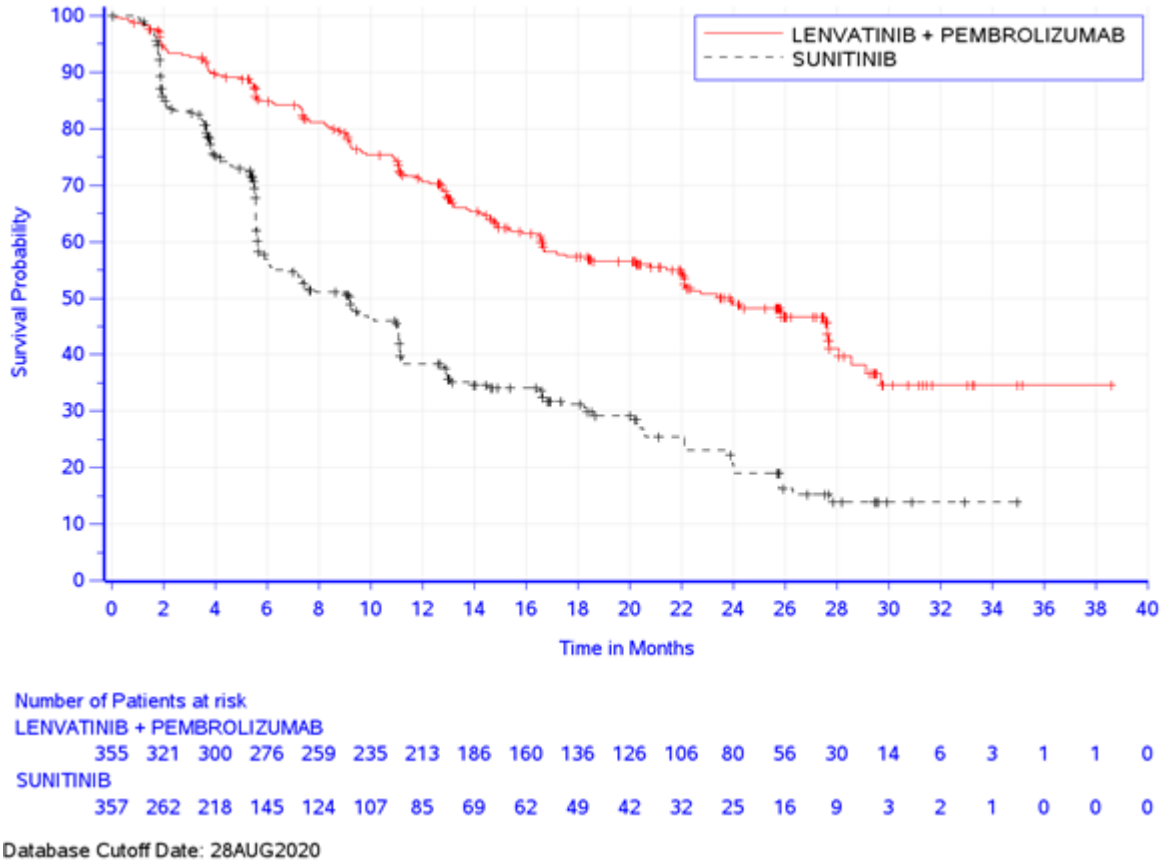
Table 9. Progression-Free Survival at IA3 – Independent Imaging Review, per RECIST 1.1 – Full Analysis Set

	Pembrolizumab + lenvatinib (N=355)	Sunitinib (N=357)
Subjects with Events, n (%)	160 (45.1)	205 (57.4)
Progressive Disease	145 (40.8)	196 (54.9)
Death	15 (4.2)	9 (2.5)
Censored, n (%)	195 (54.9)	152 (42.6)
No Baseline Tumor Assessment	0 (0.0)	1 (0.3)
No Adequate Postbaseline Tumor Assessment	6 (1.7)	22 (6.2)
No Progression and Alive at the Time of Data Cut-off	146 (41.1)	52 (14.6)
New Anticancer Treatment Started	37 (10.4)	71 (19.9)
Death or Progression after More than One Missing Assessment	6 (1.7)	6 (1.7)
Progression-Free Survival (Months)a		
Median (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Q1 (95% CI)	10.9 (8.7, 12.3)	4.2 (3.7, 5.5)
Q3 (95% CI)	NE (NE, NE)	22.1 (18.2, 25.8)
Pembrolizumab + lenvatinib vs Sunitinib		
Stratified Hazard Ratio (95% CI)[b,c]	0.39 (0.32, 0.49)	
Stratified Log-rank Test P value[c]	<0.0001	
Progression-Free Survival Rate (%) (95% CI) [atd]		
6 Months	84.9 (80.6, 88.3)	57.0 (51.1, 62.5)

12 Months	70.6 (65.3, 75.2)	38.4 (32.4, 44.3)
18 Months	57.4 (51.5, 62.8)	31.2 (25.4, 37.2)
24 Months	48.9 (42.7, 54.9)	20.7 (15.0, 26.9)
Follow-up Time for Progression-Free Survival (months)[a,e]		
Median (95% CI)	22.3 (21.1, 25.6)	16.6 (13.1, 18.5)
Q1 (95% CI)	14.9 (13.1, 16.6)	5.5 (4.9, 7.4)
Q3 (95% CI)	27.6 (27.1, 29.3)	27.5 (25.7, 29.4)

Data cut-off date: 28 Aug 2020.
Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.
Abbreviations: CI, confidence interval; IxRS, interactive voice and web response system; MSKCC, Memorial Sloan-Kettering Cancer Center; NE, not estimable; Q, quartile; RECIST, Response Evaluation Criteria in Solid Tumors
a: Quartiles are estimated by Kaplan Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties.
c: Stratified by geographic region (Region 1: Western Europe and North America, Region 2: rest of the world) and MSKCC prognostic groups (favourable, intermediate, and poor risk) in IxRS.
d: Progression-free survival rate and 95% CIs are calculated using Kaplan-Meier product-limit method and Greenwood Formula.
e: Estimates for progression-free survival follow-up time are calculated in the same way as the Kaplan-Meier estimate of PFS but with the meaning of 'censor' and 'event' status indicator reversed.

Figure 4. Analysis of Progression-Free Survival by Independent Imaging Review Full Analysis Set



Database Cutoff Date: 28AUG2020

Secondary Efficacy Endpoints

Overall survival – IA3 data cut-off (28 August 2020)

Pembrolizumab with lenvatinib treatment resulted in a statistically significant and clinically meaningful improvement in OS compared with sunitinib. The OS HR of 0.66 (95% CI: 0.49, 0.88, P=0.0049) represents a 34% reduction in the risk of death in the pembrolizumab with lenvatinib arm compared with the sunitinib arm (**Table 10** and Figure 5). The P value was less than the pre-specified P value boundary of 0.0161 and the null hypothesis was rejected. 71.5% subjects in pembrolizumab plus lenvatinib arm and 62.2% in sunitinib arm remained alive at the time of the data cut-off within the OS analysis and median OS was not reached; fewer subjects had died in the pembrolizumab with lenvatinib arm (80; 22.5%) than in the sunitinib arm (101; 28.3%) at the data cut-off date. OS rates at months 12, 18, and 24 were 91.4%, 87.1%, and 79.2%, respectively, and were higher than those in the sunitinib arm (80.2%, 74.4%, and 70.4%, respectively), indicating a consistent trend of superior survival over time. The median duration of survival follow-up was 26.7 months (95% CI: 25.9, 27.4) for the pembrolizumab with lenvatinib arm and 26.3 months (95% CI: 25.4, 27.2) for the sunitinib arm. An intersection of the OS curves is observed after approximately 33 months of follow-up.

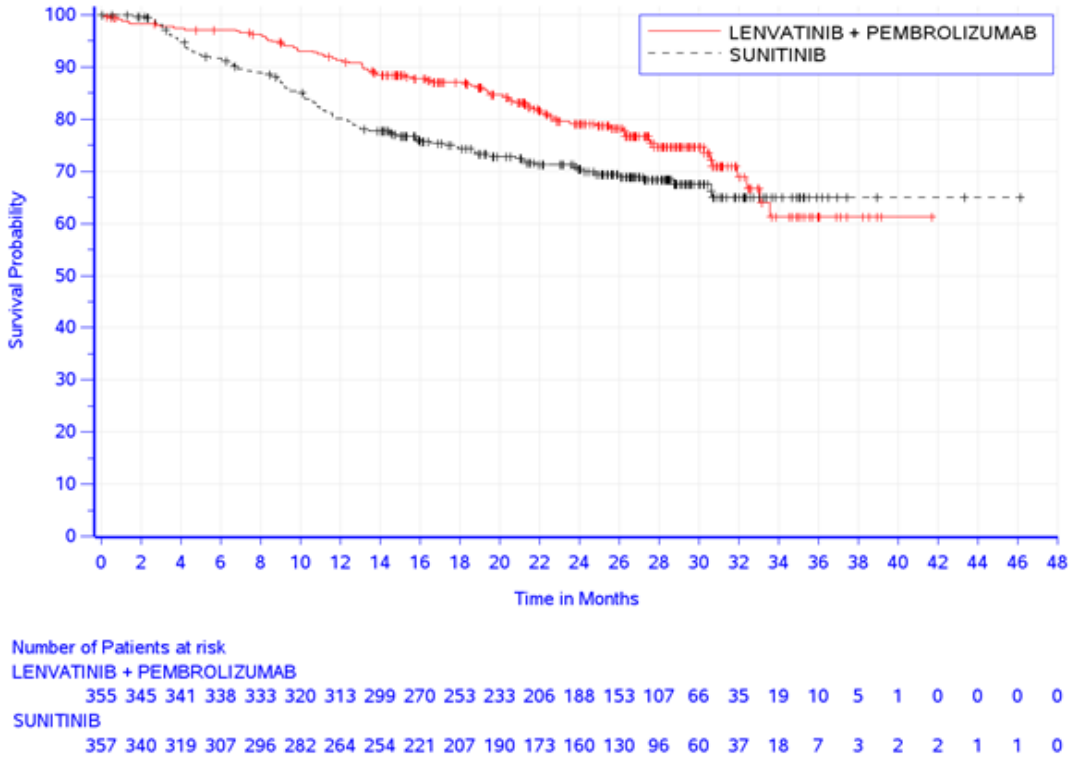
Table 10. Overall Survival at IA3 – Full Analysis Set

Category	**Pembrolizumab + lenvatinib (N=355)**	**Sunitinib (N=357)**
Death, n (%)	80 (22.5)	101 (28.3)
Censored, n (%)	275 (77.5)	256 (71.7)
Lost to Follow-up	7 (2.0)	6 (1.7)
Withdrawal of Consent	14 (3.9)	28 (7.8)
Alive	254 (71.5)	222 (62.2)
Overall Survival (months)[a]		
Median (95% CI)	NE (33.6, NE)	NE (NE, NE)
Q1 (95% CI)	27.8 (22.9, 32.4)	17.6 (12.4, 24.0)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)
Pembrolizumab + lenvatinib vs Sunitinib		
Stratified Hazard Ratio (95% CI)b,c	0.66 (0.49, 0.88)	
Stratified Log-rank Test P valuec	0.0049	
Overall Survival Rate (%) (95% CI)d at		
12 Months	91.4 (87.9, 93.9)	80.2 (75.5, 84.1)
18 Months	87.1 (83.1, 90.3)	74.4 (69.3, 78.8)
24 Months	79.2 (74.1, 83.3)	70.4 (65.0, 75.2)
Duration of Survival Follow-up (months)[a,e]		

Median (95% CI)	26.7 (25.9, 27.4)	26.3 (25.4, 27.2)
Q1 (95% CI)	21.0 (19.0, 22.3)	19.3 (16.9, 21.3)
Q3 (95% CI)	30.0 (29.1, 30.8)	30.0 (29.1, 30.9)

Data cut-off date: 28 Aug 2020.
Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.
Abbreviations: CI, confidence interval; IxRS, interactive voice and web response system; MSKCC, Memorial Sloan-Kettering Cancer Center; NE, not estimable; Q, quartile
a: Quartiles are estimated by Kaplan–Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties.
c: Stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and MSKCC prognostic groups (favourable, intermediate, and poor risk) in IxRS.
d: Overall survival rate and 95% CIs are calculated using Kaplan–Meier product-limit method and Greenwood Formula.
e: Estimates for survival follow-up time are calculated in the same way as the Kaplan–Meier estimate of overall survival but with the meaning of 'censor' and 'event' status indicator reversed.

Figure 5. Analysis of overall survival – IA3 data cut



Overall survival follow-up data – data cut-off 31 March 2021

With additional follow-up, significantly improved survival with pembrolizumab plus lenvatinib versus sunitinib continued to be observed. The OS HR was [redacted]; Table 11 and Figure 6) and represents a [redacted] reduction in the risk of death for the combination. [redacted] of patients in pembrolizumab plus lenvatinib arm and [redacted] in sunitinib arm remained alive at the time of the data cut-off and median OS was not reached with either treatment; [redacted] in the

pembrolizumab with lenvatinib arm ([redacted]) than in the sunitinib arm ([redacted]). Overall survival rates at months 12, 18, and 24 [redacted] in the pembrolizumab with lenvatinib arm compared with the sunitinib arm. Following an initial lag (commonly observed with immunotherapy treatments due to their mechanism of action), the KM curves for OS [redacted] in the pembrolizumab with lenvatinib arm versus the sunitinib arm. However, [redacted]. [redacted] [redacted] The median survival follow-up was similar for both arms. MSD conducted a post-hoc trial analysis which shows that [redacted] of patients in sunitinib arm switched to nivolumab, compared to [redacted] subjects in pembrolizumab plus lenvatinib arm. Furthermore, the sunitinib patients received [redacted]. The impact of [redacted], however an analysis was conducted whereby survival results were adjusted for patients who received any subsequent anti-cancer therapy or any anti-PD-1/PD-L1 therapy. In both cases, an improved HR vs. sunitinib compared to the unadjusted analysis, highlighting the impact of the imbalance in subsequent therapies received upon the risk of death. The results of the post-hoc analyses are reported in Appendix N. MSD note that second-line nivolumab is an approved treatment in the UK and that patients who progress to a subsequent treatment can receive this therapy as per the trial participants. A statement on NHS clinical practice by NHS England Chemotherapy Lead and Clinical Lead for the CDF during the TA581 appraisal indicated that approximately 30% of first-line TKI patients (60% of the 50% who receive a second-line treatment) are treated with nivolumab, indicating the trial to be broadly representative of clinical practice. This statement was submitted at a point in the evolution of the advanced RCC treatment landscape which reflects the scope of the current appraisal and its baseline comparators (i.e. no immunotherapies funded in first-line).

Table 11. Overall Survival – Full Analysis Set, data cut-off 31 March 2021

Category	Pembrolizumab + lenvatinib (N = 355)	Sunitinib (N = 357)
Death, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Lost to Follow-Up	[redacted]	[redacted]
Withdrawal of Consent	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Overall Survival (months)[a]		
Median (95% CI)	[redacted]	[redacted]
Q1 (95% CI)	[redacted]	[redacted]
Q3 (95% CI)	[redacted]	[redacted]
Pembrolizumab + lenvatinib vs Sunitinib		
Stratified Hazard Ratio (95% CI)[b,c]	[redacted]	
Overall Survival Rate (%) (95% CI) [a,d]		
12 Months	[redacted]	[redacted]
18 Months	[redacted]	[redacted]
24 Months	[redacted]	[redacted]
Duration of Survival Follow-Up (months)[a,e]		
Median (95% CI)	[redacted]	[redacted]
Q1 (95% CI)	[redacted]	[redacted]
Q3 (95% CI)	[redacted]	[redacted]

Data cut-off date: 31 March 2021.
Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group.
IxRS = interactive voice and web response system, MSKCC = Memorial Sloan-Kettering Cancer Center, NE = not estimable, Q = quartile.
a: Quartiles are estimated by Kaplan–Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
b: Hazard ratio is based on a Cox Proportional Hazard Model including treatment group as a factor, Efron method is used for ties.
c: Stratified by geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and MSKCC prognostic groups (favourable, intermediate, and poor risk) in IxRS.
d: Overall survival rate and 95% CIs are calculated using Kaplan–Meier product-limit method and Greenwood Formula.
e: Estimates for survival follow-up time are calculated in the same way as the Kaplan–Meier estimate of overall survival but with the meaning of 'censor' and 'event' status indicator reversed.

Figure 6. Kaplan–Meier Plot of Overall Survival – Full Analysis Set, data cut-off 31 March 2021

Objective Response Rate – IA3 data cut

The ORR in the pembrolizumab with lenvatinib arm was approximately double that of the ORR in the sunitinib arm: 71.0% (57 subjects [16.1%] with confirmed CR and 195 subjects [54.9%] with confirmed PR) and 36.1% (15 subjects [4.2%] with confirmed CR and 114 subjects [31.9%] with confirmed PR), respectively. The difference between the treatment arms was 34.9% (95% CI: 28.0, 41.7) and the odds ratio was 4.35 (95% CI: 3.16, 5.97) (nominal *P*<0.0001) in favour of the pembrolizumab with lenvatinib treatment (Table 12).

Responses were rapid, durable, and deep:

- Responses occurred early, with a median time to first objective response in the pembrolizumab with lenvatinib arm of 1.94 months in subjects with CR/PR (Table 12).
- Tumour response analysis showed an improvement in the DOR that was observed in the pembrolizumab with lenvatinib arm compared with the sunitinib arm. The median DOR in responders was 25.8 months (95% CI: 22.1, 27.9) in the pembrolizumab with lenvatinib arm and 14.6 months (95% CI: 9.4, 16.7) in the sunitinib arm (Table 12).

A greater magnitude of tumour shrinkage was observed in the pembrolizumab with lenvatinib arm; a total of 192 subjects (61.9%) had more than 50% and 98 subjects (31.6%) had more than 75% tumour shrinkage compared with 82 subjects (27.4%) having more than 50% and 38 subjects (12.7%) having more than 75% tumour shrinkage in the sunitinib arm (Table 13).

Table 12. Summary of Objective Response When Confirmation of Response Required at IA3 – Independent Imaging Review, per RECIST 1.1 – Full Analysis Set

	Pembrolizumab + lenvatinib (N=355)	Sunitinib (N=357)
Best Overall Response, n (%)		
CR	57 (16.1)	15 (4.2)
PR	195 (54.9)	114 (31.9)
Stable Disease	68 (19.2)	136 (38.1)
PD	19 (5.4)	50 (14.0)
Unknown/Not Evaluable	16 (4.5)	42 (11.8)
No Baseline Tumour Assessment	0 (0.0)	1 (0.3)
No Postbaseline Tumour Assessment	12 (3.4)	38 (10.6)
≥1 Lesion NE	1 (0.3)	2 (0.6)
Early Stable Disease (<7 Weeks)	3 (0.8)	1 (0.3)
Objective Response Rate (CR + PR), n (%)	252 (71.0)	129 (36.1)
95% CI[a]	(66.3, 75.7)	(31.2, 41.1)
Pembrolizumab + lenvatinib vs sunitinib		
Difference (%) (95% CI)[a]	34.9 (28.0, 41.7)	
Odds Ratio (95% CI)[b]	4.35 (3.16, 5.97)	
P value[b]	<0.0001	
Time to First Objective Response (Months)		
Subjects with Objective Response Only		
n	252	129
Mean (SD)	3.30 (2.635)	3.36 (2.600)
Median	1.94	1.94
Q1, Q3	1.87, 3.75	1.87, 3.71
Min, Max	1.41, 18.50	1.61, 16.62
Duration of Objective Response (Months)		
Subjects with Objective Response, n	252	129
Median (95% CI)	25.8 (22.1, 27.9)	14.6 (9.4, 16.7)
Q1 (95% CI)	12.8 (10.1, 14.7)	7.4 (3.8, 9.1)
Q3 (95% CI)	NE (NE, NE)	24.0 (19.0, NE)
Min, Max	(1.64+, 36.76+)	(1.64+, 33.15+)

Data cut-off date: 28 Aug 2020.
Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group. Stable disease must be ≥7 weeks after randomization. Durable stable disease must be ≥23 weeks after randomization. Time to first objective response (months) = (date of first objective response – date of randomization + 1) × 12 / 365.25, for subjects with best overall response of CR/PR. It is censored for subjects without best overall response of CR/PR. Duration of objective response (months) = '(Date of PD/Death or Censor Date – Date of First Objective Response + 1) × 12 / 365.25, for subjects with objective response.

Abbreviations: CI, confidence interval; CR, complete response; IxRS, interactive voice and web response system; NE, not estimable; PD, progressive disease; PR, partial response; Q, quartile; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation
a: 95% CI is constructed using the method of Normal Approximation.
b: Odds Ratio and nominal P value are calculated using the Cochran–Mantel–Haenszel method, stratified by IxRS stratification factors.
c: Quartiles are estimated by Kaplan–Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.
+: indicates the time is censored.

Disease control rate – IA3 data-cut (28 August 2020)

The disease control rate (DCR) was higher for the pembrolizumab with lenvatinib arm (90.1%) compared with the sunitinib arm (74.2%), and the clinical benefit rate (CBR) was also higher for the pembrolizumab with lenvatinib arm (84.2%) compared with the sunitinib arm (59.4%) (Table 13).

In the pembrolizumab with lenvatinib arm, tumour shrinkage per IIR occurred in 305 of 310 subjects (98.4%) evaluable for tumour shrinkage (Figure 7 and Table 13). Overall, the plots show a clear increase in tumour shrinkage in the pembrolizumab with lenvatinib arm relative to the sunitinib arm.

Table 13. Summary of Tumour Response at IA3 – Independent Imaging Review, per RECIST 1.1 – Full Analysis Set

Response with Confirmation	Pembrolizumab + lenvatinib (N=355)	Sunitinib (N=357)
Disease Control Rate (CR+PR+StSD), n (%)	320 (90.1)	265 (74.2)
95% CI[a]	(87.0, 93.2)	(69.7, 78.8)
Pembrolizumab + lenvatinib vs Sunitinib		
Difference (%) (95% CI)[a]	15.9 (10.4, 21.4)	
Odds Ratio (95% CI)[b]	3.26 (2.13, 5.00)	
P value[b]	<0.0001	
Clinical Benefit Rate (CR+PR+Durable SD), n (%)	299 (84.2)	212 (59.4)
95% CI[a]	(80.4, 88.0)	(54.3, 64.5)
Pembrolizumab + lenvatinib vs sunitinib		
Difference (%) (95% CI)[a]	24.8 (18.5, 31.2)	
Odds Ratio (95% CI)[b]	3.71 (2.60, 5.31)	
P value[b]	<0.0001	
Maximum Tumour Reduction in Sum of Diameters of Target Lesions, n/m[c] (%)		
Reduction >0%	305/310 (98.4)	267/299 (89.3)
Reduction ≥30%	257/310 (82.9)	158/299 (52.8)
Reduction ≥50%	192/310 (61.9)	82/299 (27.4)
Reduction ≥75%	98/310 (31.6)	38/299 (12.7)

Data cut-off date: 28 Aug 2020.
Percentages are based on the total number of subjects in the Full Analysis Set within the relevant treatment group. Stable disease must be ≥7 weeks after randomization. Durable stable disease must be ≥23 weeks after randomization. Time to first objective response (months) = (date of first objective response – date of randomization + 1) × 12 / 365.25, for subjects with best overall response of CR/PR. It is censored for subjects without best overall response of CR/PR. 12 / 365.25, for subjects with objective response.
Abbreviations: CI, confidence interval; CR, complete response; IxRS, interactive voice and web response system; NE, not estimable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours
a: 95% CI is constructed using the method of Normal Approximation.
b: Odds Ratio and nominal P value are calculated using the Cochran–Mantel–Haenszel method, stratified by IxRS stratification factors.
c: m is number of subjects with both baseline and postbaseline sum of diameters of target lesions and is used as the denominator for the respective percentages.

Figure 7. Percent Change in Sum of Diameters of Target Lesions from Baseline to Postbaseline Nadir – Independent Imaging Review, Per RECIST 1.1 Full Analysis Set – Pembrolizumab + lenvatinib

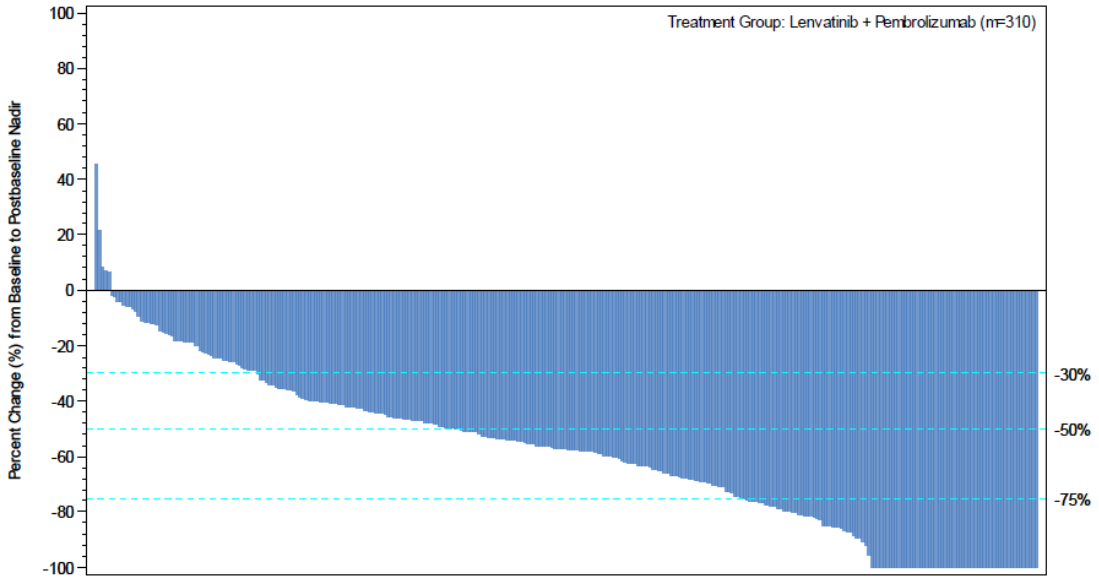
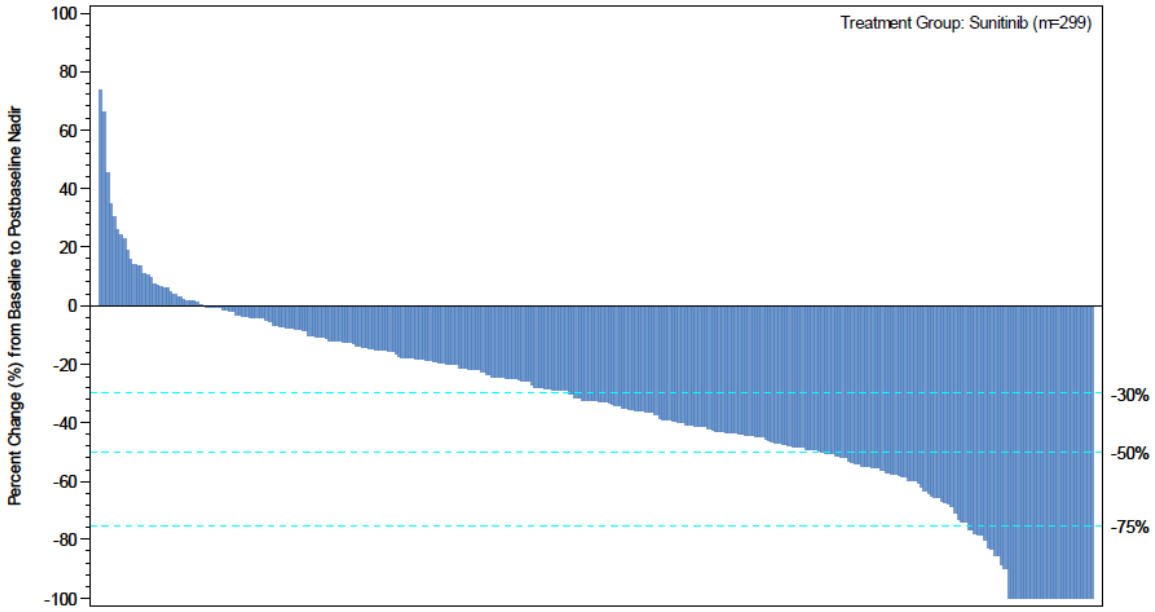


Figure 8. Percent Change in Sum of Diameters of Target Lesions from Baseline to Postbaseline Nadir – Independent Imaging Review, Per RECIST 1.1 Full Analysis Set – sunitinib arm



Patient reported outcomes

PRO Compliance Rate and Completion Rate

Completion rates for all HRQoL instruments (FKSI-DRS, EORTC QLQ-C30 and EQ-5D-3L) were notably different among the treatment arms. The rates for completion of all instruments declined below 50% at Cycle 26 for pembrolizumab + lenvatinib, and Cycle 12 for sunitinib as participants discontinued the study due to disease progression, death, or other reasons, including withdrawal of consent and adverse events. The completion rates (at least one complete score) at the off-treatment visit were 40.0% for pembrolizumab + lenvatinib, and 55.7% for sunitinib. Compliance was generally high (> 90%) in all groups during the early cycles of treatment, but lower at some later cycles and at the off-treatment visit, where compliance for any instrument was 80.2% in the pembrolizumab + lenvatinib group, and 84.0% in the sunitinib group. Altogether, these results suggest that, while still on treatment, most participants completed the HRQoL assessments. Summary of compliance of FKSI-DRS, EORTC QLQ-C30 and EQ-5D-3L by visit and by treatment are provided in Appendix L.

Analysis of change from baseline in FKSI-DRS, EORTC QLQ-C30 and EQ-5D scores

A change in FKSI-DRS score of ≥3 was considered to be clinically meaningful[30,31]. A change in EORTC QLQ-C30 score of ≥10 was considered to be clinically meaningful[32].

Overall, least square (LS) mean differences estimated at the mean follow-up time comparing each pembrolizumab plus lenvatinib with the sunitinib treatment arm are presented in Table 14. Positive differences for the LS mean (or, in the case of the EORTC QLQ-C30 symptom scales, negative differences) favour pembrolizumab plus lenvatinib treatment group over the sunitinib treatment group (Appendix L).

Statistically significant differences in the overall LS means were observed for a number of the comparisons, but none of the differences exceeded the MID for clinical significance. The pembrolizumab plus lenvatinib group had a higher overall physical functioning scale score and less severe symptoms for fatigue, dyspnoea, and constipation than the sunitinib group (Appendix L).

Table 14. Longitudinal Analysis for EORTC QLQ-C30 Symptom Scales, FKSI-DRS Score and EuroQol Visual Analog Scale (Full-Analysis-Set Population)

Study: KEYNOTE 581[a]	N[b]	N[c]	Mean at Baseline (SD)[d]	Mean Change from Baseline (SE)[e]	Pembrolizumab + Lenvatinib vs. Sunitinib	
					Mean Difference[e] [95 %-CI]	Standardized Mean Difference[f] [95 %-CI]

EORTC QLQ-C30 Symptom Scales						
Fatigue						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and Vomiting						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appetite Loss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FKSI-DRS Symptom Scales						
Total						
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D VAS						
EQ VAS Score						

Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cut-off Date: 28AUG2020
b: Number of participants: full-analysis-set population
c: Number of patients with data available for analysis
d: Mean and SD at baseline are calculated based on number of subjects with data available for analysis
e: MMRM of change from baseline with treatment, time, baseline endpoint score, and strata geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) as covariates. A continuous time assessment (relative analysis day) is used, and spatial power covariance between visits is assumed
f: Standardized mean difference (Hedges's g) is only calculated if confidence interval for mean difference does not include zero
Abbreviations: CI, Confidence Interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EQ-5D, European Quality of Life 5 Dimensions; FKSI-DRS, Functional Assessment of Cancer Therapy - Kidney Symptom Index - Disease Related Symptoms; MMRM, Mixed-effect Model Repeated Measures; MSKCC, Memorial Sloan Kettering Cancer Center; SD, Standard Deviation; SE, Standard Error; VAS, Visual Analogue Scale

The mean EQ-5D index values for the treatment arms were similar at baseline (0.83 for pembrolizumab plus lenvatinib, and 0.81 for sunitinib) (Table 15). These means decreased only very slightly during treatment before disease progression, with the mean index value for sunitinib declining to 0.80. For pembrolizumab plus lenvatinib, the mean index value before progression was 0.81, and the difference was significant (P=0.0007). For participants who discontinued treatment due to disease progression, the mean index value at the off-treatment visit was 0.75 in the pembrolizumab plus lenvatinib arm, and 0.73 in the sunitinib arm; the difference between the arms were not significant.

Table 15. Summary of Observed EQ-5D Index Scores Quality of Life Analysis Set

	Pembrolizumab + lenvatinib	**Sunitinib**
Group/Statistic	**(N = 351)**	**(N = 340)**
Baseline		
Number of observations	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
P value	[redacted]	
Pre-progression		
Number of observations	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
P value	[redacted]	
Post-progression		

Number of observations	[redacted]	[redacted]
Mean (SE)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
P value	[redacted]	

Abbreviations: CI, confidence interval; SE, standard error
Pre-progression consists of all postbaseline observations, including observations from the off-treatment visit for participants who did not discontinue treatment due to progression. Post-progression includes observations from the off-treatment visit for participants who discontinued treatment due to progression.
P value is estimated from a t test comparing treatment arm means.

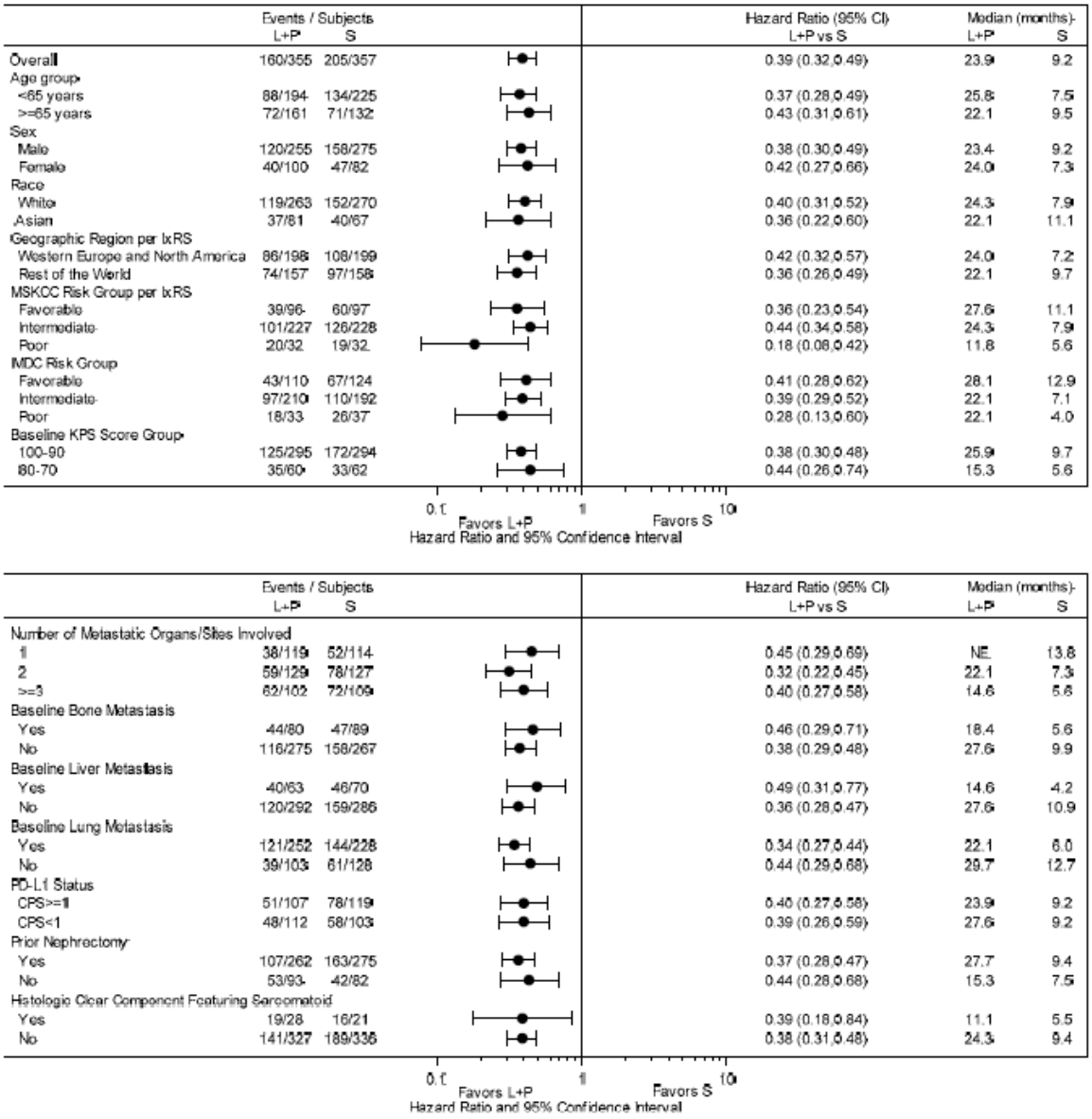
B.2.7 Subgroup analysis

Exploratory analyses for PFS, OS, and ORR were conducted for the following subgroups: age, sex, race, geographic region, MSKCC and IMDC risk groups, number of metastatic sites per IIR, KPS group, baseline bone, liver, and lung metastasis status, PD-L1 status, prior nephrectomy, and clear cell histology with sarcomatoid features.

Progression-free survival by Independent Imaging Review, per RECIST 1.1 (IA3 results 28 August 2020)

The results of the subgroup analyses indicated that benefit in favour of pembrolizumab with lenvatinib was maintained across all subgroups and was consistent with and supportive of the primary PFS analysis (Figure 9).

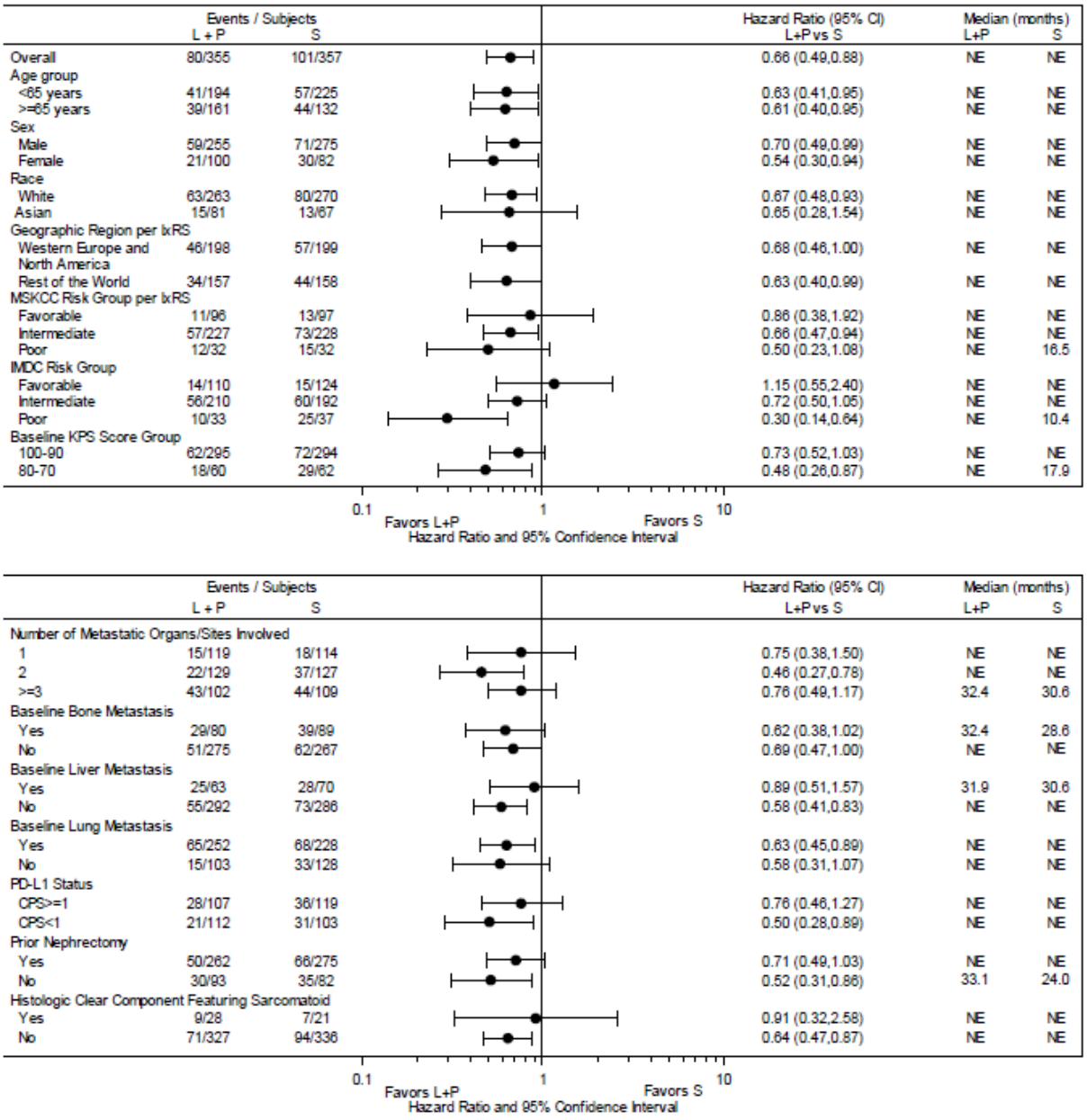
Figure 9. Forest Plot of Hazard Ratio for Pembrolizumab with lenvatinib Versus Sunitinib in Progression-Free Survival at IA3 – Independent Imaging Review, per RECIST 1.1 – Full Analysis Set



Overall survival – IA3 results 28 August 2020

The results of the subgroup analyses indicated that benefit in favour of pembrolizumab with lenvatinib was maintained across the majority of subgroups and was supportive of the OS outcome in the overall population (Figure 10). When categorised according to IMDC criteria, OS significantly favoured pembrolizumab with lenvatinib in the intermediate and poor risk groups; in the favourable risk group, OS favoured sunitinib however the 95% CI associated with the HR crossed 1. Due to the low number of events in the IMDC favourable risk group (29/234 patients), the CI is wide and thus interpretation of the data is limited.

Figure 10. Forest Plot of Hazard Ratio for Pembrolizumab with lenvatinib versus Sunitinib in Overall Survival at IA3 – Full Analysis Set



Overall survival – follow up data-cut (31 March 2021)

The OS follow-up results across the IMDC risk groups were generally consistent with those of the overall cohort. The OS HR point estimate favoured pembrolizumab with lenvatinib in the intermediate and poor risk groups according to both MSKCC and IMDC criteria. Due to the low number of events remaining low with additional follow-up and hence wide CI, interpretation of the HR is limited in the MSKCC and IMDC favourable risk groups (Table 16 and Figure 11).

Table 16. Overall Survival by Subgroup, pembrolizumab with lenvatinib vs sunitinib – Full Analysis Set

	Pembrolizumab + lenvatinib (N = 355)			Sunitinib (N = 357)			
	N	Events[a]	Median (95% CI) (months)[b]	N	Events[a]	Median (95% CI) (months)[b]	Hazard Ratio[c] (95% CI) Lenvatinib + Pembrolizumab vs Sunitinib
Overall	[redacted]						
MSKCC Risk Group per IxRS							
Favourable	[redacted]						
Intermediate	[redacted]						
Poor	[redacted]						
IMDC Risk Group							
Favourable	[redacted]						
Intermediate	[redacted]						
Poor	[redacted]						

Data cut-off date: 31 March 2021.
If a stratification factor is itself a subgroup, this factor is removed from the stratified analysis. The subgroups/strata with sample size less than 5% of the treatment group are not displayed.
Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IxRS, interactive voice and web response
system, MSKCC = Memorial Sloan-Kettering Cancer Center, NE = not estimable.
a: Subjects who died.
b: Median is estimated with Kaplan-Meier product-limit method and 95% CIs are constructed with a generalized Brookmeyer and Crowley method.
c: Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties. Stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) in IxRS.

Figure 11. Forest Plot of Hazard Ratio for Pembrolizumab plus lenvatinib vs Sunitinib in Overall Survival – Full Analysis Set


[redacted]

B.2.8 Meta-analysis

There is only one phase III randomised, controlled trial of pembrolizumab + lenvatinib compared with a relevant comparator, in our specific population of interest (patients with advanced RCC): KEYNOTE-581[25] . Therefore, it was not feasible to conduct a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

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

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

Trials included in the NMA were identified through the SLR and are presented in Table 17. An overview of the patients' characteristics in all included studies is provided in Table 18. The network of evidence identified in the SLR for pembrolizumab plus lenvatinib in first-line setting is depicted in Figure 12.

Table 17. Summary of the RCTs used to carry out the NMA

Trial ID	Intervention A	Intervention B
KEYNOTE-581[19]	Pembrolizumab + lenvatinib	Sunitinib
CABOSUN[20]	Cabozantinib	Sunitinb
COMPARZ[21]	Pazopanib	Sunitinib
CROSS-J-RCC[22]	Sorafenib	Sunitinib
SWITCH[23]	Sorafenib	Sunitinib
TIVO-1[24]	Tivozanib	Sorafenib

Table 18. Patient characteristics of randomised controlled trials included in the feasibility assessment

Trial ID	Treatment	N	Age, Median (range)	Male, n (%)	Ethnicity, White, n (%)	Ethnicity, Black, n (%)	Ethnicity, Asian, n (%)
KEYNOTE-581	Pembrolizumab + lenvatinib	355	64 (34-88)	255(71.8)	263(74.1)	NR	81(22.8)
	Sunitinib	357	61 (29-82)	275(77)	270(75.6)	NR	67(18.8)
CABOSUN	Cabozantinib	79	63	66 (83.5)	70 (88.6)	3 (3.8)	1 (1.3)
	Sunitinib	78	64	57 (73.1)	75 (96.2)	2 (2.6)	0
COMPARZ	Pazopanib	557	61 (18-88)	398 (71)	NR	NR	NR
	Sunitinib	553	62 (23-86)	415 (75)	NR	NR	NR
CROSS-J-RCC	Sunitinib	57	67 (41-79)	46 (81)	NR	NR	NR
	Sorafenib	63	66 (44-79)	53 (84)	NR	NR	NR
SWITCH	Sorafenib	182	64 (39-84)	139 (76)	NR	NR	NR
	Sunitinib	183	65 (40-83)	135 (74)	NR	NR	NR
TIVO-1	Tivozanib	260	59 (23-83)	185 (71)	249 (96)	1 (<1)	10 (4)
	Sorafenib	257	59 (23-85)	189 (74)	249 (97)	0	8 (3)

Abbreviations: NR, not reported

2.9.2 Network meta-analysis – Overview of analyses and the base case

A subset of trials that compared relevant interventions listed in the decision problem were included. The list of relevant interventions included pembrolizumab plus lenvatinib, cabozantinib, pazopanib, sunitinib, and tivozanib. Of the 35 unique trials identified in the systematic literature review, six trials included interventions of interest and were subsequently deemed eligible for inclusion in the NMA. The trials were generally comparable to KEYNOTE-581 in terms of study design and eligibility criteria relating to disease severity. However, there were some differences in baseline characteristics between KEYNOTE-581 and comparator trials:

1. CABOSUN included only IMDC intermediate and poor risk patients, subsequently a subgroup analysis was conducted in this patient population
2. CROSS-J-RCC included only MSKCC favourable and intermediate patients. However, due to the small proportion of individuals with MSKCC poor risk in the KEYNOTE-581 trial, a limited impact on the results is expected
3. TIVO-1 included first-line and second-line RCC patients

An NMA was conducted for the ITT and IMDC intermediate + poor risk group population. The list of relevant interventions included pembrolizumab and lenvatinib, cabozantinib, pazopanib, sunitinib, and tivozanib. As tivozanib was listed as an intervention of interest in the decision problem, the network included sorafenib to allow for an indirect comparison with tivozanib. The analyses were performed using ITT data for all trials with sunitinib as the common comparator. All analyses were performed in a Bayesian framework. Given that predominately only one trial was available per treatment comparison in the network, all analyses were performed using a fixed-effect model.

Fractional polynomial models (representing different survival distributions) were fit to the data under a variety of different assumptions about the shape of the hazard function. Results for the constant HRs are presented for OS and PFS. These results were generally consistent with the results with time-varying hazards. Of all the time-varying hazards models assessed, the model with the best fit was selected based on the deviance intervention criterion (DIC) and fit to the observed data. For most studies, hazard ratios were obtained from published estimates from the SLR. For the studies where hazard ratios were not originally reported, the hazard ratios were calculated with a Cox proportional hazard model based on a digitized KM curve (if available).

2.9.3 NMA results

PFS: IA3 (28 August 2020 data-cut)

ITT population

The network of RCTs for the overall population included all trials that reported PFS. This led to the inclusion of five RCTs (KEYNOTE-581[19], COMPARZ[21], SWITCH[23], CROSS-J-RCC[22], TIVO-1[24]) in the network (Figure 12). The network included sorafenib to allow for an indirect comparison to tivozanib.

For PFS, KM curves were presented for four interventions of interest (pembrolizumab plus lenvatinib, sunitinib, pazopanib, tivozanib) which is presented in Appendix M.

The results of the fixed-effects constant HR NMA are presented in Table 19. The results of the constant HR analysis showed that treatment with pembrolizumab plus lenvatinib resulted in [redacted] compared to all comparators.

Figure 12. Network of all randomized controlled trials for progression-free survival; ITT population

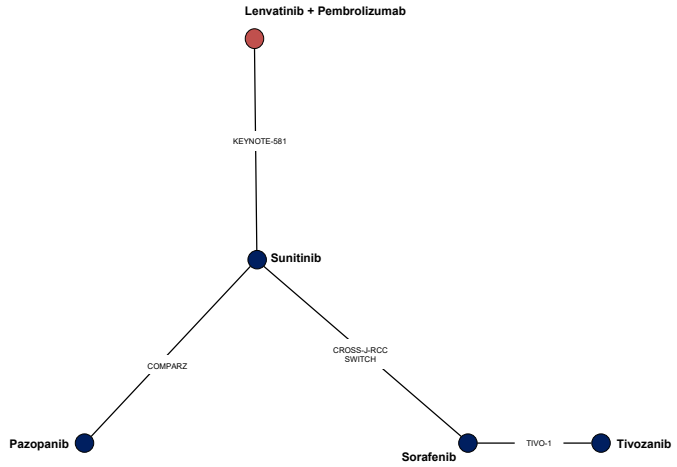


Table 19. Hazard ratios estimated from fixed-effects network meta-analysis; ITT population

Hazard Ratio (Fixed Effect)				
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	**Pembrolizumab + lenvatinib**	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	**Pazopanib**	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**Tivozanib**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	**Sorafenib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Fixed effect: DIC: 10.71; Deviance: 6.69, pD: 4.02

Overall survival NMA results based on IA3 are presented in Appendix M.

Overall survival – follow up analysis (31 March data-cut)

The analysis was performed using sunitinib as the common comparator and ITT data was used for all trials. For OS update, constant hazards data and KM curves were described for 3 interventions of interest (lenvatinib + pembrolizumab, sunitinib, and pazopanib) which is presented in Figure 13. Tivozanib was listed as an intervention of interest by NICE. A potential indirect comparison between sorafenib and tivozanib can be conducted. However, due to the crossover trial design of the two sorafenib trials (CROSS-J-RCC and SWITCH), it was not recommended to conduct an indirect comparison to tivozanib. As both trials permitted treatment switching upon disease progression this would lead to potential bias in the results.

The results of the fixed-effects constant HR NMA are shown in Table 20. The results of the constant HR analysis showed that treatment with pembrolizumab plus lenvatinib resulted in [redacted]. Meanwhile, the results showed [redacted] for pembrolizumab plus lenvatinib compared to pazopanib.

Figure 13: Network of all randomized controlled trials for overall survival update; ITT population

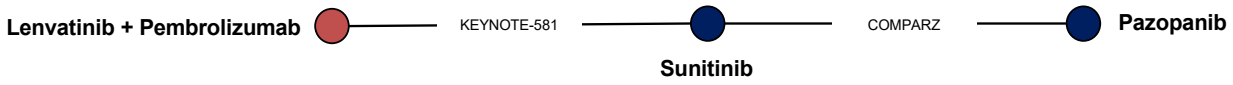


Table 20: Hazard ratios estimated from fixed-effects network meta-analysis; ITT population

Hazard Ratio (Fixed Effect)		
Sunitinib	[redacted]	[redacted]
[redacted]	**Lenvatinib + Pembrolizumab**	[redacted]
[redacted]	[redacted]	**Pazopanib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. Fixed effect: DIC: 3.36; Deviance: 1.36, pD: 2.0

The results for intermediate + poor risk subgroup are presented in Appendix M.

Uncertainties in the indirect and mixed treatment comparisons

Potential treatment effect modifiers were assessed in the feasibility assessment. Based on the feasibility assessment and data availability, potential treatment effect modifiers were assessed separately in a subgroup analysis, where feasible (i.e. IMDC risk status). The NMA analysis used of both time-varying and time-constant hazard ratios. NMA for survival outcomes based on the constant HR rely on the proportional hazard assumption. A constant HR in the context of NMA implicitly assumes that the log hazard functions of all treatments in the network run parallel, which may be considered unrealistic. As an alternative to the constant HR, which is a univariate treatment effect measure, a multivariate treatment effect measure that describes how the relative treatment effect (e.g., HR) develops over time can be used. Ouwens et al[33] and Jansen[34] presented methods for NMA of survival data using a multi-dimensional or multivariate treatment effect as an alternative to the synthesis of one treatment effect (e.g., the constant HRs). The hazard functions of the interventions in a trial are modelled using known parametric survival functions, and the difference in the parameters are considered the multi-dimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. By incorporating

additional parameters for the treatment effect, the proportional hazards assumption is relaxed and the NMA model can be fitted more closely to the available data.

Limitations to the conducted NMA include the tails of KMs which may become unstable due to censoring when follow-up times are different between trials. When the at-risk population becomes low at the end of follow-up, it can contribute to increased uncertainty, especially in tails of the time-varying HR NMA. This can be seen in the intermediate + poor risk group PFS analysis, the original sample size in KEYNOTE-581 was larger than that in the CABOSUN trial, thereby, greater uncertainty in estimates was seen in the later months of the time varying NMA. Given the structure of the network, comparisons between pembrolizumab plus lenvatinib and tivozanib in the ITT PFS analysis was mediated by multiple treatment comparisons, and were therefore more uncertain. As the distance of comparison between pembrolizumab plus lenvatinib and tivozanib was greater compared to pazopanib, results should be interpreted with more caution. Comparisons for pembrolizumab plus lenvatinib to all relevant competing interventions were predominately based on single trial data. Given the limited number of trials included in the analyses, there was insufficient data to reliably estimate between-study heterogeneity. Consequently, these results are based on fixed-effects model, despite a preference for random-effects model; some of the credible intervals may be narrower than they should be and should be interpreted with caution. The validity of the findings based on the current NMA depends on the quality of the RCTs and the extent of any violations in the similarity and consistency assumptions across studies. In an NMA of RCTs involving multiple treatment comparisons, the randomization holds only within the individual trials and not across trials. If the different direct comparisons show systematic differences in study and patient characteristics, and these differences are treatment effect modifiers, then the estimates of any indirect comparison as obtained with the NMA will be biased.

In conclusion, pembrolizumab plus lenvatinib appears to notably improve PFS and tumour response compared to the relevant comparators included in the appraisal scope. For OS, the efficacy of pembrolizumab plus lenvatinib appears to be statistically significantly greater compared to sunitinib and numerically superior but statistically non-significant compared to pazopanib.

B.2.10 Adverse reactions

The primary safety analyses of IA3 were based on data from the ASaT population of 1047 participants as of the cut-off date of 28 August 2020. In all tables, individuals are counted only once for a specific AE term by the worst severity recorded.

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

- Drug Related AEs
- Grade 3-5 AEs
- Serious AEs
- Death to AEs
- Discontinuation due to AEs
- Interruptions due to AEs
- Dose reductions due to AEs

IA3: August 2020 data-cut

Extent of exposure

The median duration of exposure was greater for pembrolizumab + lenvatinib compared with sunitinib (Table 21). When adjusted for exposure, there were no clinically meaningful differences in overall AE rates between the two groups, including SAEs and drug-related SAEs (Table 21). The rate of drug-related AEs was lower for pembrolizumab + lenvatinib compared with sunitinib.

The overall duration of treatment was defined as the duration between the earliest first dose start date of either medication and the latest last dose end date of either medication. The median duration of treatment was 17.00 months in the pembrolizumab plus lenvatinib arm and was 7.84 months in the sunitinib arm; exposure to pembrolizumab plus lenvatinib was approximately 2.5 times longer than exposure to sunitinib (Table 21).

Table 21. Extent of Exposure – Safety Analysis Set

Extent of Exposure	Lenvatinib + Pembrolizumab (N=352)	Sunitinib (N=340)
Overall: Duration of Treatment (months)[a]		
n	352	340
Mean (SD)	17.29 (9.575)	11.33 (9.463)
Median	17.00	7.84
Min, Max	0.07, 39.13	0.10, 36.96
No. of Subject-Months[b]	6086.08	3850.58
Lenvatinib: Duration of Treatment (months)[a]	Lenvatinib 20 mg	
n	352	NA
Mean (SD)	16.45 (9.839)	NA
Median	16.13	NA
Min, Max	0.07, 39.13	NA
No. of Subject-Months[b]	5790.23	NA
Pembrolizumab/Sunitinib: Duration of Treatment (months)[a]	Pembrolizumab	Sunitinib
n	352	340
Mean (SD)	14.45 (8.562)	11.33 (9.463)
Median	15.08	7.84
Min, Max	0.03, 29.60	0.10, 36.96
No. of Subject-Months[b]	5086.29	3850.58

Data cut-off date: 28 Aug 2020.
Percentages are based on the total number of subjects in Safety Analysis Set within the relevant treatment group.
Abbreviations: Max, maximum; min, minimum; NA, not applicable; SD, standard deviation
a: Duration of treatment (months) = (date of last dose of study drug – date of first dose of study drug + 1) / 30.4375. For overall duration of treatment, it is defined as the duration between the earliest first dose start date of either medication and the latest last dose end date of either medication.
b: Number of subject months = total duration of treatment (in days) across all subjects in the relevant treatment 30.4375.

The median dose intensity of lenvatinib in the pembrolizumab plus lenvatinib arm was 69.65% of the intended dose (Table 22). The median number of pembrolizumab administrations was 22.0 (Table 23). The median dose intensity of sunitinib was 83.18% of the intended dose.

Table 22. Administration of Lenvatinib and Sunitinib – Safety Analysis Set

	Pembrolizumab + lenvatinib (N=352)	Sunitinib (N=340)
	Lenvatinib 20 mg	Sunitinib
Total Dose (mg) per Subject		
n	[redacted]	340
Mean (SD)	[redacted]	9426.3 (8119.60)
Median	[redacted]	6637.5
Min, Max	[redacted]	150, 35800
Dose Intensity (mg/day) per Subject [a]		
n	[redacted]	340
Mean (SD)	[redacted]	39.52 (9.987)
Median	[redacted]	41.59
Min, Max	[redacted]	9.4, 50.0
Received Dose as Percentage of Planned Starting Dose per Subject [b]		
n	[redacted]	340
Mean (SD)	[redacted]	79.04 (19.975)
Median	[redacted]	83.18
Min, Max	[redacted]	18.8, 100.0

Data cut-off date: 28 Aug 2020.
Abbreviations: Max, maximum; min, minimum; SD, standard deviation
a: Dose intensity (mg/day) = total dose received during the study/(date of last dose of study drug – date of first dose of study drug + 1). For sunitinib only: dose intensity (mg/day) = total dose received during the study/summation of durations of the dose intervals except for drug holiday.
b: For pembrolizumab + lenvatinib, received lenvatinib dose as percentage of planned starting 20 (mg/day) × 100. For sunitinib, received dose as percentage of planned starting dose = (mg/day)/50 (mg/day) × 100.

Table 23. Administration of Pembrolizumab – Safety Analysis Set

Parameter	Pembrolizumab + lenvatinib (N=352)
No. of Administrations	
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]

Data cut-off date: 28 Aug 2020.
Abbreviations: Max, maximum; min, minimum; SD, standard deviation

Treatment-Related Adverse Events

Overall, treatment-related TEAEs (all grades) were reported for 96.9% of subjects in the pembrolizumab plus lenvatinib arm and 92.1% of subjects in the sunitinib arm; a higher percentage of subjects in the combination arm had a related TEAE that was Grade ≥3 (71.6% vs 58.8%). The frequency of treatment-related TEAEs leading to either study drug modification in the pembrolizumab plus lenvatinib arm was higher than in the sunitinib arm

(83.2% vs 65.9%, respectively). Treatment-related TEAEs leading to discontinuation of all study drugs was comparable in the lenvatinib and pembrolizumab and sunitinib arms (9.7% vs 10.0%, respectively).

The most common treatment-related TEAEs (≥30% of subjects in either arm) in the pembrolizumab plus lenvatinib arm and sunitinib arm, in decreasing incidence, were diarrhoea (54.5% vs 44.4%), hypertension (52.3% vs 39.1%), hypothyroidism (42.6% vs 23.2%), stomatitis (32.1% vs 37.4%), fatigue (32.1% vs 32.1%), decreased appetite (34.9% vs 24.7%), and palmar–plantar erythrodysesthesia (28.1% vs 35.9%) (Table 24).

Table 24. Overview of Treatment-Related Treatment-Emergent Adverse Events – Safety Analysis Set

Category	Pembrolizumab + lenvatinib (N=352) n (%)	Sunitinib (N=340) n (%)
Subjects with Any Treatment-Related TEAEs	341 (96.9)	313 (92.1)
Subjects with Any Treatment-Related TEAE Worst CTCAE Grade of		
≥3	252 (71.6)	200 (58.8)
3	207 (58.8)	175 (51.5)
4	41 (11.6)	24 (7.1)
5	4 (1.1)	1 (0.3)
Subjects with Any Treatment-Related Serious TEAEs[a]	119 (33.8)	51 (15.0)
Subjects with Any Treatment-Related Fatal TEAEs	4 (1.1)	1 (0.3)
Subjects with Any Treatment-Related Nonfatal Serious TEAEs	118 (33.5)	50 (14.7)
Subjects with Treatment-Related TEAEs[a]		
Leading to Study Drug Discontinuation[b]	110 (31.3)	34 (10.0)
Discontinuation of Lenvatinib[c]	65 (18.5)	NA
Discontinuation of Everolimus or Pembrolizumab[d]	88 (25.0)	NA
Discontinuation of Lenvatinib and Everolimus or Lenvatinib and Pembrolizumab[e]	34 (9.7)	NA
Leading to Dose Reduction[b]	237 (67.3)	169 (49.7)
Reduction of Lenvatinib[c]	237 (67.3)	NA
Leading to Dose Study Drug Interruption[b]	253 (71.9)	159 (46.8)
Interruption of Lenvatinib[c]	229 (65.1)	NA
Interruption of Everolimus or Pembrolizumab[d]	172 (48.9)	NA
Interruption of Lenvatinib and Everolimus or Lenvatinib and Pembrolizumab[e]	114 (32.4)	NA
Leading to Dose Modification[b,f]	293 (83.2)	224 (65.9)

Modification of Lenvatinib[c]	284 (80.7)	NA
Modification of Everolimus or Pembrolizumab[d]	172 (48.9)	NA
Modification of Lenvatinib and Everolimus or Lenvatinib and Pembrolizumab[e]	134 (38.1)	NA

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities
NA = not applicable, TEAE = treatment-emergent adverse event.
a: Each subject may be counted in multiple categories.
b: Lenvatinib or everolimus or pembrolizumab (or sunitinib).
c: Regardless of action taken for pembrolizumab or everolimus.
d: Regardless of action taken for lenvatinib.
e: Due to the same adverse event.
f: Dose modification includes dose reduction or interruption.

B.2.11 Ongoing studies

The KEYNOTE-581[25] study is ongoing, with an estimated study completion date of 31 July 2022.

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. As evidenced by the clinical and safety data presented, combination of pembrolizumab with lenvatinib offers a durable and well tolerated treatment option for patients with advanced RCC.

Baseline-funded treatments currently comprise TKI monotherapies only. Pembrolizumab plus lenvatinib is a transformative combination for patients with advanced RCC. Other advanced/ metastatic cancers have benefited from pembrolizumab over the years. This innovative option is now available for patients with advanced RCC.

B.2.13 Interpretation of clinical effectiveness and safety evidence

At IA3, KEYNOTE-581 pembrolizumab plus lenvatinib showed a statistically significant and clinically meaningful improvement in PFS compared with sunitinib, with a median PFS of 23.9 months and 9.2 months, respectively (HR=0.39; 95% CI: 0.32, 0.49, P<0.0001). This demonstrates a 2.5-fold increase in PFS, and a 61% reduction in the risk of disease progression or death with pembrolizumab plus lenvatinib compared with sunitinib. The results of the subgroup analyses indicated that benefit in favour of pembrolizumab plus lenvatinib treatment was maintained across subgroups and was consistent with and supportive of the primary PFS analysis (HRs range from 0.18 to 0.53).

Pembrolizumab plus lenvatinib achieved a statistically significant and clinically meaningful improvement in the key secondary endpoint of OS (HR=0.66, [95% CI: 0.49, 0.88], P=0.0049). Median OS was not reached in the pembrolizumab plus lenvatinib and sunitinib arms. The HR of 0.66 represents a 34% reduction in the risk of death in the pembrolizumab plus lenvatinib arm compared with the sunitinib arm. The KM curves for OS demonstrated a clear, early separation of the curves demonstrating OS benefit in the pembrolizumab plus lenvatinib arm versus the sunitinib arm. This is followed by an intersection of the curves after approximately 33 months of follow-up, a point in the curve with limited numbers of patients at risk due to a high level of censoring (over 70% in the pembrolizumab with lenvatinib arm), and hence considerable uncertainty. The curve intersection moved to a later timepoint with additional follow-up (i.e., between IA3 and the updated OS analysis), indicating that more information about censored patients (i.e., less uncertainty) demonstrates a maintenance of the combination's superior OS over time. It is anticipated that with additional follow-up, a divergence of the OS curves over the entire trial time horizon will be observed. Furthermore, a markedly higher proportion of subjects in the sunitinib arm received subsequent anticancer medication and specifically, anti-PD-L1 therapy. Post-hoc analyses (Appendix N) suggest that the differential use of subsequent anticancer medication, and earlier switch to subsequent anticancer medication in the sunitinib arm, impacted the OS comparison.

At the subsequent OS follow-up, median OS was not reached with either treatment; a HR of [redacted] reduction in the risk of death in the pembrolizumab plus lenvatinib arm compared with the sunitinib arm. Results of the subgroup analyses (MSKCC and IMDC risk groups) for the OS follow-up report are generally consistent with those for the overall OS analysis and corroborate the survival benefit for pembrolizumab plus lenvatinib.

Pembrolizumab plus lenvatinib provided a clinically meaningful improvement in ORR compared with sunitinib: pembrolizumab plus lenvatinib treatment resulted in a confirmed ORR of 71.0% compared with 36.1% for sunitinib (P<0.0001), with a confirmed CR rate of 16.1%. In addition to the prolonged PFS observed for the combination, pembrolizumab plus lenvatinib resulted in an over 4-fold increase in ORR and an unprecedented confirmed CR rate. Moreover, responses were rapid, durable and deep; median time to first objective response was 1.91 months, median DOR was 25.8 months (95% CI: 20.1, NE), and the proportion of subjects with ≥50% shrinkage was 57.3%.

Results of the prespecified subgroup analyses (MSKCC prognostic group, PD-L1 status, race, age, geographic region, IMDC, baseline KPS score) indicated that benefit in favour of pembrolizumab plus lenvatinib was maintained in nearly all subgroups and was supportive of the primary PFS, OS, and ORR analysis. By IMDC risk group, OS favoured pembrolizumab plus lenvatinib in the intermediate and poor risk groups, and in the favourable risk group, the HR was higher (1.15; 95% CI: 0.55, 2.40), however, due to the low number of events (n=14 for pembrolizumab, 15 for sunitinib) and very wide CI, interpretation is limited. For ORR, results favoured pembrolizumab plus lenvatinib across all IMDC risk groups.

The combination of pembrolizumab and lenvatinib has a manageable safety profile, which is generally consistent with the established safety profiles of the individual drugs when used as monotherapies, with the exception of an increased frequency of low to moderate grade hypothyroidism. Hypothyroidism is a known ADR for both pembrolizumab and lenvatinib. There were no new AEs reported. The AEs observed for the combination were effectively managed by standard clinical practice, including dose modifications, as applicable for each monotherapy. The pembrolizumab plus lenvatinib arm showed no unexpected or new safety concerns when lenvatinib and pembrolizumab were administered together.

Internal validity

KEYNOTE-581[25] is a robust, multi-centre, randomised, active controlled phase III trial of pembrolizumab + lenvatinib versus sunitinib in patients with advanced RCC who have not received prior therapy. Prior to randomisation, eligible subjects were first stratified by IMDC risk categories (favourable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of world”).

The primary endpoint was PFS (per RECIST 1.1 as assessed by BICR) in subjects treated with pembrolizumab plus lenvatinib versus sunitinib monotherapy. OS is a clinically relevant endpoint, that was directly referenced in the final scope for this appraisal and the decision problem. This endpoint selected is consistent with that used in studies of other therapeutic agents in the population of advanced RCC. The definition of progression when evaluating PFS in KEYNOTE-581[25] followed an established response evaluation criteria (RECIST 1.1), in line with European Guidance[35].

HRQoL was explored under both secondary and exploratory endpoints in the KEYNOTE-581[25] study, with changes from baseline in patients treated with pembrolizumab plus lenvatinib compared to sunitinib recorded using both the preferred EQ-5D-3L measure (according to the NICE reference case), in addition to the cancer specific EORTC QLQ-C30.

KEYNOTE-581[25] was an open-label study, with study sponsor, investigator and participant aware of the treatment administered. However, analyses or summaries generated by randomised treatment assignment and/or actual treatment received were limited and documented. In addition, there was an element of blinding in this study as independent central imaging review was performed without knowledge of the treatment group assignments of the participants.

External validity

KEYNOTE-581[25] is a global study conducted in 181 centres in 20 countries, including 93 sites in Europe. Of the patients participating in the study, 407 were enrolled at sites in Europe, including 26 from the UK.

Baseline characteristics of patients enrolled in KEYNOTE-581[25] were as expected for patients with advanced RCC. Most patients were male, white, and had undergone prior nephrectomy. Subgroup analyses confirmed the benefit of pembrolizumab + lenvatinib versus sunitinib in patients of all histologies and regardless of PD-L1 biomarker status.

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

The observed safety profile of pembrolizumab plus lenvatinib in KEYNOTE-581[25] was generally consistent with the established safety profile of pembrolizumab monotherapy in solid tumours and the observed safety profile for lenvatinib monotherapy in first line advanced RCC[36], except for a higher than expected incidence of Grade 3 to 4 hepatic AEs and a higher incidence of all hyperthyroidism grades[25].

End-of-life and severity modifier criteria

MSD does not consider pembrolizumab in combination with lenvatinib to meet the end-of-life criteria in the all-comer patient population (Table 25). However, we do believe it would

be a candidate for a severity modifier as being consulted upon in the NICE Methods and Process Review. In order to demonstrate the importance of focusing on severity of disease and quality of life, as well as quantity of life we provide calculation of how the severity modifier would be applied in this indication in section B 3.4.

Table 25. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	A randomised, open label phase II trial comparing cabozantinib with standard-of-care sunitinib in IMDC intermediate and poor risk patients with advanced RCC in the first line setting reported median OS of 21.8 months with sunitinib and 30.3 months with cabozantinib. This patient population has inferior clinical outcomes compared to an all-comer population. A randomised, open label phase II trial comparing cabozantinib with standard-of-care sunitinib in IMDC intermediate and poor risk patients with advanced RCC in the first line setting reported median OS of 21.2 months with sunitinib and 26.6 months with cabozantinib[37].	Appendix D
	A randomised, open-label, phase III trial of pazopanib versus sunitinib reported median OS as 29.3 months in the sunitinib group and 28.4 months in the pazopanib group.	Appendix D
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS does not accurately capture the OS benefit in patients treated with pembrolizumab in combination with lenvatinib; instead, the mean provides a more reliable statistical measure for estimated OS in patients treated with pembrolizumab in combination with lenvatinib, due to the longevity of the benefit observed in some patients. Median OS was not reached in KEYNOTE-581; however, at IA3 follow up data cut (March 2021) there was an improvement in 24 months OS rate with pembrolizumab + lenvatinib versus sunitinib of 10.5% (80.2% vs 69.7%).	B 2.6.1

B.3 Cost effectiveness

Summary
• A three-state partition survival model structure was developed. • The base case analysis indicates pembrolizumab plus lenvatinib to be a cost-effective treatment for untreated aRCC, when confidential discounts are applied. • Scenario analyses identified the most sensitive assumptions to be the discount rate application, reduced time horizon and treatment waning effect. • The most impactful model inputs are relative dose intensity (RDI), cohort parameters and duration of subsequent therapies.

B.3.1 Published cost-effectiveness studies

In line with the NICE guide to the methods of technology appraisal[38] , a SLR was conducted in two phases; an original search and a subsequent update, to identify relevant cost-effectiveness studies from published literature. The original search was conducted on 27 March 2019. The updated search of all the previously searched bibliographic databases and grey literature was conducted on 05 January 2021.

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

B.3.2 Economic analysis

Summary
• No cost-effectiveness studies evaluating pembrolizumab in combination with lenvatinib in the specified population were identified by a literature search. • Patient population reflected participants in the KEYNOTE-581 trial. • The partition survival model included three health states: pre-progression, post-progression and death. • Sunitinib was the primary comparator in the model. Pazopanib, tivozanib and cabozantinib (in intermediate/poor risk group only) were also included as per the appraisal final scope. • An assumption of equivalent efficacy and safety between sunitinib, tivozanib and pazopanib was followed, in line with previous aRCC TA.

A published cost-effectiveness analysis that met the relevant inclusion criteria for this submission was not identified by the systematic review. This led to the development of a *de novo* cost-effectiveness model to assess the cost-effectiveness of pembrolizumab in combination with lenvatinib compared with the relevant comparators. Key features of the economic analysis are presented in Table 26. Further details are provided in subsequent sections.

Table 26. Summary of the economic analysis

Specification	Details	Justification
Patient population	Patients aged ≥18 years with histological or cytological confirmation of RCC with a clear cell component and documented evidence of advanced disease that is treatment-naïve	Aligned with the anticipated licensed indication for pembrolizumab in combination with lenvatinib and final NICE scope
Analytical method	Partitioned survival model	The choice of modelling approach aligns with the approaches used in TA215, TA512, TA542 and TA581 for aRCC[1,11–13]. This approach is the most prevalent model structure for cancer appraisals reviewed by NICE
Model structure	Three-health states (progression-free disease, progressed disease, and death)	This structure is consistent with approaches accepted in previous NICE technology appraisals in oncology and utilises the key primary (PFS) and secondary (OS) endpoints of the KEYNOTE-581 study
Time horizon	Lifetime (40 years)	The choice of time horizon is consistent with the lifetime time horizon accepted in TA581[1]. The time horizon for estimating clinical and cost effectiveness is sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared[1]
Cycle length	1 week	The chosen cycle length ensures that the model can consider the different dosing schedules across the comparator arms, while also being the common denominator for all treatment cycles, for both the intervention and comparators. Longer cycle lengths would increase the risk of over- or under-predicting costs or QALYs when averaging across cycles
Discounting options	Costs and health outcomes at 3.5% per annum	In line with NICE reference case[38]
Perspective	NHS and PSS	In line with NICE reference case[38]

Treatment arms within model	• Pembrolizumab plus lenvatinib Comparator arms for full population: • Sunitinib • Pazopanib • Tivozanib Comparator arms for intermediate or poor IMDC subgroup: • Sunitinib • Pazopanib • Tivozanib • Cabozantinib	In line with KEYNOTE-581 intervention arm and baseline comparators in final scope
Health effects	QALYs LYs	In line with NICE reference case[38]
Clinical efficacy and safety	Data were sourced from: • KEYNOTE-581 study • Published clinical evidence • UK population general mortality	The KEYNOTE-581 study is the primary source of evidence for the efficacy and safety of pembrolizumab in combination with lenvatinib treatment, in the first-line aRCC setting
Costs and resource use	Data were informed by: • BNF for drug costs • NHS reference costs for disease management unit costs • PSSRU • A systematic review of published studies • Previous HTA appraisals within aRCC	In line with NICE reference case[38]
Utilities	Data were sourced from: • EQ-5D-3L data collected directly from patients in the KEYNOTE-581 study	In line with NICE reference case[38]

Abbreviations: aRCC, Advanced renal cell carcinoma; BNF, British National Formulary; HTA, Health technology assessment; LY, life year; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, Progression-free survival; PSS, Prescribed Specialised Services; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life year; RCC, Renal cell carcinoma

Patient population

The patient population included in the economic evaluation consisted of patients with untreated aRCC. This aligns with the anticipated licenced indication and with the appraisal final scope[39] .

The patient characteristics in the model reflected those reported for the KEYNOTE-581[25] trial and are presented in Table 27 below. As previously set out in Section B.2.6 the population in KEYNOTE-581 included patients with documented evidence and histological confirmation of aRCC. The patient population included favourable, intermediate, and poor risk prognostic groups, as defined by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. Exclusion criteria for KEYNOTE-581 excluded any patient that had previously received any anticancer therapy for RCC, including anti-VEGF therapy, or any systemic investigational anticancer agent. The baseline characteristics of the KEYNOTE-581 population are summarised in Table 27.

Table 27. Baseline characteristics of patients included in the model

Patient characteristics (n=1069)	Value	Measurement of uncertainty and distribution	Reference/ Source
Mean age (years)*	61.67	SD = 10.36	KEYNOTE-581[25]
Proportion male (%)*	74.46	-	
Mean patient weight (kg)*	81.07	SD = 18.63	
Abbreviations: SD, standard deviation **These values refer to patients recruited from European sites participating in KEYNOTE-581*			

Model structure

Consistent with economic models developed for recent NICE oncology submissions in RCC[1,11,12,40], a *de novo* partitioned survival cohort simulation model was developed to estimate health outcomes and costs for pembrolizumab in combination with lenvatinib and comparator regimens in the target patient population. This partitioned survival cohort simulation model is consistent with previous NICE appraisals in aRCC (TA169[14] , TA215[13] , TA512[12] , TA581[1]).

There are three health states in the model:

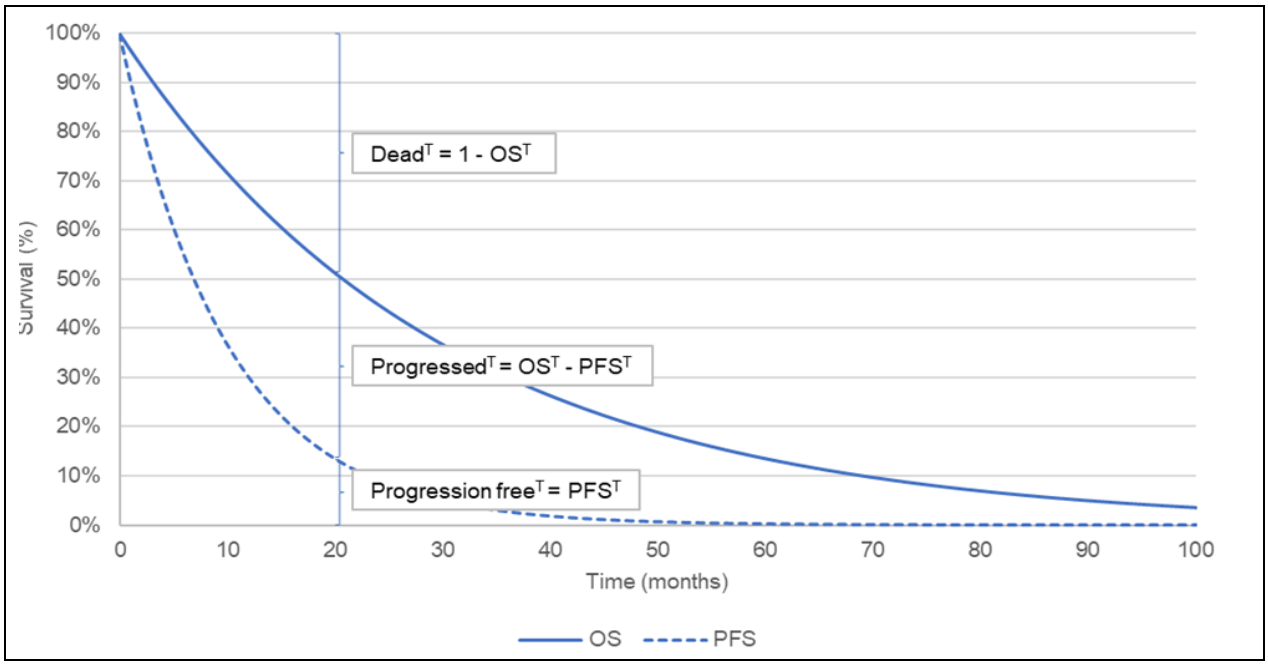
- Pre-progression, which is the starting health state, with patients staying in this state until disease progression or death
- Post-progression, which encompasses patients alive after progression and before death

- Death, which is an absorbing health state

The three health states in the partitioned survival model are mutually exclusive, meaning that patients must occupy one of the states at any given time. The selected health states are consistent with the clinical endpoints assessed in KEYNOTE-581, including the primary endpoint of PFS and the secondary endpoint of OS, and capture the disease progression of patients with aRCC.

Partitioned survival modelling uses an OS curve to estimate the proportion of patients alive over time – either from a parametric distribution or directly from KM trial data[41] . OS is then partitioned into pre-progression and post-progression health states to allow differentiation between patients' treatment patterns, monitoring costs, and if appropriate for the cancer type, the health states can be used to inform patients' HRQoL. The model uses two survival curves to estimate state membership [41]; the state membership of the dead state is estimated using the extrapolated OS Kaplan-Meier curve (Death=1-OS); the area underneath the OS curve represents the proportion of patients that were still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state were identified by the patients located underneath the PFS curve; where progression is defined by the primary censoring rule in KEYNOTE-581[25] , i.e. assessment by BICR per RECIST 1.1[35] . Hence, the area between the PFS and the OS curves represents the proportion of post-progression patients, i.e., those who were in the 'post-progression' health state (PD=OS-PFS) (Figure 14).

Figure 14. Partitioned survival model structure



Abbreviations: PFS, progression-free survival; OS, overall survival

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

For each health state, a specific cost and quality-of-life adjustment weight (i.e., utility) can be assigned within each time period for calculating the cumulative costs and cumulative QALYs over the modelled time horizon. Costs and QALYs are discounted with an annual rate of 3.5%, as stipulated by the NICE reference case[38].

Comparison of chosen methods to previous appraisals

A comparison of methods selected for this appraisal and the approaches adopted in previous aRCC appraisals is provided in Table 28. The approaches used in this submission broadly follow the preferred methods of the Committees and review groups in previous aRCC appraisals.

Table 28. Comparison of economic analysis with previous examples

	Previous appraisals							Current appraisal	
Factor	**TA169**[14]	**TA215**[13]	**TA512**[12]	**TA542**[11]	**TA581**[1]	**TA650**[42]	**TA645**[15]	**Chosen values**	**Justification**
Appraisal	Sunitinib for the first-line treatment of advanced and/or metastatic RCC	Pazopanib for the first-line treatment of aRCC	Tivozanib for treating aRCC	Cabozantinib for untreated aRCC	Nivolumab with ipilimumab for untreated aRCC	Pembrolizumab with axitinib for untreated aRCC	Avelumab with axitinib for untreated aRCC	Pembrolizumab in combination with lenvatinib for untreated aRCC	
Time horizon	10 years	10 years	10 years	20 years	40 years	40 years	40 years	40 years	Lifetime time horizon required to capture long-term outcomes of treatment
Half-cycle correction	Yes	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Not applied due to short cycle length. It is implicitly assumed that all patient transitions, health outcomes and costs occur at the beginning of each cycle
Health effects measure	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs	Consistent with NICE reference case
Discount rate	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	Consistent with NICE reference case
Perspective (NHS/PSS?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Consistent with NICE reference case

Source of utilities	Derived from trial data- 1st line Motzer et al 2007[43] and 2nd line Motzer et al 2006[44] ; and UK EQ-5D tariffs.	Pre-progression values were based on the mean EQ-5D utility value from patients without AEs in the VEG105192 [45] . In the post-progression state a decrement in utility of 15% was assumed.	Utility values derived from EQ-5D-3L questionnaires from the TIVO-1 study[46] were used for pre and post progression.	The CABOSUN trial[20] did not collect EQ-5D. Hence the utility values derived from the TIVO-1 study as reported in TA512 were used.	A regression model from Checkmate 214[47] EQ-5D utilities were used.	Utility values collected in KEYNOTE-426 trial [48]	Utility values derived from EQ-5D-5L questionnaire from the JAVELIN Renal 101 study[49] and mapped to EQ-5D-3L.	Utility values collected in KEYNOTE-581 trial; EQ—5D data[25]	Consistent with NICE reference case
Source of costs	British National Formulary, NHS reference costs, Unit Costs of Health and Social Care 2007[50]	NHS reference costs, Colosia 2008, British National Formulary, PSSRU	NHS reference costs, PSSRU, British National Formulary, TA169[14] and TA215[13]	British National Formulary, TA215[13] , TA512[12] , NHS reference costs, PSSRU and published literature	TA417[40] , Monthly Index of Medical Specialities, TA215[13] , TA169[14] , NHS reference costs, PSSRU, TA333[51], ID1029 and published literature	TA650[42] , TA169[14] , TA215[13] , TA512[12] , NICE TA542[11] , NHS reference costs, PSSRU, and published literature	NHS reference costs, PSSRU, Unit Costs of Health and Social Care[52]	TA215[13], TA333[51], TA645[15], TA542[11], TA650[42] , BNF, NHS reference costs, PSSRU, UK published literature	Consistent with NICE reference case

Treatment waning effect?	No	No	No	No	Yes- only for patients who are not cured	Explored within scenario analyses	Yes – treatment waning from two years	Explored within scenario analysis	Due to the fixed treatment duration of pembrolizumab, the treatment benefit duration is explored through a waning scenario.
Abbreviations: aRCC, Advanced renal cell carcinoma; BNF, British National Formulary; LY, life year; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, Progression-free survival; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life year; RCC, Renal cell carcinoma									

Intervention technology and comparators

The intervention (pembrolizumab in combination with lenvatinib) was included in the model as per the proposed licensed dosing regimen (i.e., pembrolizumab administered intravenously at a fixed dose of 200 mg over 30 minutes Q3W combined with lenvatinib 20 mg QD taken orally). However, it should be noted that a recent label update also permits the administration of pembrolizumab 400mg Q6W[53].

The forthcoming licence states that pembrolizumab should be administered until PD or unacceptable toxicities or for a maximum of 35 doses (approximately two years). If the patient remains progression free after 35 doses of pembrolizumab, treatment with lenvatinib will be continued as monotherapy until PD or unacceptable toxicity. The impact of a lenvatinib stopping rule (plausible for certain patient types) is explored in scenario analysis.

In line with the comparator assessed in KEYNOTE-581[25] , sunitinib (the trial control arm) was the primary comparator in the cost-effectiveness model. A summary of comparators used is presented in Table 29.

The following comparators were also assessed as per the appraisal final scope[39]:

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

In TA215[13] , TA512[12], TA542[11] and TA581[1] for pazopanib, tivozanib, cabozantinib and nivolumab with ipilimumab respectively in untreated aRCC, each appraisal concluded that pazopanib should be considered clinically equivalent to sunitinib, based on the input of clinical experts. In TA512[12] the committee concluded that tivozanib should be considered, at best, clinically equivalent to sunitinib and pazopanib. Furthermore, in TA542[11], the committee adopted the assumption of equal clinical efficacy between pazopanib and sunitinib in their decision making. This assumption of clinical equivalence was also supported by a consensus amongst six UK clinicians consulted by MSD in the preparation of this dossier[54] , during an advisory board held on October 08 2021 . Therefore, for the base case analysis of pembrolizumab in combination with lenvatinib versus tivozanib or pazopanib, the efficacy of tivozanib and pazopanib is assumed to be equal to that of sunitinib, as reported in the KEYNOTE-581 study, for the efficacy outcomes of OS, PFS, time on treatment (ToT), (i.e., a hazard ratio of 1 will be applied) and in terms of safety profile.

Table 29. Intervention and comparators according to the different types of analyses assessed in cost-effectiveness model

Population	Intervention and comparators	Clinical evidence derived from:
	Pembrolizumab plus lenvatinib vs.	
Base Case		
ITT population	▪ Sunitinib ▪ Pazopanib ▪ Tivozanib	KEYNOTE-581[25] (equal efficacy to sunitinib assumed)
Subgroups		
Intermediate/poor risk group	▪ Cabozantinib	NMA (section B.2.9)
	▪ Sunitinib ▪ Pazopanib ▪ Tivozanib	KEYNOTE-581[25] (equal efficacy to sunitinib assumed)
Abbreviations: ITT, intention to treat; NMA, network meta-analysis		

Please note that nivolumab in combination with ipilimumab (available through the CDF in the intermediate/poor risk group population only) and avelumab in combination with axitinib (available through the CDF in the ITT population, i.e., untreated aRCC) are not relevant comparators within this appraisal. Neither treatment is available through baseline funding and as such cannot be considered established standard of care, nor is the continuing availability of these treatments following the CDF data collection period predictable at the initiation of this appraisal. This is supported by a statement made in January 2019 by NICE[55] whereby products recommended for use in the CDF after 1st April 2016 should not be considered as comparators in subsequent relevant appraisals.

B.3.3 Clinical parameters and variables

Summary of key points:

- Fully parametric extrapolation approaches were followed for both OS and PFS.
- The model predicted overly optimistic long-term OS rates for sunitinib so the most conservative distribution (gamma) was selected. Exponential was selected for pembrolizumab plus lenvatinib.
- The exponential distribution was selected to extrapolate the PFS for both treatment arms, on the basis of clinical plausibility between the model and trial.
- Generalized gamma was selected to extrapolate TTD for lenvatinib and log-logistic was selected for sunitinib. Pembrolizumab KM data was used as it was sufficiently mature due to the two-year stopping rule.

The data used to inform the clinical parameters within the economic analysis are primarily informed by the results for the total ITT population from the KEYNOTE-581 study. Progression free survival was the primary endpoint in KEYNOTE-581 and is used to model PFS for patients receiving pembrolizumab plus lenvatinib vs. sunitinib. Death from any cause was recorded as a secondary outcome for both treatment groups and has been used to model OS within the economic analysis.

The PFS and OS Kaplan Meier data from KEYNOTE-581 was used to estimate survival curves for the ITT population for pembrolizumab plus lenvatinib and sunitinib. The most recent pre-specified interim analysis was IA3 (data cut-off 28th August 2020). An additional analysis was undertaken for the OS endpoint alone, with a more recent data cut-off date of 31st March 2021 (updated OS analysis). PFS data was not re-evaluated as data maturity was achieved in the IA3 data cut.

The base case analysis uses the updated OS analysis for the OS data and IA3 for PFS data.

Estimated survival data is applied in the model using parametric survival curves fitted to the Kaplan Meier data. The standard survival distributions (Exponential, Gamma, Generalised Gamma, Gompertz, Log-logistic, Log-normal, Weibull) were all assessed for goodness-of-fit and the most representative survival distributions were selected based on clinical plausibility of the results. The survival curves are used to extrapolate the survival estimates beyond the follow-up period of observed data.

This section (B.3.3) focuses on the time-to-event data for the ITT population from the KEYNOTE-581 study. Details on the time-to-event data for the intermediate/poor IMDC subgroup is presented in Section B.3.9.

Details of the modeling methods used for PFS and OS are presented in the following sections. For all time-to-event data recorded in the KEYNOTE-581 trial (PFS, OS and TTD), survival analysis was conducted in line with the guidelines presented in the NICE Decision Support Unit (DSU) Technical support document (TSD) 14[56].

Survival analysis considerations

Consideration was given to the log-cumulative hazard plots to assess the nature of the hazard functions. The nature of the log-cumulative hazard plots dictate which parametric

functions will most accurately represent the data, with non-parallel plots between the treatment arms indicating that independent functions are needed for each treatment arm, i.e., violation of the proportional hazards assumption.

Standard parametric models, including the exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma distributions were fitted to KEYNOTE-581 data for OS, PFS and TTD for pembrolizumab plus lenvatinib and sunitinib independently. Due to the randomised controlled design of the KEYNOTE-581 study, no covariates for patient characteristics were included in the parametric analyses, under the assumption that the cohorts receiving each treatment are balanced in terms of important baseline characteristics.

The final parametric curves chosen for the base case analysis were selected based on; goodness-of-fit criteria such as Akaike information criterion (AIC) and Bayesian information criterion (BIC), visual goodness-of-fit evaluations, UK clinical expert input and clinical plausibility.

Overall survival

The base case analysis considers the OS data using the updated OS analysis data cut-off from the KEYNOTE-581 study. The OS KM data for patients receiving both pembrolizumab plus lenvatinib, and sunitinib have been previously presented in Figure 6. The statistically significant OS HR of 0.72 represents a 28% reduction in the risk of death with the combination. The KM plots show that the two lines intersect at two locations, once at the beginning of the follow-up period (commonly observed with immunotherapies due to the biological mechanism of action i.e., a lag in treatment effect relative to TKI monotherapy) and then again in the later section of the curve, at approximately 43 months follow-up (see section B.2.6).

Due to a high degree of censoring prior to this time point (over 70% in the pembrolizumab plus lenvatinib arm and over 65% in the sunitinib arm[25]), precise knowledge of the date of death for the majority patients is unknown, leading to very low numbers at risk (i.e., the numbers of patients confirmed to be alive at this time point are low in both arms, due to their last date of follow-up preceding this time point). At the point of the curve intersection, there are only 15 out of 355 patients at risk within the pembrolizumab plus lenvatinib arm, and 14 out of 357 patients within the sunitinib arm. With low patient numbers at risk, individual patient death events assume a greater impact on the survival estimates and the data are

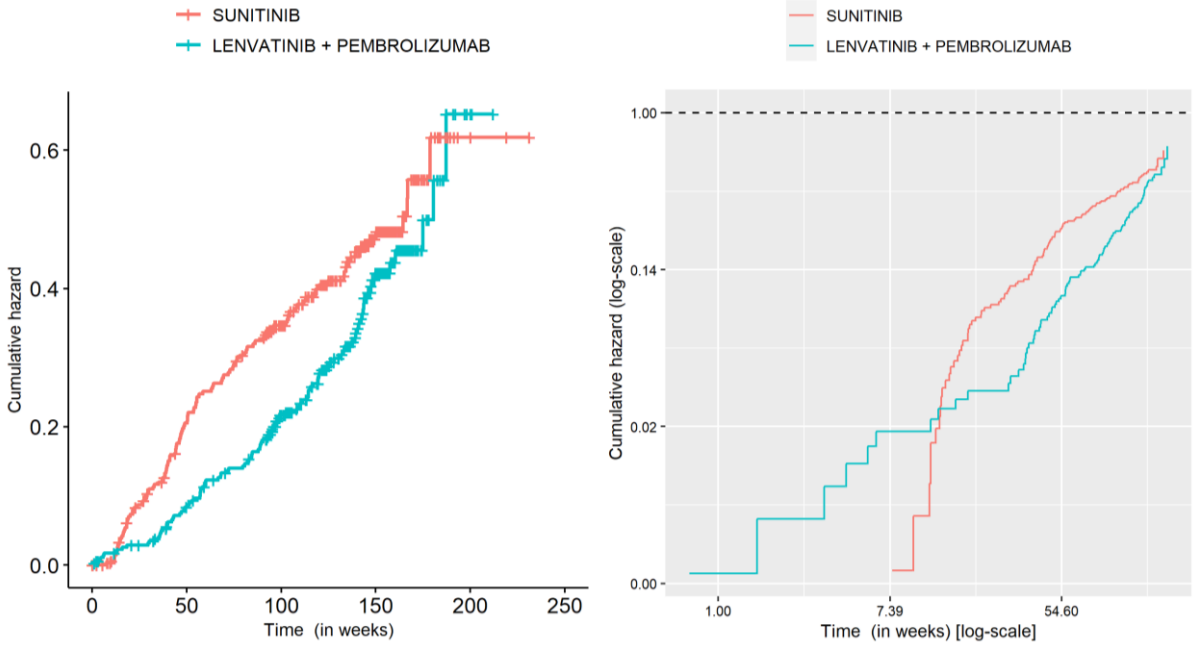
highly uncertain in this section of the curves. For example, the sharp drop of approximately 7% in pembrolizumab plus lenvatinib OS that causes the curves to intersect is the result of a single event. No further events are observed in either treatment arm for the remainder of the follow-up period. For this reason, it is assumed that the crossing of the survival curves is a consequence of the combination of infrequent events and heavy censoring, leading to low numbers of patients at risk, and is subject to significant uncertainty, which is expected to resolve with additional follow-up. This resolution is expected to occur because the censoring in the tail of the curve reflects the last time patients were followed up rather than them being "lost to follow up". This uncertainty means that the tails of the curves should be interpreted with a high level of caution and efforts are made in the analysis to control for, and minimize, the impact of this uncertain part of the KM curve on long-term survival estimation.

The log-cumulative hazards plot suggests that the proportional hazards assumption (i.e., that the treatment effect is proportional for all time points between the treatment arms) does not hold for the ITT population over the full time period, as indicated by the non-parallel and intersecting lines over the total follow-up period. This suggests that the instantaneous mortality risk varies over time inconsistently between the treatment arms. The cumulative hazards and log-cumulative hazards plots are presented in Figure 15.

The Schoenfeld residual plot (Figure 16) suggests that the relative hazards are likely to vary over time and therefore the proportional hazards assumption is unlikely to hold. The Schoenfeld residual test had a P-value of 1.00, which would suggest that the proportional hazards assumption should not be rejected. However, the test is not flexible enough to consider a decrease and then increase in the log hazard ratios.

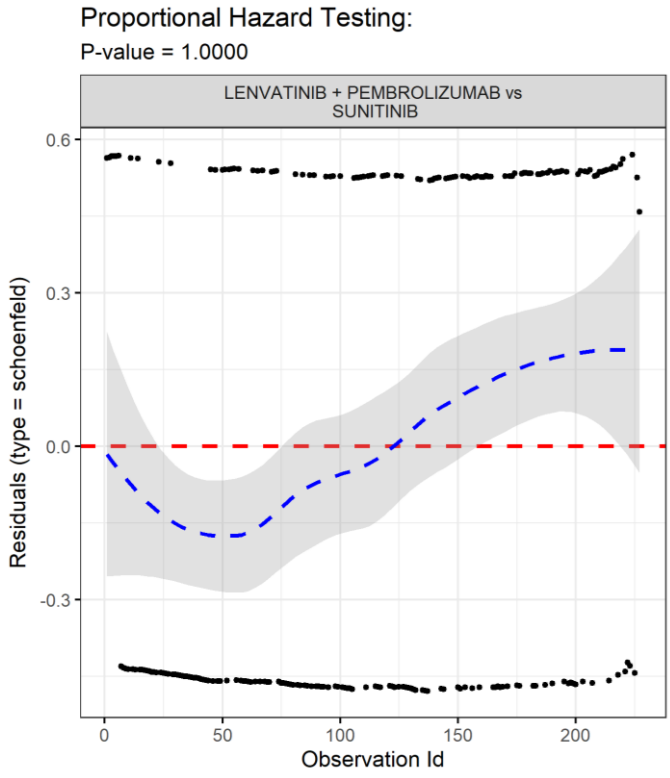
For these reasons, parametric curves have been fitted independently for each treatment arm.

Figure 15. Cumulative hazards and log-cumulative hazards plots (Overall survival, Updated OS Analysis)



Abbreviations: OS, overall survival
Key: Cumulative hazards (left) and log-cumulative hazards (right) of overall survival over time between pembrolizumab plus lenvatinib versus sunitinib.

Figure 16. Schoenfeld residual plot (Overall survival, Updated OS Analysis)



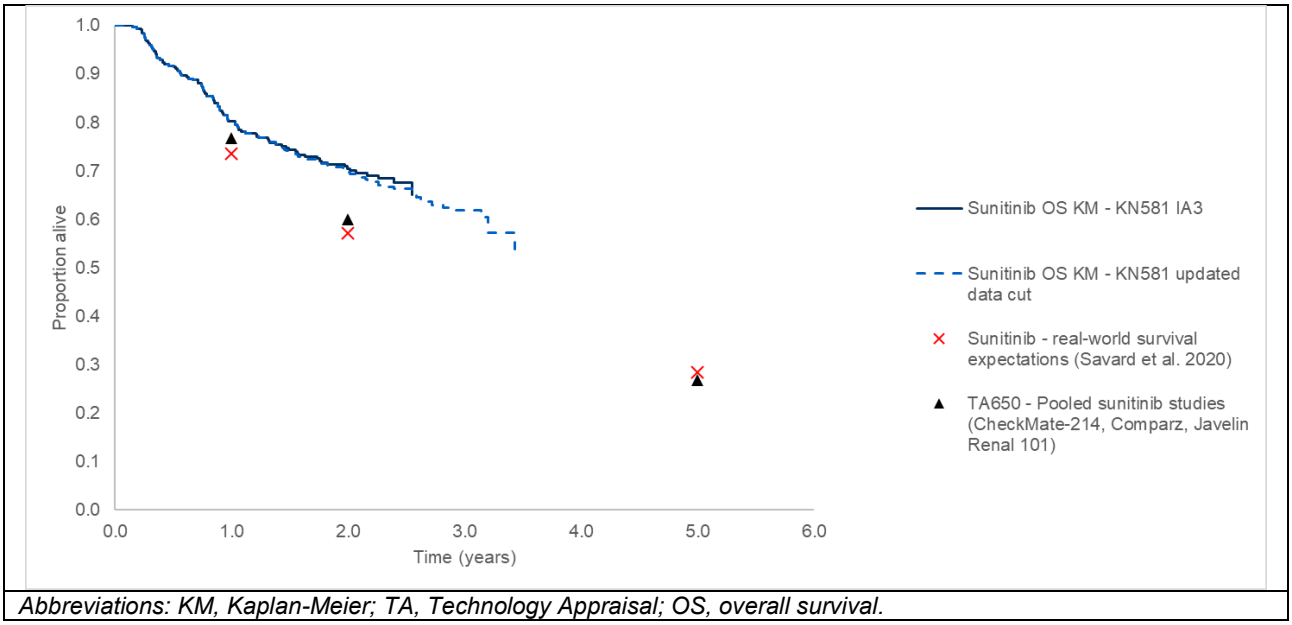
Abbreviations: OS, overall survival
Key: Schoenfeld residual for graphical diagnosis of proportional hazards in overall survival between pembrolizumab plus lenvatinib versus sunitinib

Sunitinib OS

OS for patients receiving sunitinib in the economic analysis is estimated using the Kaplan Meier data from KEYNOTE-581, presented in section B.2.6. OS data for sunitinib patients has previously been investigated in patients with clear cell aRCC by Savard et al. (2020)[57], and in the CheckMate 214, COMPARZ, and JAVELIN Renal 101 study[21,49,58]. The Savard et al. (2020) study reported the proportion of first line sunitinib patients alive at one, two and five years to be 73.54%, 57.14% and 28.35%, respectively[57]. The pooled data from the CheckMate 214, COMPARZ, and JAVELIN Renal 101 studies suggest that the proportion of patients alive at one, two and five years having received first-line sunitinib is 76.80%, 60.00% and 26.73%, respectively[21,49,58].

Initial estimates suggest that the OS for sunitinib observed in KEYNOTE-581 is superior than has been observed in previous investigations, with an observed two-year survival rate of 70.4%. This is notably superior to the most optimistic survival estimates from the historical sunitinib data i.e., 60%[21,49,58]. A graphical representation of the sunitinib OS data from KEYNOTE-581 and the historical trial data is presented in Figure 17.

Figure 17. Sunitinib OS Kaplan-Meier data (KEYNOTE-581 versus historical data)



Abbreviations: KM, Kaplan-Meier; TA, Technology Appraisal; OS, overall survival.

The comparisons of KM data between the sunitinib patients in KEYNOTE-581 and historical data are naïve and do not adjust for differences in population characteristics. The longer tail for sunitinib OS in KEYNOTE-581 may be due to the distribution of prognostic factors producing more favourable outcomes for patients than reported in previous studies (such as

the higher proportion of favourable IMDC risk patients). In addition to this, a high proportion of patients received subsequent immunotherapy in the sunitinib arm (32.1%), the clinical profile of which is expected to contribute to longer OS[25].

Key patient characteristics and prognostic factors from KEYNOTE-581 and a selection of prior studies where sunitinib survival has been reported is presented in Table 30 below. Notable differences in baseline patient prognostic factors and the extent of subsequent treatment have been observed, which helps explain the improved performance of the sunitinib arm in KEYNOTE-581, as indicated by the survival rates presented in Table 31.

Table 30: Prognostic factors for sunitinib patients from both historical trials and KEYNOTE-581

Prognostic factor	Savard et al. (2020)[57]	CheckMate 214[47]	COMPARZ[21]	JAVELIN Renal 101[49]	KN426[48]	KEYNOTE-581[25]
N	1,796	422	553	444	429	357
Median age (range) - years	63.7 (NR)	61.0 (21-85)	62.0 (23-86)	61.0 (27-88)	61 (26-90)	61 (29–82)
IMDC risk group						
Favourable, n (%)	318 (18.0%)	0 (0.0%)	NR	96 (21.6%)	131 (30.5%)	124 (34.7%)
Intermediate, n (%)	1,031 (58.3%)	333 (79.0%)	NR	276 (62.2%)	246 (57.3%)	192 (53.8%)
Poor, n (%)	420 (23.7%)	89 (21.0%)	NR	71 (16.0%)	52 (12.1%)	37 (10.4%)
Not reported (%)	0 (0.0%)	0 (0.0%)	NR	1 (0.2%)	0 (0.0%)	4 (1.1%)
MSKCC risk group						
Favourable, n (%)	NR	NR	152 (27.0%)	100 (22.5%)	NR	97 (27.2%)
Intermediate, n (%)	NR	NR	328 (59.0%)	293 (66.0%)	NR	228 (63.9%)
Poor, n (%)	NR	NR	52 (9.0%)	45 (10.1%)	NR	32 (9.0%)
Not reported, n (%)	NR	NR	21 (4.0%)	6 (1.4%)	NR	0 (0.0%)
Number of metastatic organs, n (%)						
1	1,303 (79.6%)	84 (20.0%)	108 (20.0%)	174 (39.2%)	96 (22.4%)	108 (30.3%)
>1	333 (20.4%)	337 (80.0%)	445 (80.0%)	254 (57.2%)	331 (77.2%)	246 (68.9%)
Patients who received subsequent lines of therapy, n (%)	915 (50.9%)	296 (54.0%)	NR	174 (39.2%)	147 (34.3%)	206 (57.7%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; NR, not reported

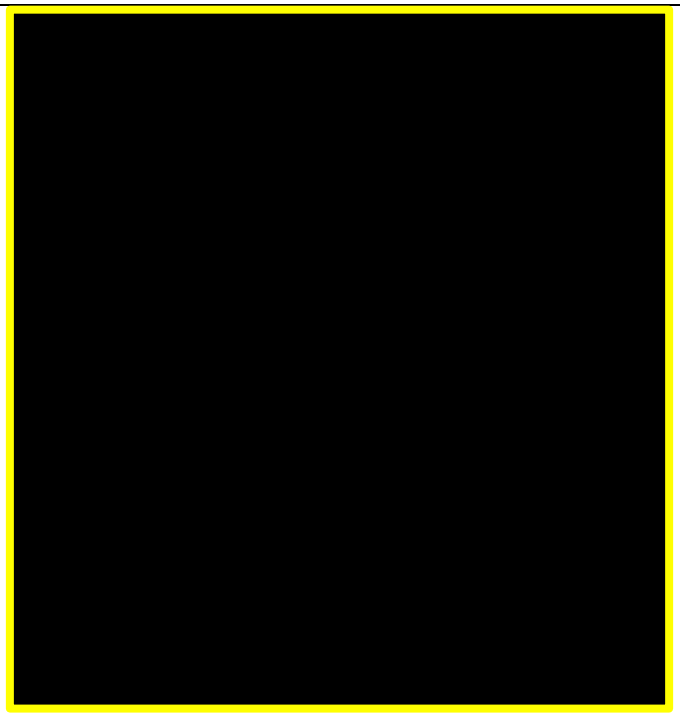
Table 31: Survival rates at years 1, 2, and 5 for sunitinib patients from historical trials, and KEYNOTE-581

	1-year survival rate	2-year survival rate	5-year survival rate
Savard et al. (2020)	73.54%	57.14%	28.35%
Pooled – CheckMate 214, COMPARZ, and JAVELIN Renal 101 studies	76.80%	60.00%	26.73%
KEYNOTE-581 – Sunitinib patients	80.20%	69.7%	NR

Abbreviations: N/A, not applicable

Standard independent parametric models - exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull models - have been fitted to the observed survival data for each treatment arm of the KEYNOTE-581 trial. A graph containing plots of the fitted survival curves for sunitinib patients is presented in Figure 18 and longer-term survival estimates with all distributions is presented in Figure 19. The associated statistical goodness-of-fit measures are presented in Table 32 and the predicted 5-, 10-, and 20-year survival probabilities for each distribution are presented in Table 33.

Figure 18. Sunitinib OS parametric survival curves



Abbreviations: OS, overall survival
Key: Overall survival parametric curves plotted to the sunitinib Kaplan-Meier data, KEYNOTE-581

Figure 19. Long-term sunitinib survival estimates

Abbreviations: OS, overall survival

Table 32: Statistical goodness-of-fit measures for sunitinib OS curves

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table 33: Predicted 5-, 10- and 20-year survival for sunitinib fitted OS curves

Distribution	5-year OS	10-year OS	20-year OS
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Abbreviations: OS, overall survival			

All of the fitted distributions show an estimated 5-year survival probability that is considerably higher than has been observed in historical trials (28.35%). Furthermore, with a mean age of 62 years for patients entering the trial, it is assumed that no aRCC patients will survive for the full model time horizon i.e., 40 years.

The generalized gamma model provides the best statistical fit to the observed data with the lowest AIC (1621.39) and BIC (1633.02); however this model was excluded from the curve selection process, along with the log-normal, log-logistic, and Gompertz models, based on the plausibility of the long-term extrapolations. The distributions predict a 5-year survival probability considerably higher than what has been observed historically. Furthermore, the long-term survival estimates produced were not in line with clinical expectation (i.e., long-term survival estimates predict between [redacted] and [redacted] of patients to be alive at 40 years, rather than the 0% expected); see Figure 19.

Of the remaining curves (Exponential, Weibull, and gamma), all appeared to have a similar fit to the observed Kaplan-Meier data based on visual inspection. The AIC and BIC for the three remaining models were also within an approximate range, implying comparable goodness-of-fit.

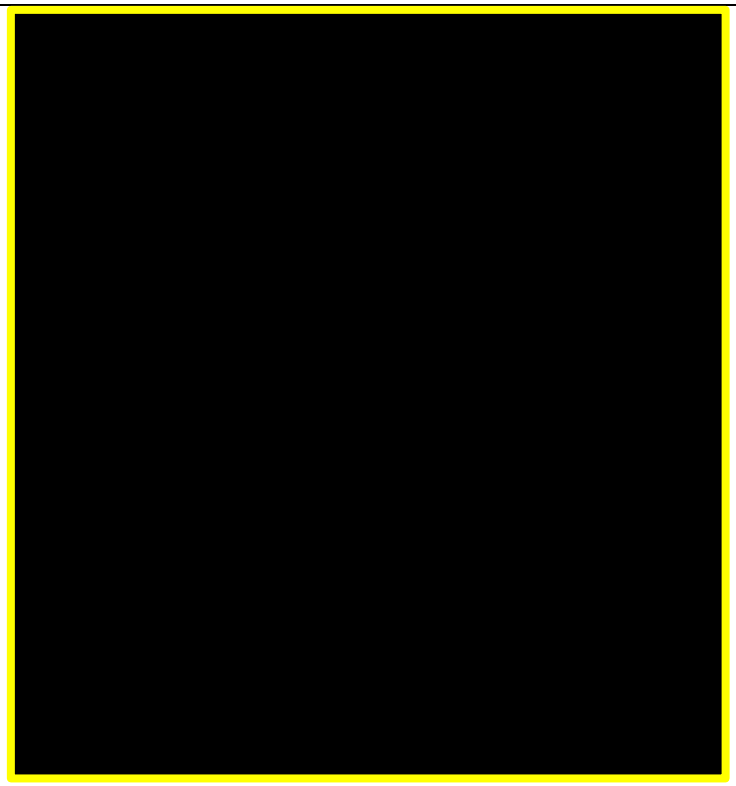
Given that the survival estimates generated by the analysis of this data are generally more optimistic than historical estimates, the most conservative survival distribution was selected in order to increase clinical plausibility of the sunitinib survival projections. Hence the gamma distribution was selected, which predicts that [redacted] of patients remain alive at five years, and [redacted] of patients remain alive at ten years. The estimated 5-year survival probability remains substantially higher than observed in Savard et al. 2020 (difference of [redacted])[57], supporting the need for a conservative approach to sunitinib survival estimates.

The gamma curve is selected as the base case model for sunitinib OS based on the clinical plausibility of the long-term extrapolation.

Pembrolizumab plus lenvatinib OS

The same standard survival distributions have been fitted to the survival data for the patients who received pembrolizumab plus lenvatinib within the KEYNOTE-581 trial. A graph showing all the fitted survival curves for patients receiving pembrolizumab plus lenvatinib is presented in Figure 20, and longer-term survival estimates with all distributions is presented in Figure 21. Statistical goodness-of-fit measures, AIC and BIC are presented in Table 34. The predicted 5-, 10-, and 20-year survival probabilities for each distribution are presented in Table 35.

Figure 20: Fitted parametric curves for Pembrolizumab plus lenvatinib OS



Abbreviations: OS, overall survival
Key: Overall survival parametric curves plotted to the Pembrolizumab plus Lenvatinib Kaplan-Meier data, KEYNOTE-581.

Figure 21. Long-term pembrolizumab plus lenvatinib survival estimates

Table 34: Statistical goodness-of-fit measures for the Pembrolizumab plus Lenvatinib OS curves

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table 35: Predicted 5-, 10-, and 20-year pembrolizumab plus lenvatinib fitted OS curves

Distribution	5-year OS	10-year OS	20-year OS
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]

Distribution	5-year OS	10-year OS	20-year OS
Gompertz	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Abbreviations: OS, overall survival			

When considering the most suitable survival curve to represent the long-term extrapolation of the survival data, consideration was given to goodness-of-fit criteria, as well as clinical plausibility. AIC and BIC only apply to the observed period, and the divergence of the curves beyond the trial period plays an important role in assessing the representativeness of each distribution.

Comparisons versus longer-term external survival data for clear cell aRCC patients were made to assess the longer-term plausibility of the survival curves.

The log-logistic and log-normal curves were excluded due to the implausible heaviness of the tails, which produce survival estimates that were considered to be overly optimistic (i.e., predicting approximately [redacted] and [redacted] of patients alive at 40 years, respectively), see Figure 21.

Of the remaining parametric models, all curves appeared to have a relatively good fit to the observed data up to approximately three years, based on a visual inspection of the curves.

The Gompertz model provides the best statistical fit to the observed data in the pembrolizumab plus lenvatinib arm, with the lowest AIC and BIC. However, due to the immaturity of the OS data, clinical plausibility of the long-term extrapolations was considered more meaningful than statistical goodness-of-fit to the observed portion of the data in the curve selection process. The Gompertz and generalized gamma models both assume a 10-year survival probability of [redacted] which lacks clinical validity, as clinical opinion sought confirmed that survival to 10 years has been observed in aRCC patients.

The gamma and Weibull distributions estimate similar or inferior 10- and 20-year OS probabilities than the most conservative estimate for the sunitinib OS (Table 33). On face validity, this appears contrary to clinical expectation. When investigating the KM data for OS between the two treatment arms, pembrolizumab plus lenvatinib demonstrates consistently stronger OS estimates than sunitinib (apart from at the very end of the follow-up period in which there are very few patients at risk). From a clinical perspective, it is expected that the

addition of an immunotherapy to a TKI (i.e., pembrolizumab plus lenvatinib) would provide superior OS estimates than patients receiving sunitinib alone. Furthermore, the PFS curves show that patients receiving pembrolizumab plus lenvatinib consistently have a reduced risk of disease progression, compared with patients receiving sunitinib, at all time points. It is counter-intuitive to assume that patients who progress later, will die earlier. For these reasons, the gamma and Weibull distributions are considered inappropriate to extrapolate the long-term OS estimates for pembrolizumab plus lenvatinib.

These considerations indicate the exponential model to be a plausible predictor of the pembrolizumab plus lenvatinib long-term OS. The exponential model predicts [redacted] of patients to be alive at 10 years and [redacted] of patients to be alive at 20 years. This aligns more closely with clinical survival expectations for aRCC patients than the other distributions that have been explored (it is the only distribution that is neither implausibly low based on a comparison with sunitinib or implausibly high given the age and disease burden of the aRCC population). The exponential model follows the assumption that the hazard function is constant for the entire time horizon, i.e., the instantaneous probability of dying does not vary over time. The cumulative hazard function for pembrolizumab plus lenvatinib presented in Figure 15 shows a reasonably constant gradient for the majority of the follow-up period (prior to when the numbers at risk diminish, at about 170 weeks). This supports the assumption that a constant hazard applies to patients within the pembrolizumab plus lenvatinib arm, and therefore an exponential model is appropriate to estimate the OS for these patients.

The exponential model was therefore selected as the preferred survival curve for pembrolizumab plus lenvatinib based on the plausibility of the long-term extrapolations and the cumulative hazard plot.

Treatment waning

Based on the independent estimation of survival curves for pembrolizumab plus lenvatinib and sunitinib, the length of the follow-up period and the immunotherapy precedent, there is no clear evidence to indicate a treatment waning. In the base case analysis, no treatment waning effect is assumed.

The OS curves were fitted independently for both treatment arms and the long-term extrapolations estimated independently using the fitted curves. The results of the long-term survival estimates demonstrate that the long-term treatment effect will differ for both treatment arms based on the observed data (i.e., extrapolations based on full KM data

indicate no convergence of survival over time). The total follow-up period is approximately four years, which includes substantial follow-up after patients discontinued pembrolizumab (two years), and no clear evidence of a treatment waning effect has been observed in the pembrolizumab plus lenvatinib arm (see Figure 15). As discussed previously, the observed curve intersection should be viewed as an artefact of low patient numbers and uncertainty over death dates for the majority of both treatment arm cohorts. Furthermore, longer-term follow-up of patients receiving IO in advanced RCC has indicated a maintenance of survival benefit beyond treatment discontinuation (i.e., treatment waning has not been detected)[59].

A scenario analysis is presented which explores the impact of a gradual treatment waning effect five years following discontinuation of pembrolizumab for all patients, where the cycle-specific hazard for the pembrolizumab plus lenvatinib arm gradually becomes equal to that in the comparator arm over the subsequent two years.

Summary of OS curves for pembrolizumab plus lenvatinib and sunitinib

A summary of the KEYNOTE-581 OS Kaplan-Meier curves and the base case survival extrapolations for pembrolizumab plus lenvatinib (exponential) and sunitinib (gamma) is presented in Figure 22.

Figure 22: Summary of OS models

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Pazopanib and tivozanib OS

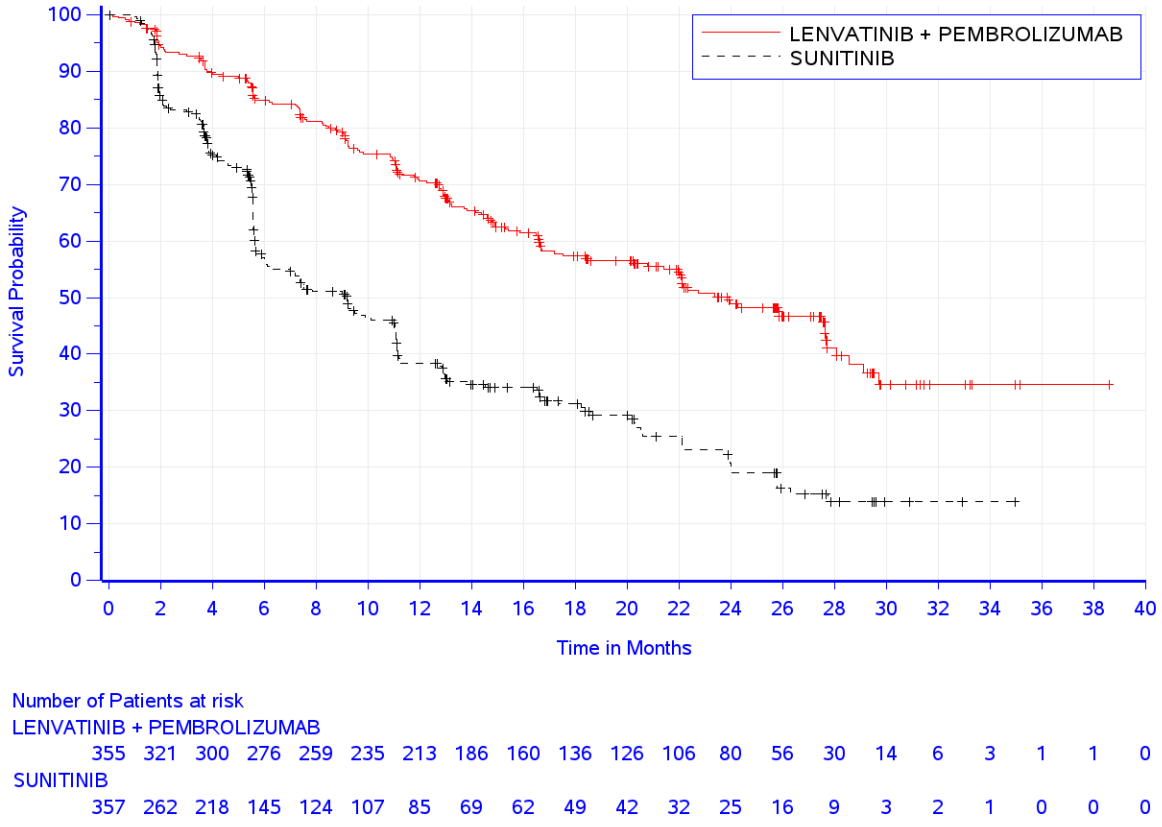
OS for pazopanib and tivozanib was assumed equal to sunitinib, therefore a hazard ratio of 1 was applied for all time points, with sunitinib acting as the reference arm.

Progression-free survival

The PFS for pembrolizumab plus lenvatinib and sunitinib within the economic analysis is estimated using the KM data from the KEYNOTE-581 study. The PFS KM data for both treatment arms from the KEYNOTE-581 study is presented in Figure 23.

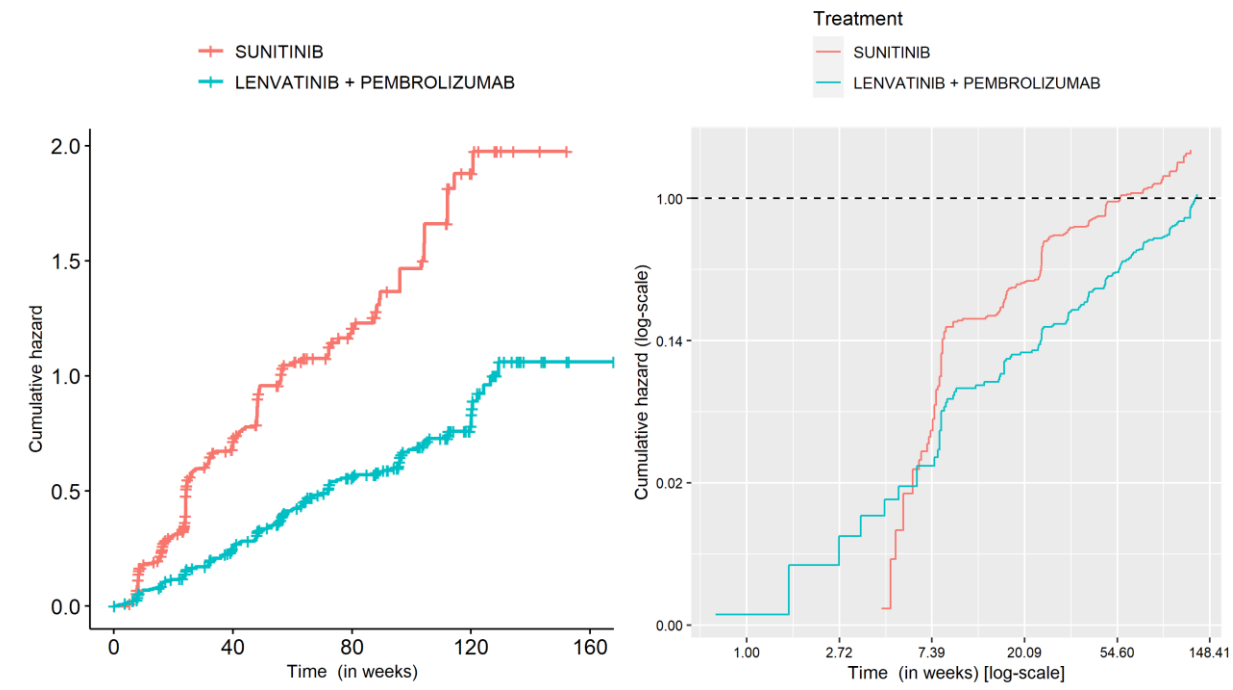
Evaluation of the proportional hazards assumption was performed using the log-cumulative hazards plot and the Schoenfeld residual plot, presented in Figure 24 and Figure 25 respectively. The Schoenfeld residual test had a P-value of 1.00, suggesting that the proportional hazards assumption should not be rejected. However, as discussed, the test is not flexible enough to consider a decrease and then increase in the log hazard ratios. The log-cumulative hazards plot suggests that the proportional hazards assumption does not hold for the full period of observed data. As reported in NICE DSU TSD 14[56] , it is generally considered unnecessary to rely on the proportional hazards assumption when patient-level data is available. Therefore, parametric models without treatment effect parameters were explored independently for the pembrolizumab plus lenvatinib, and sunitinib treatment arms.

Figure 23. PFS Kaplan-Meier data



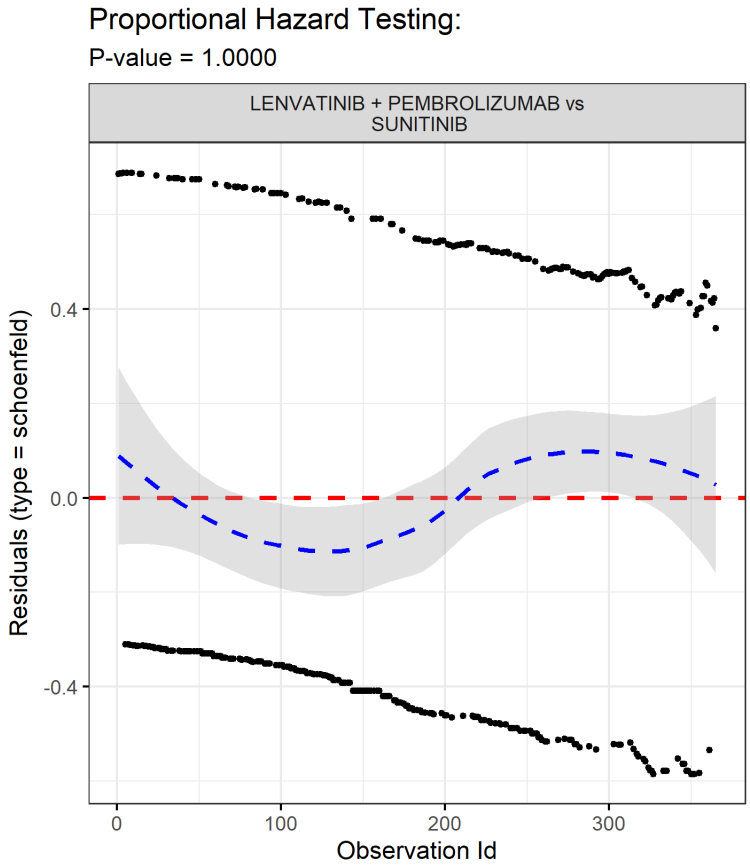
Abbreviations: PFS, progression-free survival

Figure 24. PFS cumulative hazards and log-cumulative hazards plots



Abbreviations: PFS, progression-free survival
Key: Cumulative hazards (left) and log-cumulative hazards (right) of progression-free survival over time between Pembrolizumab plus Lenvatinib versus Sunitinib

Figure 25. Schoenfeld residual plot PFS



Abbreviations: PFS, progression-free survival
Key: Schoenfeld residual for graphical diagnosis of proportional hazards in progression-free survival between Pembrolizumab plus Lenvatinib versus Sunitinib

Sunitinib PFS

The standard survival functions were fitted to the PFS data for patients receiving sunitinib from the KEYNOTE-581 trial. Plots of the fitted survival curves are presented in Figure 26. The associated statistical goodness-of-fit criteria are presented in Table 36.

For sunitinib, the generalized gamma (which has the best statistical goodness-of-fit to the observed data) was excluded based on an overly optimistic long-term extrapolation (with [redacted] of patients estimated to be alive and progression-free at 40 years).

All the other distributions appear to fit the data well, based on visual inspection, and generate similar estimates of the longer-term PFS probabilities. The maturity of the trial PFS dataset permits a comparison between the trial and model median PFS; an important tool in determining the clinical plausibility of the modelled projections. The gamma curve was selected based on the clinical plausibility of the long-term extrapolation: median modelled

PFS for sunitinib when using the gamma curve ([redacted] years) was marginally longer than that observed in KEYNOTE-581 (0.77 years; difference of [redacted]). This choice is also consistent with the model selection for the sunitinib OS curve, which presents face validity, given the correlation between these outcome measures.

Figure 26: Sunitinib PFS fitted survival curves

Abbreviations: PFS, progression-free survival
Key: One-piece progression-free survival parametric curves plotted to the sunitinib Kaplan-Meier data, KEYNOTE-581

Table 36: Statistical goodness-of-fit criteria for Sunitinib PFS data

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma†	[redacted]	[redacted]

Abbreviations: †, preferred distribution; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Pembrolizumab plus lenvatinib PFS

The standard survival functions were fitted to the PFS data for pembrolizumab plus lenvatinib patients in the KEYNOTE-581 study. Plots of the fitted survival curves are presented in Figure 27. The associated statistical goodness-of-fit criteria are presented in Table 37.

For the pembrolizumab plus lenvatinib curves, the AIC results lie within a range of five points, which implies that there is no model with a significantly better statistical fit to the data (according to AIC). Median PFS when using the exponential curve (the model with the [redacted] BIC) is [redacted] years, which is consistent with that observed in KEYNOTE-581 (1.99 years; difference of [redacted] years). The log-logistic and log-normal curves were excluded from consideration on the basis of overly optimistic projections, predicting approximately [redacted] of patients to be alive and progression-free at 40 years.

As with the OS curve selection process, the principle of a constant hazard function supports the appropriateness of using the exponential distribution to model PFS in pembrolizumab plus lenvatinib patients i.e., the gradient of the cumulative hazard function was broadly constant. This curve selection is consistent with the OS selection, a logical consistency given that PFS and OS are correlated endpoints.

Figure 27: Pembrolizumab plus lenvatinib PFS fitted survival curves

Abbreviations: PFS, progression-free survival
Key: One-piece progression-free survival parametric curves plotted to the pembrolizumab plus lenvatinib Kaplan-Meier data, KEYNOTE-581

Table 37. Statistical goodness-of-fit criteria for pembrolizumab plus lenvatinib PFS data

Distribution	AIC	BIC
Exponential†	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: †, preferred distribution; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Summary of PFS curves for pembrolizumab plus lenvatinib and sunitinib

A summary of the KEYNOTE-581 PFS Kaplan-Meier curves and the base case survival extrapolations for pembrolizumab plus lenvatinib (exponential) and sunitinib (gamma) is presented in Figure 28. A scenario analysis exploring the impact of using two-piece survival models for both treatment arms is presented in Section B.3.9.

Figure 28. PFS survival curves for Pembrolizumab plus Lenvatinib and Sunitinib

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival
Key: One-piece progression-free survival parametric curves plotted to the pembrolizumab plus lenvatinib Kaplan-Meier data, KEYNOTE-581

Pazopanib and tivozanib PFS

PFS for pazopanib and tivozanib was assumed equal to sunitinib, therefore a hazard ratio of 1.0 was applied to the sunitinib arm for all time points.

Treatment waning:

Treatment waning is not considered for the PFS estimates due to the maturity of the trial data and because most patients will have progressed in the pembrolizumab plus lenvatinib

arm before any treatment waning effect might begin, hence any potential waning effect is reflected in the extrapolated curves.

Time to treatment discontinuation

Time-on-treatment (TOT) (or time to discontinuation (TTD)) data was recorded as part of the KEYNOTE-581 study for pembrolizumab and lenvatinib separately. TTD KM data for pembrolizumab, lenvatinib and sunitinib is presented in Figure 29.

Parametric models were explored for the individual components of each treatment regimen.

For pembrolizumab, KM data is used directly to model TTD without the need for parametric extrapolation. This is due to the maturity of the pembrolizumab TTD data and a stopping rule (discussed below), which survival models struggle to appropriately account for due to the sudden change in the shape of the curve at the point of the stopping rule.

The model applies a two-year stopping rule for pembrolizumab as part of the pembrolizumab plus lenvatinib regimen. This assumes that all remaining patients stop treatment with pembrolizumab after two years. Kaplan Meier data is used to inform the rate of discontinuation for pembrolizumab up to two years.

Plots of the parametric survival curves for lenvatinib and sunitinib are presented in Figure 30 and Figure 31 respectively. The associated AIC and BIC values are presented in Table 38 and Table 39.

For lenvatinib, the generalized gamma curve is used in the base case analysis. Given the maturity of the TTD data, the curve selection is based on visual inspection and statistical goodness-of-fit to the data (AIC).

For sunitinib, extrapolation is performed using the log-logistic distribution. The log-logistic curve is selected based on visual inspection of the curve and statistical goodness-of-fit to the observed data (AIC/BIC), given the maturity of the data.

Figure 29: TOT Kaplan-Meier data (KEYNOTE-581, full population)

Abbreviations: KM, Kaplan-Meier; TOT, time on treatment
Key: Plot of Kaplan-Meier curve in time on treatment

Figure 30: Lenvatinib TTD fitted survival curves

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation
Key: One-piece time to treatment discontinuation parametric curves plotted to the pembrolizumab plus lenvatinib Kaplan-Meier data, KEYNOTE-581

Table 38: Lenvatinib TTD AIC/BIC

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma†	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: †, preferred distribution; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; TTD, time to treatment discontinuation

Figure 31: Sunitinib TTD fitted survival curves

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation
Key: One-piece time to treatment discontinuation parametric curves plotted to the pembrolizumab plus lenvatinib Kaplan-Meier data, KEYNOTE-581

Table 39: Sunitinib TTD AIC/BIC

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic†	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: †, preferred distribution; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; TTD, time to treatment discontinuation

A summary of the selected TTD data for each treatment arm is presented in Figure 32. The selected curve for pembrolizumab is the KM combined with the two-year stopping rule. For the lenvatinib treatment arm, the generalized gamma curve is selected. For sunitinib, the log-logistic parametric curve is applied. Time-on-treatment equivalence between sunitinib and pazopanib/tivozanib is assumed in line with the ERG preference in TA581[1] .

Figure 32: TTD extrapolations for Pembrolizumab, Lenvatinib and Sunitinib independently

[redacted]

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation
Key: Selected time to treatment discontinuation extrapolation for each treatment arm, compared to general population.

B.3.4 Measurement and valuation of health effects

Summary of key points:

- EQ-5D-3L responses were collected directly in the trial, so mapping was not required.
- The time-to-death approach to HRQoL was followed in the base case, as it reflects the atrial patient experience more accurately than the health state-based approach.
- AE disutility was assumed to be accounted for in the state value in base case.

Health-related quality-of-life data from KEYNOTE-581

HRQoL was evaluated in the KEYNOTE-581 study[25] using the EuroQoL EQ-5D-3L. The EQ-5D-3L descriptive system of health states comprises five dimensions ('5D'): (1) mobility; (2) self-care; (3) usual activities; (4) pain/discomfort and (5) anxiety/depression. Those are rated by a verbal 3-point rating scale allowing for distinction of three levels ('3L') of severity: Level 1: no problems; Level 2: some problems; Level 3: extreme problems per dimension and providing a 1-digit number for each dimension. The digits for the 5 dimensions can be combined in a 5-digit code describing the patient's health state. A total of 243 combinations and hence different health states are possible. The utility value for each state is assigned using a set of preference weights (tariffs) elicited from the general population. As these responses were elicited directly from patients, the estimated utilities that they informed were used directly in the cost-effectiveness model, in accordance with the NICE reference case[38].

As discussed in section B.1.3, aRCC is associated with a significant patient burden. Common signs and symptoms of advanced RCC (aRCC) include anorexia, fatigue, pain, anaemia, hypercalcaemia and venous thromboembolism[60].

In KEYNOTE-581[25] , for both treatments, the EQ-5D questionnaire was administered at baseline (prior to first dose), on day 1 of each subsequent cycle until treatment discontinuation, as well as 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). Therefore, post-progression utility data from the trial patients was limited. For pembrolizumab in combination with lenvatinib, each cycle length had a 21-day duration[25] . For sunitinib, each cycle length was equal to 42 days[25] . This is described in more detail in Section B.2.6.

The analysis of the EQ-5D-3L utilities below is based on the Full Analysis Set (FAS) population (a total of 1,042 subjects). UK preference-based scores were used for all patients analysed from the KEYNOTE-581 clinical trial[25]. The data cut-off date from IA3 of KEYNOTE-581[25] used for this analysis is 28 August 2020. The UK scoring functions were developed based on the time trade-off (TTO) technique[61].

When estimating utilities, two approaches were considered, with the time-to-death method selected in the base case. Cost-effectiveness was estimated using the health state-based approach in a scenario analysis (see section B.3.8).

<u>Time-to-death utility approach</u>

In the time-to-death utility approach, utility values are specified for the following intervals of time-to-death based on KEYNOTE-581 EQ-5D data:

- 360 or more days to death
- 270 to 369 days to death
- 180 to 269 days to death
- 90 to 179 days to death
- 30 to 89 days to death
- Less than 30 days to death

This approach reflects the accepted decline in cancer patients' quality of life during the terminal phase of the disease, defining health state utilities based on time to death.

The approach was developed by Batty et al. (2011)[62] and Hatswell et al. (2014)[63] . Hatswell et al noted that disease progression may not fully capture all predictive factors of patient utility and that time-to-death provides a good fit to patient data. Furthermore, due to the post-progression data collection schedule in this trial, data were collected for newly progressed patients but not for those whose condition had deteriorated further (see schedule above). The time-to-death approach mitigates against this bias, by categorising utility valuations according to time-to-death (regardless of whether death arises from a progression-free or progressive disease state) rather than by progression status.

The approach has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum-based chemotherapy or palliative radiotherapy[64–67] , untreated metastatic squamous NSCLC[68] , untreated PD-L1 positive metastatic NSCLC[69] , untreated metastatic colorectal cancer with MSI-H or MMRd[70] , advanced melanoma patients[62,63], untreated advanced oesophageal cancer[71] , and recurrent or metastatic squamous cell head and neck cancer[72] . Furthermore, the applicability of this deterioration to this cancer was validated with a panel of UK RCC clinicians.

EQ-5D scores collected from patients within each time interval were used to estimate mean utility for that category. The analyses of the intervals related to time-to-death lower than 360 days focused on patients with observed death dates. Patients whose death dates were censored (i.e., death date unknown) were excluded because their EQ-5D values could not be linked to a known time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since

their EQ-5D data related to a survival of at least 360 days, independent of when the death date was censored.

In the model, utilities were applied based on the distribution of patients across different categorizations of time to death in each weekly cycle. In a given weekly cycle, the proportion of patients within each time to death category was estimated based on the modelled OS within each treatment arm.

- Health-state utility approach

This approach, commonly employed in previous oncology economic modelling literature, defines health states based on time relative to disease progression, and hence generates results to be used in a partition survival model by health state. For this analysis, values were estimated separately for the on- and off-treatment patients, both pre- and post-progression. As previously mentioned, the paucity of post-progression data collection in KEYNOTE-581 makes it difficult for this approach to robustly reflect the patient experience; responses were collected at the point of treatment discontinuation and at the 30-day post-treatment discontinuation follow-up visit. This means that the post-progression utility values are unlikely to accurately reflect the rapid deterioration of patients' quality of life in this cancer as they approach death. The reference case asserts a preference for using utility data ascertained from the relevant clinical trial, hence using utility values sourced from the literature, as a substitute, would require substantial justification as utility data from KEYNOTE-581 is available. Furthermore, reliable substitute utility values from the literature to alleviate this issue were not identified (see Appendix H). Due to this limitation, the post-progression utility is not considered to be representative of the lived experience of patients in their terminal phase.

EQ-5D data analysis

For each of the utility approaches, mean EQ-5D utility scores were estimated for the patient category through linear mixed effect regressions and were pooled across arms. In addition, 95% CIs were estimated for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was investigated.

The FAS population comprised of subjects who were randomized, received a study treatment, and completed at least one EQ-5D-3L questionnaire. Descriptive analyses and conventional linear regressions are therefore limited in that the assumption of independence

between observations is not held – observations may be more correlated if they are from the same patient than if they are from different patients. Linear mixed effects regressions account appropriately for this potential within-patient correlation. Since one patient could have multiple utility measures within the same health state or time-to-death category, mixed linear effects models with random intercept were used for this analysis to account for within-subject correlation. Experiencing an AE is included as a covariate in the mixed-effects models, providing an estimation of AE disutility. In the base case, AE disutility is considered to be accounted for by the health state value. A scenario analysis where AE disutility is considered as an independent decrement in presented in section B.3.8.

Under the time-to-death approach, the final linear mixed effects model includes parameters corresponding to Grade ≥3 AEs, time-to-death boundary, IMDC score, baseline age and baseline sex. Other variables that were considered but ultimately excluded by a process of backwards selection were interaction terms for the treatment received/time to death categories. The general formulation (with a treatment main effect) is as follows, where i denotes individual, j denotes observation time when the EQ-5D-3L measures was taken, and there are k other covariates:

$$Utility_{ij} = \beta_0 + \beta_1 Time\ to\ death_{ij} + \sum_k \beta_k x_{ijk} + e_i$$

Under the health state approach, the final linear mixed effects model includes parameters corresponding to Grade ≥3 AEs, health state, treatment status, IMDC score, baseline age, baseline sex, and interaction terms for Grade ≥3 AEs/treatment status, and health state/treatment status. Other variables that were considered but ultimately excluded by a process of backwards selection were interaction terms for Grade ≥3 AEs/progression-status and Grade ≥3 AEs/progression-status/treatment status. The general formulation (with a treatment main effect) is as follows, where i denotes individual, j denotes observation time when the EQ-5D-3L measures was taken, and there are k other covariates.

$$Utility_{ij} = \beta_0 + \beta_1 Progression\ Status_{ij} + \sum_k \beta_k x_{ijk} + e_i$$

The parameter estimates for both utility approaches are presented in Appendix O. Utilities used in the model were derived by applying the parameter estimates to the characteristics of the FAS and treatment-specific group for each model covariate (mean age, proportion male, proportions in each IMDC score grouping). The estimated utilities are presented in Table 40 (base case) and Table 41 (scenario analysis) below. Pooled utility (across arms)

reflects the statistically insignificant difference between utility scores between the treatment arms in KEYNOTE-581.

Table 40. EQ-5D health utility scores by time-to-death (pooled treatment arms)

Time-to-death category	Utility value	SE	95% CI
360plus Days	[redacted]	[redacted]	[redacted]
270 - 359 Days	[redacted]	[redacted]	[redacted]
180 - 269 Days	[redacted]	[redacted]	[redacted]
90 - 179 Days	[redacted]	[redacted]	[redacted]
30 - 89 Days	[redacted]	[redacted]	[redacted]
0 - 29 Days	[redacted]	[redacted]	[redacted]
Abbreviations: CI, confidence interval; SE, standard error			

Table 41. EQ-5D health utility scores by health-state (pooled treatment arms)

Health state	Utility value	SE	95% CI
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]
Progressed (on treatment)	[redacted]	[redacted]	[redacted]
Progressed (off treatment)	[redacted]	[redacted]	[redacted]
Abbreviations: CI, confidence interval; SE, standard error			

Mapping

HRQoL was derived from the KEYNOTE-581 EQ-5D data[25] . Utilities were evaluated using the EQ-5D 3L questionnaire directly from patients participating in the KEYNOTE-581 trial[25] , in accordance with the NICE reference case[38] . Utility mapping was therefore not required for this submission.

Health-related quality-of-life studies

Published HRQoL for patients with aRCC were identified through a SLR. This review sought to identify the impact of first-line treatments approved, recommended, or under development on humanistic burden/patient-reported outcomes (PRO) in patients with aRCC. In the systematic literature review of utilities performed for this indication, 24 unique studies reported PRO data for patients with aRCC receiving first-line treatments. 17 studies were RCTs and the remaining seven were observational studies. The majority of participants were from Europe (12 studies), North America (nine studies), and Asia and Australia (four studies). South America and Africa were less common in the studies (three and two studies,

respectively). Study years spanned 2000 to 2018. No study reported utility values relevant to the UK population. Please refer to Appendix H for a list of the studies identified by the SLR.

Adverse reactions

To assess the potential disutility associated with Grade ≥3 AEs, the disutility associated with patients experiencing Grade ≥3 AEs were analysed as a fixed effect in both linear fixed effects models. For the health-state utility fixed effects model, this disutility was calculated as 0.101 (p-value = ≤0.001), for the time-to-death utility fixed effects model, this disutility was calculated as 0.044 (p-value = ≤0.001). This divergence between the value according to method speaks to a high level of uncertainty. In the base case, it is assumed that any disutility due to AEs is inherently captured by existing utility values, reflecting the approach taken in TA645. In a scenario analysis which investigates the impact of a separate AE disutility (see section B.3.8), total AE disutility values are calculated using the selected utility value for each AE multiplied by a weighted average of AE duration from KEYNOTE-581.

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

Table 42. Summary of utility values used in base case

State	Utility score	Reference in submission (section and page number)	Justification
≥360 days	[redacted]	Section B.3.4 Health-related quality-of-life data from clinical studies	Utility values from KEYNOTE-581 in line with NICE reference case[38]
270 to 359 days	[redacted]		
180 to 269 days	[redacted]		
90 to 179 days	[redacted]		
30 to 89 days	[redacted]		
0 to 29 days	[redacted]		
AE disutility†	[redacted]	Section B3.4 Adverse reactions	

†Not applied in base case, however impact is tested in a scenario analysis
Abbreviations: AE, adverse event

Severity Modifiers eligibility

NICE have published "NICE health technology evaluations: the draft manual" in August 2021[73] , outlining updated methods for technology appraisal in 2022 and beyond. Rather than the previous policy of affording a higher willingness-to-pay threshold to treatments which meet end-of-life criteria (see section B.2.13), multipliers should be applied to the

baseline threshold for diseases identified as severe, as determined by the Proportional QALY Shortfall or Absolute QALY Shortfall method. Given the age and morbidity profile of the advanced RCC population (see section B.1.3), the Proportional QALY Shortfall method is the relevant approach. In order to investigate whether advanced RCC meets these criteria to be classified as a severe disease, the lifetime QALY gain of patients receiving standard of care (as estimated by the cost-effectiveness model) is expressed as a proportion of the estimated lifetime QALY gain of healthy patients of the same age and gender distribution, to understand the extent to which the disease deprives the patient of their remaining QALYs. The weightings and thresholds in the table below have been proposed by the draft manual:

Table 43. Severity modifier categories and QALY weights

QALY weighting (Option 1)	QALY weighting (Option 2)	Proportional QALY shortfall	Absolute QALY shortfall
1	1	≤0.85	≤12
x1.2	1.25	0.85 to 0.95	12 to 18
x1.7	1.5	>0.95	>18

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

Summary of key points:
• List prices were employed in the analysis • No administration costs were assumed for oral treatments • Subsequent therapy costs were modelled according to a real-world distribution in the base case.

A SLR was conducted to identify relevant cost and health care resource use data associated with the first-line treatment and management of patients with aRCC, for the purpose of populating the economic model. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

The costs included in the model comprise:

1. Treatment-related costs (including subsequent treatment costs)
    a. Acquisition costs
    b. Administration costs
2. Disease management costs
3. Adverse-event costs
4. End-of-life care costs

Resource use and monitoring costs are applied to the progression-free and progressed health states.

Intervention and comparators' costs and resource use

Drug costs

Table 44 presents the list prices of drugs, sourced from the UK British National Formulary (BNF) online database (accessed 6 October 2021)[74].

Drug acquisition costs are applied in line with the dosing schedules for each treatment detailed in Table 45. A simple relative dose intensity (RDI) is applied to all treatments, with the exception of lenvatinib in the pembrolizumab plus lenvatinib treatment arm, due to the non-linear relationship between lenvatinib mg and price (see below) – RDI is expressed as a reduction (mg) of the dose a patient receives.

For the intravenously administered drugs dosed by patient weight (included as second-line treatments only), no wastage costs are assumed in the base case and hence these are excluded from the total cost calculations. This constitutes a conservative assumption, as it relies on NHS practice to ensure efficient administration of the treatments in all cases through vial sharing. In the base case, the cost per mg of a treatment is multiplied by the dose (mg) per cycle, to derive acquisition costs. The impact of vials not being shared is explored in a scenario analysis, where wastage costs are included. For weight-dosed treatments, method of moments is applied to calculate an average number of vials received.

It is assumed there are no wastage costs associated with treatments that are administered orally.

For treatments with multiple pack options, the pack with the lowest cost per mg was used (employing the assumption that the NHS has access to this “best value” as much as possible).

The estimated acquisition cost per dose is shown in Table 46. Costs are assumed to apply as they are incurred, therefore an average ‘cost per cycle’ was not calculated.

Pembrolizumab plus Lenvatinib

The dosing schedule for pembrolizumab and lenvatinib is modelled in line with KEYNOTE-581 as oral lenvatinib 20 mg/day plus intravenous pembrolizumab 200 mg every 3 weeks.

The list price of pembrolizumab 25 mg/ml concentrate solution is £2,630.00 per 4mL vial, leading to a cost per 200mg dose of £5,260.00. A commercial access agreement is currently in place, as discussed in section B.1.2. Lenvatinib is available as 30 x 4mg capsules or 30 x 10mg capsules. Both packs cost £1,437.00 in the UK and therefore the price per unit is the same, irrespective of strength. Assuming a strength of 10mg, the cost per 20mg dose of lenvatinib is £96.00. Since the relationship between the dose and price of lenvatinib is not linear, actual dosing data by week for lenvatinib was employed to ensure accurate costing.

Comparators

Drug acquisition costs for the comparator drugs were taken from the BNF online database. Dosing for the comparator drugs was based on the KEYNOTE-581 protocol[25] for sunitinib, and the relevant SmPC for pazopanib[75], tivozanib[76] and cabozantinib[77]. Given that all comparator drugs are administered orally, no wastage is assumed in the administration of first-line treatments.

Table 44. Treatment pack costs for intervention/comparators

Treatment	Pack size	Form	Units	Cost per pack
Pembrolizumab	1	25 mg/ml (vial)	4 mL	£2,630.00
Lenvatinib	30	capsule	4 mg	£1,437.00
	30	capsule	10 mg	£1,437.00
Sunitinib	28	capsule	12.5 mg	£784.70

Treatment	Pack size	Form	Units	Cost per pack
	28	capsule	25 mg	£1,569.40
	28	capsule	50 mg	£3,138.80
Pazopanib	30	tablet	200 mg	£560.50
	30	tablet	400 mg	£1,121.00
Tivozanib	21	capsule	1.34 mg	£2,052.00
Cabozantinib	30	tablet	20 mg	£5,143.00
	30	tablet	40 mg	£5,143.00
	30	tablet	60 mg	£5,143.00

Table 45. Dosing schedules

Regimen	Treatment	Prescribed dose	Dose per administration	Frequency	Administration method
Pembrolizumab plus lenvatinib	Pembrolizumab	200 mg	200 mg	Q3W	IV
	Lenvatinib	20 mg	20 mg	Once daily	Oral
Sunitinib	Sunitinib	50 mg	50 mg	Once daily (4 weeks on plus 2 weeks off)	Oral
Pazopanib	Pazopanib	800 mg	800 mg	Once daily	Oral
Tivozanib	Tivozanib	1.34 mg	1.34 mg	Once daily (21 days plus 7 days off)	Oral
Cabozantinib	Cabozantinib	60 mg	60 mg	Once daily	Oral

Abbreviations: IV, Intravenous; kg, kilogram; mg, milligram; Q1W, weekly; Q2W, every two weeks; Q3W, every three weeks

Table 46. Acquisition costs per dose, including and excluding wastage

Regimen	Treatment	Dose per administration	Cost per dose (including wastage)	Cost per dose (excluding wastage)
Pembrolizumab plus lenvatinib	Pembrolizumab	200 mg	£5,260	£5,260
	Lenvatinib	20 mg	N/A	£96
Sunitinib	Sunitinib	50 mg	N/A	£112
Pazopanib	Pazopanib	800 mg	N/A	£75
Tivozanib	Tivozanib	1.34 mg	N/A	£98
Cabozantinib	Cabozantinib	60 mg	N/A	£171
Abbreviations: kg, kilogram; mg, milligram; MoM, method of moments; N/A, not applicable.				

Time-on-treatment

As per the anticipated licence, patients treated with pembrolizumab are treated until disease progression or unacceptable toxicities or for a maximum of 35 doses (two years). As per KEYNOTE-581, a stopping rule has been implemented for the combination whereby patients do not receive pembrolizumab treatment beyond 24 months. If the patient remains progression-free after 35 doses of pembrolizumab, treatment with lenvatinib is continued as monotherapy until disease progression or unacceptable toxicity.

To estimate the duration of treatment of pembrolizumab time-on-treatment (ToT) data from KEYNOTE-581[25] was used to reflect both early discontinuation attributable to AEs, and other reasons for discontinuing before progression, as well as additional weeks of treatment that some patients may receive whilst awaiting confirmation of progression. The time on each treatment is initially defined by TTD (time to treatment discontinuation) data.

The approach to modelling time-on-treatment for the other treatments has been discussed in section B.3.3.

Administration costs

Administration costs per dose for pembrolizumab in combination with lenvatinib and the comparator therapies are presented in Table 47.

Pembrolizumab plus lenvatinib

The time required for the administration of pembrolizumab is 30 minutes, as per the SmPC[78] . The Health Resource Groups (HRG) code "SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance" based on the latest NHS reference costs 2019 - 2020 was used as the administration cost for pembrolizumab in combination with lenvatinib. Oral treatments were assumed to be taken by patients at home and hence incur no administration costs. Therefore, for patients continuing treatment of lenvatinib after two years (when pembrolizumab treatment has stopped), no administration cost was assumed.

Comparators

Oral treatments were assumed to incur no administration costs, and all baseline funded comparators in the appraisal scope are administered orally. It is assumed patients will self-administer the treatments at home, so no administration costs are applied.

Table 47: Drug administration costs

Regimen	Type of administration required	NHS reference cost code	Cost per dose (including wastage)
Pembrolizumab plus lenvatinib	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61
Lenvatinib monotherapy	Self-administration	Assumption	£0.00
Sunitinib	Self-administration	Assumption	£0.00
Pazopanib	Self-administration	Assumption	£0.00
Tivozanib	Self-administration	Assumption	£0.00
Cabozantinib	Self-administration	Assumption	£0.00
Abbreviations: NHS, National Health Service			

Health-state unit costs and resource use

A comprehensive literature search was conducted and then updated on 05 January 2021, to identify costs and resource use in the treatment of, and on-going management of, locally advanced or metastatic RCC. Please see Appendix I for details of the search strategy and literature identified.

Resource use is assumed to be linked to the health state rather than to the treatment arm. Patients incur disease management costs whilst in the progression-free and progressed disease health states. Table 48 presents the resource use and unit costs for monitoring and disease management in both states.

Resources include outpatient consultations (first attendance), outpatient consultations (subsequent attendance), CT scans, and blood tests. The previous Technology Appraisal for cabozantinib in untreated aRCC [11]. informed resource utilisation per health state. Unit costs were based on the latest NHS reference costs (2019/2020)[52]. As 21-day frequencies were reported in TA542, these were converted to 7-day frequencies to align with the cycle length in this analysis. The estimated monitoring and disease management costs per cycle were £16.90 for both the pre-progression and post-progression periods. A one-off cost of £222.69 was applied in the first cycle of the model for the first attendance outpatient consultation.

Table 48: Resource use costs

	Resource	Resource use (per cycle)	Reference	Unit cost	Reference
PFS	Outpatient consultation (first attendance)	1	TA542; converted 7-day cycle	£220.03	NHS reference costs (2019/2020). Consultant Lead, non-admitted face-to-face attendance, First. Nephrology (WF01B)[52]
	Outpatient consultation (follow-up attendance)	0.08		£170.93	NHS reference costs (2019/2020). Consultant Lead, non-admitted face-to-face attendance, Follow-up. Nephrology (WF01A)[52]
	CT Scan	0.03		£94.00	NHS reference costs (2019/2020). Imaging: Outpatient. Computerized tomography scan of three areas, without contrast (RD25Z)[52]
	Blood test	0.08		£1.81	NHS reference costs (2019/2020). Clinical biochemistry (DAPS04)[52]
	Total cost per week	**Cycle 1 - £222.69**		**Subsequent Cycles - £16.90**	
PPS	Outpatient consultation (follow-up attendance)	0.08	TA542; converted 7-day cycle	£170.93	NHS reference costs (2019/2020). Consultant Lead, non-admitted face-to-face attendance, Follow-up. Nephrology (WF01A)[52]
	CT Scan	0.03		£94.00	NHS reference costs (2019/2020). Imaging:

	Resource	Resource use (per cycle)	Reference	Unit cost	Reference
					Outpatient. Computerized tomography scan of three areas, without contrast (RD25Z)[52]
	Blood test	0.08		£1.81	NHS reference costs (2019/2020). Clinical biochemistry (DAPS04)[52]
	Total cost per week		**Every cycle – £16.90**		
Abbreviations: CT, computerised tomography; PFS, progression free survival; PPS, post progression survival					

End-of life-costs

A cost for end-of-life care is applied in the analysis upon death. End-of-life costs presented in the model are derived from a 2014 Nuffield Trust report[79] , with some additional items added in line with previous TA feedback. The report estimated the cost of hospital care in the last three months of life for patients within two years of a cancer diagnosis to be £5,890 (2013/14 prices). This value (after inflation) was submitted by the company in the cabozantinib NICE single technology appraisal (TA542)[11] , however the ERG believed that it was an underestimate due to the omission of costs for local authority funded social care, district nursing and GP visits. Based on the same report, and inflating to 2016/17 prices, the TA542 ERG estimated end-of-life care to cost £7,961. This estimate was inflated to 2019/20 values and used in the current submission.

Table 49: End of life costs

End of life (secondary source)	Costs
NICE TA650[42] (ERG): base case value	£8,442.02
Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence	

Adverse reaction unit costs and resource use

The safety results of the trial are presented in section B.2.10. The model includes the costs of managing Grade ≥3 AEs that occurred in >5% of patients in either treatment arm. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in B.3.4.

The costs of managing Grade ≥3 AEs with an incidence of >5% in either arm were primarily sourced from NHS reference costs 2019/2020 using the PSSRU guidance[52,80] . Annual patient AE costs were calculated using the frequency of AEs

reported in KEYNOTE-581, for pembrolizumab plus lenvatinib and sunitinib[25] . The frequency of AEs for treatment arms not included in KEYNOTE-581 were as reported in the relevant NICE technical appraisals.

The annual rate of AEs is calculated as the frequency of AEs multiplied by the number of patients within the clinical trial, and then divided by the total patient years (total number of patients in the clinical trial multiplied by the duration of the clinical trial).

The annual rate of an AE multiplied by the relevant NHS reference cost associated with its resolution gives the annual patient AE costs, per treatment, and is then applied to the life years per cycle.

Table 50: Adverse event costs

Adverse event	Unit costs*	Assumptions
Anaemia	£607.95	Weighted average for NES iron deficiency anaemia SA04G to SA04L
Neutropenia	£607.95	Assumed to incur same cost as anaemia (as per TA645)
Thrombocytopenia	£804.66	Weighted average for NES SA12G to SA12K
Diarrhoea	£3,130.35	Weighted average for NES FD10E to FD10H
Stomatitis	£3,130.35	Assumed to incur same cost as diarrhoea (as per TA645)
Asthenia	£840.95	Non-elective short stay unit cost plus Cost of F2F community nurse plus contact, Assumption from TA581. £801.95 plus community-based Band 5 nurse (1 hour) £39
Fatigue	£801.95	Assumed to incur a non-elective short stay cost (as per TA645)
Amylase increased	£607.95	Assumed to incur same cost as anaemia (as per TA645)
Lipase increased	£607.95	Assumed to incur same cost as anaemia (as per TA645)
Neutrophil count decreased	£607.95	Assumed to incur same cost as anaemia (as per TA645)
Platelet count decreased	£801.95	Assumed to incur a non-elective short stay cost (as per TA498)
Weight decreased	£801.95	Assumed to incur a non-elective short stay cost (as per TA645)
Decreased appetite	£0.00	Assumption
Hypertriglyceridaemia	£0.00	Based on the assumption: Regular blood tests (already considered under disease management costs; as per TA542 and TA650)
Hyponatraemia	£1,329.93	Weighted average for KC05G to KC05N
Proteinuria	£200.20	Consultant led follow-up visit - Medical oncology. Service code 370 (as per TA542)
Hypertension	£392.87	NES EB04Z
*Key: *NHS reference costs (2019/2020) [52]*		

Miscellaneous unit costs and resource use

Costs associated with subsequent therapies received by patients after treatment discontinuation

In the aRCC treatment pathway, first-line patients can progress to subsequent lines of treatment and subsequent cost of care is a relevant cost to include in an analysis of first-line treatments, given that divergent pathways are followed contingent on the first-line treatment received. The costs of subsequent treatments, following progression and cessation of initial treatment, are applied as a once-off cost in the cycle of progression as a simplifying assumption.

The proportion of patients receiving the cost of subsequent treatments in each model cycle is estimated as the proportion of patients who transition out of the pre-progression health state without dying. The distribution of subsequent treatments administered in the KEYNOTE-581 trial is not considered to be representative of UK clinical practice (e.g., first-line immunotherapy patients are typically not re-treated with a further course of this drug class, which did occur in a small proportion of patients in the trial [<5%]). To align with UK clinical practice, a real-world distribution of second-line therapies was used to cost the progression to a subsequent treatment. A limitation of the analysis is that further treatments beyond the second line were not included in the model, hence the results represent an under-estimate of the costs for patients who receive three or more lines of treatment in the advanced setting. The real-world distribution was informed by a statement on clinical practice by the NHS England Chemotherapy Lead and Clinical Lead for the CDF, submitted during the TA581 appraisal[1] – a point in the evolution of the advanced RCC treatment landscape which reflects the scope of the current appraisal and its baseline comparators (i.e., no immunotherapies funded in first line). This statement indicated 50% of patients progress to a subsequent treatment. The distribution of subsequent therapies observed in KEYNOTE-581, or in pivotal trials of comparator treatments (where appropriate), is explored in a scenario analysis. The details of both distributions are discussed below.

1. **Real world-based distribution of subsequent treatments in UK clinical practice**

Table 51 presents the distribution of subsequent therapies based on UK clinical practice, according to the aforementioned statement submitted as part of the TA581 appraisal (deemed to be representative of practice without immunotherapies funded in first line). No treatment is modelled for 50% of patients.

Table 51: Distribution of second-line therapies used in the base case (real-world based distribution)

First line treatment	Subsequent treatment, %								
	Sunitinib	**Pazopanib**	**Cabozantinib**	**Nivolumab**	**Everolimus**	**Axitinib**	**Lenvatinib**	**Total**	**Source***
Pembrolizumab plus lenvatinib	20.00%	30.00%	0.00%	0.00%	0.00%	0.00%	0.00%	50%	*Based on NHSE statement in TA581*
Sunitinib	0.00%	0.00%	12.50%	30.00%	0.00%	7.50%	0.00%	50%	*Based on NHSE statement in TA581*
Pazopanib	0.00%	0.00%	12.50%	30.00%	0.00%	7.50%	0.00%	50%	*Based on NHSE statement in TA581*
Tivozanib	0.00%	0.00%	12.50%	30.00%	0.00%	7.50%	0.00%	50%	*Based on NHSE statement in TA581*
Cabozantinib	0.00%	0.00%	0.00%	30.00%	12.50%	7.50%	12.50%	63%	*Based on NHSE statement in TA581*
*Key: *TA581 appraisal[1]*									

2. Trial based distributions of subsequent therapies

In a scenario analysis, upon disease progression, patients were assumed to incur the costs of subsequent therapies in line with the proportion of patients receiving subsequent therapy in KEYNOTE-581 or in pivotal trials of comparator interventions. Please see Table in Appendix N for the distribution of subsequent therapies.

Unit costs for each subsequent treatment, dosing schedule, and the cost per dose are shown in Table 52. Administration costs per dose are shown in Table 53. Subsequent treatment costs are calculated based on the assumed distribution of treatments (above), the mean time on treatment (Table 55), and the proportion of PFS events, excluding death events (Table 54). The full subsequent treatment cost is then applied in the cycle of progression to the proportion of patients that progress without dying. The total subsequent treatment drug costs and administration costs are shown in Table 55.

Table 52: Unit costs and dosing schedules

Subsequent treatment	Pack size/ form	Units	Cost per pack	Dosing schedule	Dose per administration	Cost per dose (including wastage)	Cost per dose (excluding wastage)
Pembrolizumab	1 25 mg/ml (vial)	4 ml	£2,630.00	200 mg IV Q3W	200 mg	£5,260	£5,260
Sunitinib	28 (capsule)	12.5 mg	£784.70	50 mg orally QD	50 mg	N/A	£112
	28 (capsule)	25 mg	£1,569.40				
	28 (capsule)	50 mg	£3,138.80				
Pazopanib	30 (tablet)	200 mg	£560.50	800 mg orally QD	800 mg	N/A	£75
	30 (tablet)	400 mg	£1,121.00				
Tivozanib	21 (capsule)	1.34 mg	£2,052.00	1.34 mg orally QD	1.34 mg	N/A	£98
Cabozantinib	30 (tablet)	20 mg	£5,143.00	60 mg orally QD	60 mg	N/A	£171
	30 (tablet)	40 mg	£5,143.00				
	30 (tablet)	60 mg	£5,143.00				
Nivolumab	1 (10 mg/ml (vial)	4 ml	£439.00	240 mg IV Q2W	50 mg	£2,775	£2,668
	1 (10 mg/ml (vial)	10 ml	£1,097.00				
	1 (10 mg/ml (vial)	24 ml	£2,633.00				
Avelumab	1 (20 mg/ml (vial)	10 ml	£768.00	800 mg IV Q2W	800 mg	£3,072	£3,072
Everolimus	30 (tablet)	2.5 mg	£1,200.00	10 mg orally QD	10 mg	N/A	£89

	30 (tablet)	5 mg	£2,250.00				
	30 (tablet)	10 mg	£2,673.00				
Axitinib	56 (tablet)	1 mg	£703.40	5 mg orally BID	5 mg	N/A	£63
	56 (tablet)	3 mg	£2,110.20				
	56 (tablet)	5 mg	£3,517.00				
	56 (tablet)	7 mg	£4,923.80				
Lenvatinib	30 (tablet)	4 mg	£1,437.00	18 mg QD orally	18 mg	N/A	£96
	30 (tablet)	10 mg	£1,437.00				
Temsirolimus	1 (25 mg/ml vial)	1.2 ml	£620.00	25 mg Q1W IV	25 mg	£620	£517
Atezolizumab	1 (60 mg/ml vial)	20 ml	£3,807.69	1,200 mg Q3W IV	1,200 mg	£3,808	£3,808
Ipilimumab	1 (5 mg/ml vial)	10 ml	£3,750.00	1 mg/kg Q3W IV	81 mg*	£7,987	£6,080
	1 (5 mg/ml vial)	40 ml	£15,000.00				
Bevacizumab	1 (25 mg/ml vial)	4 ml	£242.66	15 mg/kg Q3W IV	1,216 mg*	£2,940	£2,810
	1 (25 mg/ml vial)	16 ml	£924.40				
Abbreviations: BID, twice a day; kg, kilogram; mg, milligram; ml, millilitre; QD, daily; Q1W, weekly; Q2W, every two weeks; Q3W, every three weeks.							

Table 53: Subsequent therapy administration costs per dose

Regimen	Type of administration required	NHS reference cost code	Cost per dose (including wastage) *
Pembrolizumab	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61
Sunitinib	Self-administration	Assumption	£0.00
Pazopanib	Self-administration	Assumption	£0.00
Cabozantinib	Self-administration	Assumption	£0.00
Nivolumab	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61
Everolimus	Self-administration	Assumption	£0.00
Axitinib	Self-administration	Assumption	£0.00
Lenvatinib	Self-administration	Assumption	£0.00
Temsirolimus	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61
Atezolizumab	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61
Ipilimumab	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61
Bevacizumab	Deliver Simple Chemotherapy, at First Attendance	SB12Z	£299.61

*Key: *NHS reference costs[52]*
Abbreviations: NHS, National Health Service

Table 54: Proportion of PFS events that are progression

First line treatment	Proportion of PFS events that are progression	Source[25]
Pembrolizumab plus lenvatinib	91%	KEYNOTE-581 Table 14.2.1.1.1 (Pembrolizumab plus lenvatinib)
Sunitinib	96%	KEYNOTE-581 Table 14.2.1.1.1 (Sunitinib)
Pazopanib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Tivozanib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Cabozantinib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Nivolumab plus ipilimumab	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled

First line treatment	Proportion of PFS events that are progression	Source[25]
Pembrolizumab plus axitinib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Avelumab plus axitinib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Everolimus	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Axitinib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Lenvatinib plus everolimus	92%	KEYNOTE-581 Table 14.2.1.1.1 (Lenvatinib plus Everolimus)
Nivolumab	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Temsirolimus	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Atezolizumab plus bevacizumab	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Nivolumab plus cabozantinib	93%	KEYNOTE-581 Table 14.2.1.1.1 Pooled
Abbreviations: PFS, progression free survival.		

Table 55: Subsequent treatment costs

Subsequent treatment	Mean time on treatment (months) in KEYNOTE-581[25]	Total drug cost	Total admin cost
Pembrolizumab	[redacted]	£59,931	£2,960
Sunitinib	7.65	£17,407	£0
Pazopanib	6.79	£15,444	£0
Cabozantinib	7.76	£40,479	£0
Nivolumab	8.04	£32,355	£3,028
Everolimus	13.40	£36,335	£0
Axitinib	9.06	£34,644	£0
Lenvatinib	10.31	£27,053	£0
Temsirolimus	1.91	£5,137	£2,152
Atezolizumab	17.58	£97,005	£6,618
Ipilimumab	8.14	£32,416	£3,066
Bevacizumab	1.48	£6,300	£557

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

Summary of base-case analysis inputs

The full list of variables used in the cost-effectiveness analysis is presented in Table 56 below.

Table 56: Summary of variables applied in the economic model

Parameters	Mean / Deterministic value	Lower	Upper	Value in PSA	Section in the submission document
General Information					
Model cycle length (weeks)	1			Not varied in SA	See Section B.3.2
Model time horizon (years)	40				
Discount rate: Costs	3.5%				
Discount rate: Health outcomes	3.5%				
Patient Information					
Patient age (yrs)	61.67	55.5	67.83	Not varied in PSA	See Section B.3.2
Proportion male (%)	74.46	0.67	0.82		
Average patient weight (kg)	81.07	72.96	89.17		
Clinical inputs					
PFS – Pembrolizumab plus lenvatinib	Exponential				See Section B.3.3
PFS Sunitinib	Gamma				
OS – Pembrolizumab plus lenvatinib	Exponential				
OS Sunitinib	Gamma				
TTD – Pembrolizumab plus lenvatinib	Pembrolizumab TTD KM				
TTD Sunitinib	Parametric curve (gen gamma)				
Utility Inputs					
Utility by time-to-death					
Utility time to death >=360 days	[redacted]				See Section B.3.4
Utility time to death days [270,359)	[redacted]				
Utility time to death days [180,269)	[redacted]				
Utility time to death days [90,179)	[redacted]				
Utility time to death days [30,89)	[redacted]				
Utility time to death <30 days	[redacted]				
AE-related disutility	[redacted]				

Regimen Related Costs					
Drug costs (per administration)					
Pembrolizumab	£5,260			Not varied in SA	See Section B.3.5
Sunitinib	£112				
Pazopanib	£75				
Tivozanib	£98				
Cabozantinib 40mg	£114				
Cabozantinib 60mg	£171				
Nivolumab	£2,668				
Ipilimumab	£6,080				
Axitinib	£63				
Avelumab	£3,072				
Everolimus 5mg	£45				
Everolimus 10mg	£89				
Lenvatinib 18mg	£86				
Lenvatinib 20mg	£96				
Temsirolimus	£517				
Atezolizumab	£3,808				
Bevacizumab	£2,810				
Administration cost for IV					
Deliver Simple Chemotherapy at First Attendance	£299.61				See Section B.3.5
Disease Management Costs					
Weekly cost in progression-free state (cycle 1)	£222.69				See Section B.3.5
Weekly cost in progression-free state (subsequent cycles)	£16.90				
Weekly cost in progressive disease state	£16.90				
Subsequent drug cost (following pembrolizumab plus lenvatinib)	£7,354				
Subsequent treatment cost (following comparator)	£16,602				
Subsequent treatment administration cost (following intervention)	£0				
Subsequent treatment administration cost (following comparator)	£1,002				
Cost of terminal care (one-off cost)	£8,442				
% AE Pembrolizumab plus levatinib					
Anaemia	1%			Not varied in SA	See Section B.3.3
Neutropenia	0%				
Thrombocytopenia	0%				
Diarrhoea	7%				
Stomatitis	1%				

Asthenia	4%				
Fatigue	3%				
Amylase increased	7%				
Lipase increased	9%				
Neutrophil count decreased	1%				
Platelet count decreased	1%				
Weight decreased	6%				
Decreased appetite	3%				
Hypertriglyceridaemia	3%				
Hyponatraemia	3%				
Proteinuria	6%				
Hypertension	20%				
% AE Sunitinib					
Anaemia	6%			Not varied in SA	See Section B.3.3
Neutropenia	6%				
Thrombocytopenia	6%				
Diarrhoea	6%				
Stomatitis	2%				
Asthenia	5%				
Fatigue	5%				
Amylase increased	3%				
Lipase increased	9%				
Neutrophil count decreased	6%				
Platelet count decreased	7%				
Weight decreased	0%				
Decreased appetite	2%				
Hypertriglyceridaemia	7%				
Hyponatraemia	5%				
Proteinuria	3%				
Hypertension	20%				
AE Management costs					
Pembrolizumab plus lenvatinib	£617.25				See Section B.3.5
Sunitinib	£764.84				
Pazopanib	£180.11				
Tivozanib	£355.66				
Cabozantinib	£829.95				
Abbreviations: AE, adverse event; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; TTD, time to treatment discontinuation; IV, intravenous; SA, sensitivity analysis					

Assumptions

Table 57 summarizes the assumptions adopted in the economic model.

Table 57: List of assumptions used in the economic model

Model input and cross reference	Source/assumption	Justification

Time horizon	A time horizon of 40 years is sufficient to capture the relevant consequences of first line RCC treatment.	NICE reference case requests a lifetime horizon.
Discount rates	Costs and health effects should be discounted at 3.5% per annum.	NICE reference case requests a 3.5% discount rate.
Model structure	A partitioned survival analysis structure is appropriate to model the decision problem.	Established modelling precedent in the disease area.
Overall survival	The risk of death in any given cycle is at least equal to the risk of death observed in age- and sex-matched members of the general population.	Standard assumption to avoid survival estimates that are higher than patients without aRCC.
	For the base case, one-piece (separately fitted) parametric curves were chosen for pembrolizumab plus lenvatinib, and sunitinib. Other TKIs were assumed equal to sunitinib.	Curve selection was based on clinically plausible survival predictions compared with KN-581 and visual inspection.
	No treatment waning was applied.	Clear evidence of a wane in treatment effect was not identified in the trial data.
Progression-free survival	The risk of a PFS event in any given cycle is at least equal to the risk of death observed in age- and sex-matched members of the general population. PFS is also capped by OS in the model.	Standard assumption to avoid survival estimates that are higher than patients without aRCC. PFS is a subset of OS so logically cannot exceed it.
	For the base case, one-piece (KM plus parametric curve) were chosen for pembrolizumab plus lenvatinib, and sunitinib. Pazopanib was assumed equal to sunitinib	Curve selection was based on clinically plausible survival predictions compared with KN-581 and visual inspection
	No treatment waning was applied to any of the treatment arms.	PFS data were more mature and supportive of a durable treatment effect.
Time to treatment discontinuation	A TTD cap, capping to the OS curve, is applied to all treatment arms to ensure no logical inconsistencies.	Preventing any time-on-treatment longer than survival.
	The TTD KM and parametric curve was used for pembrolizumab and lenvatinib respectively in the	Parametric models could not appropriately account for the sudden change in shape of the

	pembrolizumab plus lenvatinib treatment arm. The parametric curve was used for sunitinib. Pazopanib and tivozanib were assumed to have TTD equal to that of sunitinib.	pembrolizumab TTD at the two-year stopping rule.
	A stopping rule was applied to pembrolizumab (24 months) in the pembrolizumab plus lenvatinib treatment arm.	Stopping rules applied in line with expectations for how pembrolizumab would be used in clinical practice (follows the trial).
Subsequent therapies	No adjustment to effectiveness data to account for the distribution of subsequent therapies is made.	Absence of data to support an alternative hypothesis.
	A one-off cost for subsequent therapies (drug costs plus administration costs) are applied upon disease progression.	Simplifying assumption.
	The base case uses the distribution of subsequent therapies observed in UK clinical practice.	A subsequent therapy distribution which reflects England and Wales practice was deemed appropriate for estimating costs to the NHS, given that KN-581 is an international study.
Utilities	The base case uses a time-to-death utility approach, applying an incremental utility value to each patient dependent upon the numbers of days until death, instead of a health state utility approach.	It is expected that health-related quality of life deteriorates as the patient nears death. UK clinical experts consulted support this approach. Also data collection in the trial provided more robust data for this approach.
	AE utility decrements that are specific to individual AEs are not included in the base case.	The impact of AEs is captured through the utility regression analysis. A separate disutility value is believed to represent double counting.
Costs	List prices for all treatments are assumed, rather than PAS prices.	Due to the nature of the MSD-Eisai collaboration for this combination, list prices are employed to protect the confidentiality of the PAS of both drugs.

	Drug wastage costs (aka no vial sharing) is applied in the base case.	Efficient administration of intravenous (IV) treatments is assumed, in line with NHS best practice.
	A relative dose intensity (RDI) per treatment, based on relevant literature, is applied in the model.	To capture the real cost to the NHS.
	A value of £0 is used for oral administration costs.	Patients assumed to administer these treatments at home, so no cost incurred from an NHS perspective.
Uncertainty	For uncertain parameters with an absence of distributional data, the standard error was assumed to be 10% of the base case mean.	Necessary assumption considering data availability.
	A willingness-to-pay threshold of £20,000 per QALY gained is used to calculate the INMB.	To conservatively meet the NICE thresholds of £20,000 to £30,000 per QALY gained.
Abbreviations: AE, adverse event; aRCC, Advanced renal cell carcinoma; INMB, Incremental net monetary benefit; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; TTD, time to treatment discontinuation; IV, intravenous; SA, sensitivity analysis; QALY, Quality-adjusted life year; RCC, Renal cell carcinoma; RDI, relative dose intensity		

B.3.7 Base-case results

Due to the nature of the multiple technology appraisal and the associated confidentiality agreements between both submitting companies, all results are provided as list price ICERs, ensuring PAS net prices for both pembrolizumab and lenvatinib are kept confidential.

Summary of key points:

- Pembrolizumab plus lenvatinib accrued more LYs and QALYs than all comparators, but also incurred higher costs.
- ICERs reported use the list prices for all comparators, but with the incorporation of confidential discounts, the combination is expected to be a cost-effective use of NHS resources.
- Plausible variation of the input parameters indicates the base case results to be robust.

Base-case incremental cost-effectiveness analysis results

The economic analysis was conducted using data from the most recent interim analyses i.e., IA3 for all endpoints except for OS where the updated OS analysis (as described in section B.2.6) was used.

The results of the economic model are presented in Table 58, Table 59 and Table 60. Table 58 presents the analysis versus the trial comparator (sunitinib). In the base case analysis, patients treated with pembrolizumab in combination with lenvatinib accrued 6.08 LYs and [redacted] QALYs, compared to 4.72 LYs and [redacted] QALYs for patients in the sunitinib cohort. Hence the model predicts an incremental life year gain of 1.36 years and an additional [redacted] QALYs for treatment with the combination. The ICER, when pembrolizumab plus lenvatinib is compared to sunitinib, is £114,492 with all therapies costed at list price.

Table 60 below presents the base case incremental cost-effectiveness results versus non-trial comparators. PAS net prices for certain therapies are known (e.g., sunitinib, pazopanib [ref TA169[14], TA215[13]]) but not for all. To facilitate consistent comparisons, each therapy is costed at its list price The ICERs range from £112,407 versus tivozanib to £115,822 versus pazopanib.

The QALY gain estimated by the model indicates that pembrolizumab in combination with lenvatinib has the potential to be cost-effective compared to sunitinib, when considering the relevant willingness-to-pay threshold and taking into account confidential discounts. As described in Section B3.4, the adoption of an adjusted ICER threshold by applying the severity modifier indicated by the Proportional Shortfall method[81], for which RCC patients in this trial qualify, reinforces this potential. The QALY gain estimated for the standard-of-care arm indicates a QALY shortfall of >85% compared to that of the age and gender-matched general population. The designation of aRCC as a severe condition is detailed in Section B.1.3.

Table 58. Base-case results versus trial comparator (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Sunitinib	[redacted]	4.72	[redacted]	-	-	-
Pembrolizumab plus lenvatinib	[redacted]	6.08	[redacted]	[redacted]	[redacted]	£114,492
Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years						

Table 59. Base-case fully incremental results (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pazopanib	[redacted]	4.72	[redacted]	[redacted]	[redacted]	-
Sunitinib	[redacted]	4.72	[redacted]	[redacted]	[redacted]	Strictly Dominated
Tivozanib	[redacted]	4.72	[redacted]			Strictly Dominated
Pembrolizumab plus lenvatinib	[redacted]	6.08	[redacted]	[redacted]	[redacted]	£115,822
Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years						

Table 60. Base case results versus external comparators (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pazopanib	[redacted]	4.72	[redacted]	-	-	-
Pembrolizumab plus lenvatinib	[redacted]	6.08	[redacted]	[redacted]	[redacted]	£115,822
Tivozanib	[redacted]	4.72	[redacted]	[redacted]	[redacted]	-
Pembrolizumab plus lenvatinib	[redacted]	6.08	[redacted]	[redacted]	[redacted]	£112,407
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

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

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitive analyses (PSA) were conducted to explore the impact of model parameter uncertainty on results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. A PSA was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters, are detailed in B.3.6.

The incremental cost-effectiveness results obtained from the PSA are presented in Table 61, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 33 and Figure 34 respectively.

Table 61. Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator (list price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Sunitinib	[redacted]	[redacted]	[redacted]		
Pembrolizumab plus Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	£106,375
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Figure 33: Scatterplot of PSA results (1,000 simulations) versus trial comparator (list price)

Abbreviations: QALYs, quality-adjusted life years, WTP, willingness to pay

Figure 34: Cost-effectiveness acceptability curve versus trial comparator (list price)

Abbreviations: QALYs, quality-adjusted life years

The cost-effectiveness acceptability curve shows that, with the application of list prices in the base case, there is a very low chance of pembrolizumab in combination with lenvatinib being cost-effective when compared to sunitinib at a threshold which takes into account the condition severity according to the Proportional Shortfall approach. As with the deterministic ICERs, the true assessment of the combination's cost-effectiveness should be made with the incorporation of confidential discounts, in order to understand the true cost of an additional QALY to the NHS in this population.

Deterministic sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results. The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

Deterministic sensitivity analyses were conducted for a number of key variables using the 5% and 95% confidence intervals for the variables where available (arbitrary variation such as +/-10% was employed where variance information was not available), including:

- Baseline characteristics (i.e., age, % male)
- Drug administration costs
- Resource utilisation
- Subsequent treatment duration
- Health state-based utility and time-to death-based utility
- AE costs and AE-related disutility
- Background mortality

The results of the deterministic sensitivity analysis for pairwise comparisons of pembrolizumab in combination with lenvatinib versus sunitinib are presented in Table 62 and Figure 35 below. By far the most impactful parameters were the RDI of pembrolizumab and sunitinib – which have direct implications for the drug costs of these treatments. The other ten most influential parameters include model cohort parameters such as mean starting age, proportion who are male and proportions categorised into IMDC risk profiles. Furthermore, the list includes mean durations of

certain treatments (nivolumab, cabozantinib and pazopanib) administered subsequently in the trial, indicating the significant influence of the patient pathway, and the implications that the introduction of pembrolizumab in combination with lenvatinib as a first-line therapy, may have for the pathway as a whole.

Table 62. Summary of the most influential parameters determined by OWSA

Parameter	Input value		ICER		
	Lower bound	Upper bound	Lower bound	Upper bound	Absolute Difference
RDI - Pembrolizumab in 'Pembrolizumab plus lenvatinib'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI - Sunitinib in 'Sunitinib'	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at model start	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment: Mean duration following Sunitinib - Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug Costs: Admin costs, IV - simple, first	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment: Mean duration following Pembrolizumab plus lenvatinib - Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment: Mean duration following Sunitinib - Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients poor IMDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of male patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment: Mean duration following Pembrolizumab plus lenvatinib - Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; OWSA, one-way sensitivity analysis; RDI, relative dose intensity

Figure 35. OWSA tornado diagram

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; IV, intravenous; OWSA, one-way sensitivity analysis

Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. The following scenarios were investigated and the results are presented in Table 63.

- Using undiscounted results (Scenario 1).
- Using 6% discounted rates for costs, LYs, and QALYs (Scenario 2).
- Using the fully fitted exponential parametric function to extrapolate OS for pembrolizumab in combination with lenvatinib at a constant hazard ratio versus sunitinib – 0.72 (Scenario 3)
- Using 1.5% discount rates for costs, LYs, and QALYs (Scenario 4)
- Using a 20-year time horizon (Scenario 5)
- Using a 30-year time horizon (Scenario 6)
- Using trial-based subsequent treatments (Scenario 7)
- Using health state-based utility values (Scenario 8)
- Excluding wastage costs (Scenario 9)
- Modelling AEs which require hospitalization only, which has an impact only for costs; see section B.3.5 (Scenario 10)
- Using the two-piece survival extrapolation to extrapolate PFS for both treatment arms. This scenario was investigated as this method produces a similarly close modelled estimate of median PFS to that reported in the trial. The methodology applies a break point at 28 weeks, where prior to 28 weeks the Kaplan Meier data is used directly, and then survival curves are fitted to the data post 28 weeks. A break point of 28 weeks was selected based on an apparent change in shape of the Kaplan Meier data at this point for patients in the sunitinib arm, and the results of the Chow test. The selected survival functions were the exponential distribution for both treatment arms, based on goodness-of-fit measures and clinical plausibility. (Scenario 11)
- Include the disutility of AEs as a separate decrement (Scenario 12)

- Assuming a treatment waning effect; that the OS treatment benefit associated with the use of pembrolizumab plus lenvatinib begins to wane five years following discontinuation for all patients, and adopts the hazard of the sunitinib arm over the two subsequent years i.e., from year 7 to 9 in the model (Scenario 13)
- Applying a stopping rule to Lenvatinib at two years; pembrolizumab patients stop treatment after 35 cycles/two years. The impact of stopping treatment with both components of the combination is investigated in this scenario (Scenario 14).

Table 63. Scenario analysis results versus trial comparator (list price)

Scenario No.	Description	Inc. Costs	Inc. LYs	Inc. QALYs	ICER (QALYs)	Difference vs. base case
Base case	-	[redacted]	**1.36**	[redacted]	**£114,492**	-
Scenario 1	Undiscounted results	[redacted]	2.03	[redacted]	£77,655	-£36,387
Scenario 2	6% discount rates	[redacted]	1.07	[redacted]	£144,226	+£29,734
Scenario 3	PEMplusLEN OS - constant HR versus sunitinib - 0.72	[redacted]	1.39	[redacted]	£112,491	-£2,001
Scenario 4	1.5% discount rates	[redacted]	1.69	[redacted]	£92,696	-£21,796
Scenario 5	20-year time horizon	[redacted]	1.21	[redacted]	£128,992	+£14,499
Scenario 6	30-year time horizon	[redacted]	1.34	[redacted]	£115,945	+£1,453
Scenario 7	Trial-based subsequent treatments	[redacted]	1.36	[redacted]	£117,240	+£2,748
Scenario 8	Health state-based utility values	[redacted]	1.36	[redacted]	£116,452	+£1,960
Scenario 9	Exclude wastage costs	[redacted]	1.36	[redacted]	£114,493	+£1
Scenario 10	Hospitalization AEs only	[redacted]	1.36	[redacted]	£114,638	+£146
Scenario 11	Two-piece approach to PFS extrapolation (exponential in both arms)	[redacted]	1.36	[redacted]	£114,599	+£107
Scenario 12	Include AE disutility	[redacted]	1.36	[redacted]	£115,258	+£766
Scenario 13	Treatment waning from year 7 t 9	[redacted]	0.96	[redacted]	£161,795	+£47,303
Scenario 14	Lenvatinib stopping rule at two years	[redacted]	1.36	[redacted]	£104,078	-£10,414

Abbreviations: AE, adverse event; HR, hazard ratio; PEM+LEN, pembrolizumab plus lenvatinib

Summary of sensitivity analyses results

Using list prices, the combination of pembrolizumab and lenvatinib has a low probability of demonstrating cost-effectiveness versus sunitinib at the £30,000 per QALY threshold, or higher threshold when taking into account the condition severity and the QALY shortfall approach. With the application of confidential discounts, the true cost-effectiveness of the combination can be assessed.

One-way sensitivity analysis shows that the most impactful inputs are the relative dose intensities for pembrolizumab and sunitinib, with baseline cohort parameters and those related to the mean duration of subsequent treatments.

Scenario analysis showed the most sensitive scenarios relate to the discount rate application, reduced time horizon and the waning of the pembrolizumab plus lenvatinib treatment effect. These ranged from £77,655 to £161,795. With the application of confidential discounts, it is expected that most scenarios will present ICERs under the willingness-to-pay threshold, and therefore pembrolizumab in combination with lenvatinib should be considered a cost-effective combination when the true cost of a QALY to the NHS is considered.

B.3.9 Subgroup analysis

The analysis for the intermediate-poor risk (as defined by the IMDC criteria) subgroup of patients with untreated aRCC has been pre-specified in the final appraisal scope, and as with the overall population, the comparators are those which are available through baseline commissioning. Therefore, cabozantinib is a relevant additional comparator in this subgroup. The sub-group analysis employed the same model settings for the trial intervention and comparator as for the overall population. The assumption of equivalent efficacy between sunitinib and pazopanib/tivozanib was also followed.

As in the overall population analyses, the following settings were employed:

- OS: fully parametric curves for pembrolizumab plus lenvatinib (exponential) and sunitinib (gamma)
- PFS: fully parametric curves for pembrolizumab plus lenvatinib (exponential) and sunitinib (gamma)
- TTD: generalized gamma for lenvatinib and log-logistic for sunitinib.

Due to the absence of head-to-head comparative data, NMA data was used to inform the comparison vs. cabozantinib, with sunitinib (the mutual comparator) as the reference treatment. As with the overall population, the proportional hazards assumption was violated, so time-varying hazards are more appropriate (i.e., rather than a constant hazard). Time-varying hazard ratios were explored by fitting first-order and second-order fractional polynomial models in line with guidance. For the relative

treatment effects in the second order fractional polynomial framework, models were assessed which assume:

- treatment only has an impact on two of the three parameters describing the hazard function over time (i.e., one scale and one shape parameter)
- treatment has an impact on all three parameters describing the hazard function over time (i.e., one scale and two shape parameters).

First-order fractional polynomial models were selected for the cabozantinib data, based on clinical plausibility of the long-term survival estimates. Of the first order fractional polynomial models, P1=0 model was selected due to having the lowest DIC.

The subgroups, and relevant comparators considered, are as follows:

- Intermediate/poor risk group
    - Comparators: sunitinib, pazopanib, tivozanib, cabozantinib

Further detail on the statistical analysis and characteristics of the subgroups can be found in section B.2.7. The results of the cost-effectiveness analysis are presented in the tables below.

Table 64. Base-case results versus trial comparator in intermediate-poor risk subgroup (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Sunitinib	[redacted]	3.51	[redacted]	[redacted]	[redacted]	-
Pembrolizumab plus lenvatinib	[redacted]	5.30	[redacted]	[redacted]	[redacted]	£90,141
Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years						

Table 65. Base case results versus external comparators in intermediate-poor risk subgroup (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pazopanib	[redacted]	3.51	[redacted]	[redacted]	[redacted]	-
Pembrolizumab plus lenvatinib	[redacted]	5.30	[redacted]	[redacted]	[redacted]	£91,355
Tivozanib	[redacted]	3.51	[redacted]	[redacted]	[redacted]	-
Pembrolizumab plus lenvatinib	[redacted]	5.30	[redacted]	[redacted]	[redacted]	£89,369
Cabozantinib	[redacted]	3.95	[redacted]	[redacted]	[redacted]	-
Pembrolizumab plus lenvatinib	[redacted]	5.30	[redacted]	[redacted]	[redacted]	£77,730

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

The model predicts an incremental life year gain of 1.35 years and an additional [redacted] QALYs for treatment with the combination, compared to cabozantinib. Using list prices, incremental costs of [redacted] are estimated, leading to an ICER of £77,730.

B.3.10 Validation

Validation of cost-effectiveness analysis

Clinical benefit

The efficacy outcomes of pembrolizumab in combination with lenvatinib observed in the KEYNOTE-581 trial[25] have been compared to the outcomes from the cost-effectiveness model. Further comparison of results generated from the model with outcomes from KEYNOTE-581 are detailed in Appendix J.

Expert validation

A global model was adapted to the UK setting. The key assumptions employed in the base case and tested in the sensitivity analyses, alongside the clinical plausibility of the model outputs themselves, were validated with a panel of six UK clinicians.

The review agreed that the overall model structure was appropriate given the lack of sufficiently granular long-term outcomes for all relevant comparators and the assumptions for the model were logical. Validity checks to ensure consistency

between the clinical trial data and model outcomes for endpoints for which there was sufficient information were also conducted.

In line with TSD14[56] , a range of survival models were tested and compared based upon how they fit to the observed trial data and how plausible the extrapolated portions are. As the long-term survival estimates for the trial comparator (sunitinib) were considered to be superior to those reported in previous TAs (Section B.3.3), the most conservative estimate of sunitinib survival was adopted i.e., the gamma distribution, in order to reduce the gap with clinical experience. Furthermore, baseline characteristics of the KEYNOTE-581 population are detailed in Section B.3.3, that characterise the more favourable prognostics of the patient population receiving sunitinib, which is a contributing factor to the long-term survival estimates for sunitinib in KEYNOTE-581. Extrapolated portions were also consistent with published estimates from Savard et al. 2020[57] – see Figure 36.

Figure 36. Comparison of selected survival curves and trial data (ITT)

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Quality control

The model was quality-assured by the internal processes of the economists who produced the economic model at BresMed, who found no major implementation errors or bugs.

The following criteria were assessed during model review:

- A manual review of all programming using formulae within Microsoft Excel and code in VBA
- Confirmation that the mathematical calculations, programming, and formulae are consistent with the specification and are logically applied
- A review of the patient flow sheets, model scope, results outputted, and sensitivity analysis functionality
- Extreme value testing (setting in zero values to parameters and stress testing the model in general) to assess whether the outcomes, and changes in outcomes, make intuitive sense for the options selected – in addition to editorial checks (text descriptions, referencing, navigation and graphical outputs) within the model

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab in combination with lenvatinib for first-line treatment of patients with aRCC. The economic evaluation reflects patients who participated in KEYNOTE-581 and is relevant to all groups of patients who could potentially benefit from the use of the technology, as identified in the decision problem.

A study assessing the cost-effectiveness of pembrolizumab in combination with lenvatinib for the target population was not identified in the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the untreated aRCC population eligible for pembrolizumab in combination with lenvatinib, as per the positive CHMP opinion[82] and anticipated marketing authorisation in the EU. As

mentioned previously, clinical efficacy estimates from the KEYNOTE-581 trial, which assessed patients in line with the anticipated licenced indication, were used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially receive treatment with pembrolizumab in combination with lenvatinib, referred to as the ITT population in the model.

Generalisability of the analysis to the clinical practice in England

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

- The patient population in KEYNOTE-581 and the economic evaluation are reflective of patients with aRCC in the UK.
- The economic model structure is consistent with previous oncology models submitted to NICE for this indication
- The resource utilitisation and unit costs are reflective of UK clinical practice and were derived from the NHS Reference Costs and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab in combination with lenvatinib.
- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and alternative data sources and scenarios related to the estimation of QALYs and costs.

Strengths and weaknesses of the evaluation

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

- OS, PFS and ToT data for pembrolizumab were used from the KEYNOTE-581 trial, however due to limited follow-up data there is uncertainty surrounding the long-term effects of pembrolizumab in combination with lenvatinib on clinical outcomes. Where possible, validation versus external benchmarks was sought, and mitigating steps were followed when divergence was observed, such as the employment of conservative distributions.
- OS, PFS and ToT extrapolation: The approaches to OS, PFS and ToT extrapolation were based on statistical and clinical plausibility considerations.

- Estimation of utilities: Utility values were obtained directly from EQ-5D responses elicited from patients in the trial. The base case followed a time-to-death approach, following consultation with clinical experts that HRQoL diminishes as patients approach death.
- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to two years, i.e., 35 cycles, as specified in the KEYNOTE-581 protocol .
- Resource use and unit costs used in the analysis are reflective of UK clinical practice.

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

In conclusion, this submission demonstrates the clinical and cost-effectiveness of pembrolizumab in combination with lenvatinib relative to sunitinib, within its expected marketing authorization, as a first-line treatment of patients with aRCC.

It is expected that this economic evaluation will indicate that when confidential discounts are applied, pembrolizumab in combination with lenvatinib is a cost-effective combination for the treatment of patients with untreated aRCC.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

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

Company responses to clarification questions

December 2021

File name	Version	Contains confidential information	Date
ID3760_LEN+PEM_RCC_company responses_clarification questions	1	Yes [AiC]	15th December 2021

Abbreviations

Abbreviation	Definition
aRCC	Advanced renal cell carcinoma
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CSR	Clinical study report
DIC	Deviance information criteria
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EVE	Everolimus
FP	Fractional polynomial
HR	Hazard ratio
IMDC	International Metastatic RCC Database Consortium
ITCRP	International Clinical Trials Registry Platform
ITT	Intention-to-treat
LEN	Lenvatinib
MHRA	Medicine and Healthcare products Regulatory Agency
MSKCC	Memorial Sloan Kettering Cancer Center
NMA	Network meta-analysis
OS	Overall survival
pD	Effective number of parameters
PEM	Pembrolizumab
PFS	Progression-free survival
PH	Proportional hazards
RDI	Relative dose intensity
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SUN	Sunitinib
WHO	World Health Organization

Section A: Clarification on effectiveness data

Indirect treatment comparisons

A1. Priority question: Please clarify which Wald Chi-Square statistics and p-values in Appendix D4, Table 43 correspond to OS and PFS for each trial. The ERG notes that OS data are not available for inclusion in the networks from the CROSS-J-RCC, Esucudier 2009, SWITCH and SWITCH II trials, but that PFS data are available for these trials.

We reviewed Table 43 in Appendix D4. The column headings of OS and PFS were regrettably switched. This has now been corrected. Please note, that the previously provided PFS values were for proportional hazards (PH) assessment of overall CLEAR data, including all arms (LEN+PEM, LEN+EVE, SUN). We have revised Table 43 to provide PH assessment data for LEN+PEM vs SUN arms only for clarity (Table 1).

Table 1: Updated Company submission Table 43 (Assessment of proportional hazards assumption, ITT populations)

Trial ID	PFS		OS	
	Wald Chi-Square	Pr > ChiSq	Wald Chi-Square	Pr > ChiSq
CLEAR (11, 56)	[redacted]	[redacted]	[redacted]	[redacted]
CABOSUN (5)	[redacted]	[redacted]	[redacted]	[redacted]
COMPARZ (14)	[redacted]	[redacted]	[redacted]	[redacted]
CROSS-J-RCC (18)	[redacted]	[redacted]	[redacted]	[redacted]
Escudier 2009 (21)	[redacted]	[redacted]	[redacted]	[redacted]
Motzer 2007 (25, 26)	[redacted]	[redacted]	[redacted]	[redacted]
SWITCH (28)	[redacted]	[redacted]	[redacted]	[redacted]
SWITCH II (29)	[redacted]	[redacted]	[redacted]	[redacted]
TIVO-1 (31)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ChiSq, Chi-square; ITT, intention-to-treat; NR, not reported; OS, overall survival; PFS, progression-free survival; Pr, probability.

A2. <u>Priority question</u>: Please provide assessments of proportional hazards assumptions in the risk subgroups for OS (updated OS analysis) in the CLEAR trial (in the format of Appendix D4, Table 44).

An assessment of proportional hazards assumptions for the CLEAR trial risk subgroups has now been added to Table 44 of the Company submission. This updated Table 44 is presented as Table 2.

Table 2: Updated Company submission Table 44 (Assessment of proportional hazards assumptions, risk subgroups)

Trial Name	PH Test	
	Wald Chi-Square	Pr > ChiSq
CABOSUN OS IMDC intermediate or poor	[redacted]	[redacted]
CABOSUN PFS IMDC intermediate or poor	[redacted]	[redacted]
CABOSUN PFS IMDC intermediate	[redacted]	[redacted]
CABOSUN PFS IMDC poor	[redacted]	[redacted]
CLEAR PFS FDA IMDC favourable	[redacted]	[redacted]
CLEAR PFS FDA IMDC intermediate	[redacted]	[redacted]
CLEAR PFS FDA IMDC intermediate or poor	[redacted]	[redacted]
CLEAR PFS FDA IMDC poor	[redacted]	[redacted]
CLEAR PFS FDA MSKCC favourable	[redacted]	[redacted]
CLEAR PFS FDA MSKCC intermediate	[redacted]	[redacted]
CLEAR PFS FDA MSKCC intermediate or poor	[redacted]	[redacted]
CLEAR PFS FDA MSKCC poor	[redacted]	[redacted]
CLEAR OS IMDC intermediate or poor	[redacted]	[redacted]
CLEAR OS MSKCC intermediate or poor	[redacted]	[redacted]

Note: Proportionality of hazards was tested in base case and intermediate/poor risk subgroups for OS as these are the only population/risk subgroups for which the results from fractional polynomial NMAs for OS were included in NICE submission.
Abbreviations: FDA, Food and Drug Administration; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival; PH, proportional hazard.

A3. <u>Priority question:</u> Please provide a list of all fixed- and random-effects fractional polynomial models estimated for the indirect treatment comparisons. For each model please provide:

a. Number of data points

b. Number of model parameters

c. Posterior mean residual deviance

d. pD (i.e., the effective number of parameters)

e. Deviance information criteria (DIC).

Please also provide further details of how the clinical plausibility of the fitted fractional polynomial models was assessed and for which models clinical plausibility was assessed.

Selection of model for fractional polynomial (FP) NMA

A range of models (i.e. different combinations of polynomials; the first order and second order) were assessed for goodness-of-fit by comparing their DIC values and, the model with the lowest DIC (best fit = 1st) was chosen for the analyses. Where the difference in DIC between two models was ≤2 for an analysis scenario, a sensitivity analysis was also run to see if the choice of model impacted the results (including the projected estimates of hazard ratios further into the time horizon).

A DIC information for final FP analyses of OS and PFS document (data on file) that includes the number of datapoints, the effective number of parameters (pD), and DIC for one or more models for each scenario has now been provided (1). DIC of the 2nd/3rd/4th best fitted models, whenever they had very similar fit to the best fitted model are also included. Further, please find separate .csv files from DIC analyses with #data, #parameters for all models examined.

The clinical plausibility of the FP models was not formally assessed by clinical experts, however in all scenarios considered, the LEN+PEM and sunitinib curves cross. As reported in the original submission, this was considered clinically

implausible by clinical experts (Section 5.10, Company submission), and therefore the FP modelling approaches were also not considered plausible.

Request for additional indirect clinical effectiveness evidence

A4. Priority question: Please include CHECKMATE 214 trial data (nivolumab plus ipilimumab versus sunitinib) in all indirect comparisons for the intermediate/poor risk subgroup.

The timings of the Cancer Drug Fund (CDF) review for nivolumab with ipilimumab overlap with this appraisal, however presently nivolumab with ipilimumab is still only available within the CDF as detailed in the decision problem (2). Under the current NICE process guidance (NICE position statement: consideration of products recommended for use in the CDF as comparators, or in a treatment sequence, in the appraisal of a new cancer product) (3), a product would not be considered a comparator unless routinely commissioned prior to the start of the appraisal. Therefore, to ensure compliance with the NICE process, which has been applied for all other drugs assessed by NICE for patients with advanced renal cell carcinoma (aRCC), Eisai are unable to provide the requested results at this stage.

Furthermore, please note, it is challenging to change from the agreed decision problem and incorporate new comparators into the indirect comparisons and cost-effectiveness model mid-process due to resource and capacity limitations.

Systematic literature review

A5. Quality assessment: Please confirm whether two reviewers independently performed the quality assessment of the included studies.

We confirm that the quality assessment of included studies was conducted by two independent reviewers.

A6. Search strategy: Please provide the date limits applied to the original and updated searches for each of the sources searched, including databases, conference proceedings and registries.

Date limits applied to the original and updates searches for the clinical systematic literature review (SLR) are presented below:

EMBASE search:

Original search (27th March 2019):

Database search: No limit

Conference search: 2017 onwards

1st SLR update (1st September 2020):

Database search: No limit

Conference search: 2019 onwards

2nd SLR update (5th January 2021):

Database search: No limit

Conference search: 2020 onwards

3rd SLR update (4th June 2021):

Database search: No limit

Conference search: 1st December 2020 to 4th June 2021

MEDLINE search:

Original search (27th March 2019): No limit

1st SLR update (1st September 2020):

Database: No limit

Conference abstracts: 2019 onwards

2nd SLR update (5th January 2021):

Database search: No limit

Conference search: 2020 onwards

3rd SLR update (4th June 2021):

Database search: No limit

Conference search: 1st December 2020 to 4th June 2021

CENTRAL and CDSR (via Cochrane Library)

Original search (27th March 2019): No limit

1st SLR update (1st September 2020): 2019 onwards

2nd SLR update (5th January 2021): 2020 onwards

3rd SLR update (4th June 2021): 2021 onwards

Trial registry searches:

Clinicaltrials.gov: 8th May 2019 & 16th November 2020

EMA EPARs: 6th May 2019 & 16th November 2020

WHO ICTRP: 9th May 2019 & 16th November 2020

For the cost-effectiveness, health-related quality of life, and cost and healthcare resource use literature reviews, no 3rd update in June 2021 was conducted. Please refer to the Company submission Appendix G.2.1, Appendix H2.1 and Appendix I2.1, respectively, for full details of search dates for these searches.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide cost effectiveness results for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab.

The timings of the CDF review for nivolumab with ipilimumab overlap with this appraisal, and presently nivolumab with ipilimumab is only available within the CDF as detailed in the decision problem (2). Under the current NICE process guidance (NICE position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product) (3), a product would not be considered a comparator unless routinely commissioned prior to the start of the appraisal. Therefore, to ensure compliance with the NICE process, which has been applied for all other drugs assessed by NICE for patients with aRCC, Eisai are unable to provide the requested results at this stage.

Furthermore, please note, it is challenging to change from the agreed decision problem and incorporate new comparators into the indirect comparisons and cost-effectiveness model mid-process due to resource and capacity limitations.

B2. Priority question: Please provide cost effectiveness results (lenvatinib plus pembrolizumab versus all relevant comparators) for the favourable risk subgroup of patients.

Eisai has received European Medicines Agency (EMA) and Medicine and Healthcare products Regulatory Agency (MHRA) approval for Kisplyx® (lenvatinib), and is indicated for the treatment of adults with advanced renal cell carcinoma in combination with pembrolizumab, as first-line treatment. Approvals were received from the EMA and MHRA on 26th November 2021 (4) and 29th November 2021 (5, 6), respectively. The indication is for the overall aRCC population, not differentiated by risk subgroups.

Methodologically, the CLEAR trial design was not statistically powered for subgroup analyses, only for the overall advanced RCC population in line with our indication. As stated in the EMA's European public assessment report (EPAR), Section 3.3, '*The OS data are currently immature to allow for the informative analyses in the key subgroups, in particular IMDC and MSKCC favourable prognosis subgroups, while the updated analysis in the overall population supports benefit, with hazard ratio (HR) of 0.72 (0.55, 0.93)' (7).* Therefore, any analyses of the favourable risk subgroup will be highly uncertain and will not add value to the decision-making process.

Data for the intermediate and poor risk subgroup was provided in line with the decision problem (final scope) (2) to enable a comparison with cabozantinib. However, our intention is to provide a first-line treatment option to all eligible patients with advanced RCC. Consideration of the favourable risk subgroup was not outlined in the decision problem. Neither was the favourable risk subgroup considered in the previous decision problems of untreated advanced RCC appraisals for avelumab with axitinib (TA645) (8) and pembrolizumab with axitinib (TA650) (9).

B3. <u>Priority question</u>: Please provide the following Kaplan-Meier analyses:

A. Time to death from any cause (OS)

B. PFS per Independent Radiologic Review (IIR) [FDA censoring rule]

C. PFS per Independent Radiologic Review (IIR) [EMA censoring rule]

D. Time to study treatment discontinuation (TTD)

    a. Please provide TTD data for lenvatinib, pembrolizumab and sunitinib separately

Please use the following specifications:

<u>Trial data set</u>: CLEAR

<u>Format</u>: Please present analysis outputs using the format used in the sample table below

<u>Populations</u>: (i) The ITT population of the CLEAR trial

(ii) The population with favourable risk including all patients lost to follow-up or withdrawing from the trial

(iii) The population with intermediate/poor risk including all patients lost to follow-up or withdrawing from the trial

Trial arms: (i) Lenvatinib plus pembrolizumab

(ii) Sunitinib

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Life tables for the ITT population were previously provided in the Company submission reference pack (ID3760 submission_life tables_Oct 2021). An updated excel file has been provided to additionally include life tables for the intermediate/poor risk population, in line with the decision problem (10).

We have not provided the life tables for the favourable risk population, based on the same rationale given in our response to clarification question B2.

B4. Please provide the data and details of the calculations used to estimate RDI for each of the treatments in the NICE scope. Please provide estimates by risk group.

Overall population

Lenvatinib

A weighted average dose intensity for lenvatinib was calculated to account for usage of the 4 mg and 10 mg capsules based on cumulative days on the doses used in CLEAR (i.e. 0 mg, 4 mg, 8 mg, 10 mg, 14 mg, 20 mg, 28 mg, and 40 mg). The cumulative days on each dose as a percentage of the sum of all cumulative days was multiplied by the number of 4 mg and 10 mg capsules required for each dose to obtain the average number of 4 mg and 10 mg capsules used within CLEAR. This was then multiplied by the respective dose to derive a weighted average dose and divided by the total dose of 20 mg to derive a weighted average RDI. The data used for the calculations is summarised in Table 3.

Table 3: Lenvatinib, overall population, RDI calculations

Dose (mg)	Cumulative days	% of days (relative to total dose)	Number of capsules	
			4 mg	10 mg
0	[redacted]	[redacted]	0	0
4	[redacted]	[redacted]	1	0
8	[redacted]	[redacted]	2	0
10	[redacted]	[redacted]	0	1
14	[redacted]	[redacted]	1	1
20	[redacted]	[redacted]	0	2
28	[redacted]	[redacted]	2	2
40	[redacted]	[redacted]	0	4
Total	**176,240**	**100.00%**	**0.429†**	**1.195†**
Weighted average dose			[redacted]	
RDI			[redacted]	

†Sum product of number of capsules and % of days.
Abbreviation: RDI, relative dose intensity.

Pembrolizumab

In CLEAR, dose reductions for pembrolizumab were not permitted, however dose delays and interruptions could occur. An administration intensity was therefore calculated to represent these delays defined as the mean number of administrations received divided by the mean number of administrations expected during the time

the patient was considered to be on pembrolizumab. In order to account for the administration schedule of pembrolizumab, the number of expected administrations was defined as $1 + \lfloor t_{ONPEMB}/21 \rfloor$, where t_{ONPEMB} is the time on pembrolizumab in days, and 21 represents the 3-weekly dosing schedule. The number was rounded down to the nearest integer to calculate the expected number of administrations. The data feeding into the calculations for pembrolizumab are presented in Table 4.

Table 4: Pembrolizumab, overall population, RDI calculations

Treatment	Mean number of administrations received	Mean number of administrations expected	RDI
Pembrolizumab	[redacted]	[redacted]	[redacted]

Abbreviation: RDI, relative dose intensity.

Sunitinib

For sunitinib, the RDI was taken directly from CLEAR. This is presented in Table 18 of the CSR (provided in the Company submission reference pack), where the mean received dose as percentage of planned starting dose per patient was [redacted].

Pazopanib and tivozanib

RDIs for comparators not evaluated in the CLEAR study were obtained from the relevant NICE technology appraisals (Table 5**Error! Reference source not found.**). The RDI of pazopanib was based on the manufacturer submission for NICE TA215 (11), with the figure of 86% calculated using the mean daily dose of pazopanib in the VEG105192 trial (687.5 mg) divided by the target dose (800 mg). For tivozanib, the RDI of 93.9% was sourced from Page 47 of the ERG report for NICE TA512 (12).

Table 5: Pazopanib and tivozanib, RDI from previous TAs

Treatment	RDI	Source
Pazopanib	86%	NICE TA215 (11)
Tivozanib	93.9%	NICE TA512 (11)

Abbreviations: IV, intravenous; NICE, National Institute for Health and Care Excellence; RDI, relative dose intensity; TA, technology assessment .

Intermediate/poor risk population

Lenvatinib

The data used for the calculations of the weighted average dose intensity for lenvatinib for the intermediate and poor risk population is summarised in Table 6.

Table 6: Lenvatinib, intermediate and poor population, RDI calculations

Dose (mg)	Cumulative days	% of days (relative to total dose)	Number of capsules	
			4 mg	10 mg
0	[redacted]	[redacted]	0	0
4	[redacted]	[redacted]	1	0
8	[redacted]	[redacted]	2	0
10	[redacted]	[redacted]	0	1
14	[redacted]	[redacted]	1	1
20	[redacted]	[redacted]	0	2
28	[redacted]	[redacted]	2	2
40	[redacted]	[redacted]	0	4
Total	**118,600**	**100.00%**	**0.422**[†]	**1.188**[†]
Weighted average dose			[redacted]	
RDI			[redacted]	

[†]Sum product of number of capsules and % of days.
Abbreviation: RDI, relative dose intensity.

Pembrolizumab

The data feeding into the RDI calculations for pembrolizumab in the intermediate and poor population is presented in Table 7.

Table 7: Pembrolizumab, intermediate and poor population, RDI calculations

Treatment	Mean number of administrations received	Mean number of administrations expected	RDI
Pembrolizumab	[redacted]	[redacted]	[redacted]

Abbreviation: RDI, relative dose intensity.

Cabozantinib

The RDI of 94.3% for cabozantinib, which was not evaluated in the CLEAR study, was obtained from Table 48 of the company submission for NICE TA542 (13) (Table 8).

Table 8: Cabozantinib, overall population, RDI from previous TA

Treatment	RDI	Source
Cabozantinib	94.3%	NICE TA542 (13)

Abbreviations: RDI, relative dose intensity; TA, technology assessment.

Favourable risk population

We have not provided the RDIs for the favourable risk population, based on the same rationale given in our response to clarification question B2.

B5. Please provide the details of the subsequent anticancer therapies received by patients in the CLEAR trial by treatment arm. Please provide estimates by risk group.

Overall population

Details of the anticancer therapies received by patients in the CLEAR trial in the ITT population (full analysis set) are presented in Table 14.1.4.4.1 of the CLEAR study CSR (final PFS analysis, data cut-off 20th August 2020) which was provided in the Company submission reference pack. Table 9 presents the anticancer therapies received by patients in the CLEAR trial in the ITT population based on the updated OS analysis (data cut-off 31st March 2021).

Table 9: Summary of anti-cancer medications during survival follow-up, updated OS analysis (31st March 2021)

	LEN+PEM N=355 n (%)	Sunitinib N=357 n (%)	Total N=712 n (%)
Patients started study treatment	[redacted]	[redacted]	[redacted]
Patients discontinued study treatment	[redacted]	[redacted]	[redacted]
Patients received any subsequent anti-cancer medication during survival follow-up by type	[redacted]	[redacted]	[redacted]
Anti-VEGF therapy	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]	[redacted]
Sitravatinib	[redacted]	[redacted]	[redacted]
PD-1/PD-L1 checkpoint inhibitor	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]	[redacted]
BI 754091	[redacted]	[redacted]	[redacted]
Cemiplimab	[redacted]	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]	[redacted]
MEDI 0680	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
mTOR inhibitor	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]

	LEN+PEM N=355 n (%)	Sunitinib N=357 n (%)	Total N=712 n (%)
Temsirolimus	[redacted]	[redacted]	[redacted]
CTLA-4 inhibitor	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
Tremelimumab	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Abemaciclib	[redacted]	[redacted]	[redacted]
Aldesleukin	[redacted]	[redacted]	[redacted]
BI 754111	[redacted]	[redacted]	[redacted]
BMS 986205	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Ciforadenant	[redacted]	[redacted]	[redacted]
Cobimetinib	[redacted]	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]
Gevokizumab	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]
Interleukin inhibitors	[redacted]	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]	[redacted]
Monoclonal antibodies	[redacted]	[redacted]	[redacted]
Pexastimogene devacirepvec	[redacted]	[redacted]	[redacted]
PT 2977	[redacted]	[redacted]	[redacted]
Savolitinib	[redacted]	[redacted]	[redacted]
Talazoparib	[redacted]	[redacted]	[redacted]
Number of regimens, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
Duration of first anti-cancer regimen during survival follow-up (months)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

Percentages are based on the total number of patients in the FAS within the relevant treatment group.
Patients with 2 or more anti-cancer medications may be counted in multiple categories.
Medications were coded using WHO Drug Dictionary version WHODDMAR20B3G.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LEN, lenvatinib; max, maximum; min,

minimum; mTOR, mammalian target of rapamycin; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death ligand-1; PEM, pembrolizumab; SD, standard deviation; VEGF, vascular endothelial growth factor.

Intermediate/poor risk population

Details of the anticancer therapies received by patients in the CLEAR trial in the IMDC intermediate/poor risk subgroup are presented in Table 10 for the updated OS analysis (data cut-off 31st March 2021). Please note, this is post-hoc subgroup analysis and subject to loss of randomisation. Data should be treated with caution.

Table 10: Summary of anti-cancer medications during survival follow-up, IMDC risk group, intermediate or poor risk, updated OS analysis (31st March 2021)

	LEN+PEM N=243 n (%)	Sunitinib N=229 n (%)
Patients started study treatment	[redacted]	[redacted]
Patients discontinued study treatment	[redacted]	[redacted]
Patients received any subsequent systemic anticancer medication during survival follow-up by type	[redacted]	[redacted]
VEGF inhibitors	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]
Sitravatinib	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]
PD1 or PD-L1 checkpoint inhibitors	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
BI 754091	[redacted]	[redacted]
Cemiplimab	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]
MEDI 0680	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
mTOR inhibitors	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Temsirolimus	[redacted]	[redacted]
CTLA-4 inhibitors	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]

	LEN+PEM N=243 n (%)	Sunitinib N=229 n (%)
Tremelimumab	[redacted]	[redacted]
Other	[redacted]	[redacted]
BI 754111	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Ciforadenant	[redacted]	[redacted]
Cobimetinib	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Gevokizumab	[redacted]	[redacted]
Interleukin inhibitors	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]
Monoclonal antibodies	[redacted]	[redacted]
Pexastimogene devacirepvec	[redacted]	[redacted]
PT 2977	[redacted]	[redacted]
Savolitinib	[redacted]	[redacted]
Talazoparib	[redacted]	[redacted]
Number of regimens, n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
Duration of first anti-cancer regimen during survival follow-up (months)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Percentages are based on the total number of patients in the FAS within the relevant treatment group.
Patients with 2 or more anti-cancer medications may be counted in multiple categories.
Medications were coded using WHO Drug Dictionary version WHODDMAR20B3G.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LEN, lenvatinib; max, maximum; min, minimum; mTOR, mammalian target of rapamycin; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death ligand-1; PEM, pembrolizumab; SD, standard deviation; VEGF, vascular endothelial growth factor.

We have not provided the subsequent anti-cancer therapies for the favourable risk population, based on the same rationale given in our response to clarification question B2.

Section C: Textual clarification and additional points

C1. Priority question: Please provide the following documents:

a. **Eisai. First-line advanced renal cell carcinoma (RCC). Systematic literature review report. EVA-31482-00. 10th August 2021. Version 8.1. Data on file. 2021**
b. **Eisai. Overall survival of lenvatinib plus pembrolizumab versus sunitinib adjusted for subsequent anticancer medication using 2-stage estimation and IPCW approach for OS follow up. March 2021 datacut. Data on file. 2021 (reference 137 of the CS)**
c. **Eisai. Overall survival of lenvatinib plus pembrolizumab versus sunitinib adjusted for subsequent anticancer medication using 2-stage estimation and IPCW approach for OS. August 2020 data cut. Data on file. 2021 (reference 140 of the CS)**
d. **Analysis plan for Health Related Quality of Life (referred to in Section 9.7.1.10 of the Clinical Study Report)**
e. **Report of Health Related Quality of Life results at Interim Analysis 3 (referred to in Section 9.7.1.10 of the Clinical Study Report)**

The requested references have now been provided.

C2. Please provide the September 2021 Advisory Board report (data on file).

The requested reference has now been provided.

References

1. Eisai. DIC information in final FP analysis of OS and PFS, NICE scenarios_STC. Data on file. 2021.
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3. National Institute of Health and Care Excellence. Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. 2019. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf
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Additional clarification questions (Eisai): Renal cell carcinoma (advanced, untreated) - lenvatinib (with pembrolizumab) [ID3760]

Received on 21st December 2021

- **Please provide utility estimates for the intermediate/poor risk group and the favourable risk group of patients.**
- **Please include the utility values by risk group into your cost effectiveness estimates for lenvatinib plus pembrolizumab versus all relevant comparators.**

Utility estimates for the intermediate/poor risk population were incorporated into the cost-effectiveness model and were summarised in Table 33 of the Company submission. All relevant comparators were included in the cost-effectiveness model that was submitted.

We have not provided utility estimates for the favourable risk population, based on the same rationale given in our response to clarification question B2.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

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

MSD response to clarification questions

December 2021

File name	Version	Contains confidential information	Date
MSD response to clarification questions [REDACTED]	Final	Yes	15/12/2021

Section A: Clarification on effectiveness data

CLEAR trial

A1. Priority question: Please repeat the testing of Schoenfeld Residuals for overall survival (OS) (updated OS analysis) and progression-free survival (PFS).

A p-value of 1.00 from a test of Schoenfeld's residuals implies that the slope of the scales residuals is exactly zero, which does not appear to be the case from visual inspection of Figure 16 and Figure 25 of the company submission (CS).

Response:

MSD have re-checked the analysis and identified a format issue in the code. The p-values of 1.00 presented in the CS should be replaced as follows:

Dataset	P-value
Progression-free survival (IA3)	0.0705
Overall survival (IA3)	0.0002
Overall survival (updated)	0.0001

Indirect treatment comparisons

A2. Priority question: Please provide a list of all fixed- and random-effects fractional polynomial models estimated for the indirect treatment comparisons. For each model please provide:

a. Number of data points

b. Number of model parameters

c. Posterior mean residual deviance

d. pD (i.e., the effective number of parameters)

e. Deviance information criteria (DIC).

Response:

A list of all fixed- and random-effects fractional polynomial models estimated for the indirect treatment comparisons are provided below.

PFS ITT Fractional Polynomial Models

	Model	Number of data points	Number of model parameters	Posterior mean residual deviance	pD	DIC
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS ITT Fractional Polynomial Models

	Model	Number of data points	Number of model parameters	Posterior mean residual deviance	pD	DIC
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS Update ITT Fractional Polynomial Models

	Model	Number of data points	Number of model parameters	Posterior mean residual deviance	pD	DIC
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS Intermediate + Poor Risk Group Fractional Polynomial Models

	Model	Number of data points	Number of model parameters	Posterior mean residual deviance	pD	DIC
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS Intermediate + Poor Risk Group Fractional Polynomial Models

	Model	Number of data points	Number of model parameters	Posterior mean residual deviance	pD	DIC
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS Update Intermediate + Poor Risk Group Fractional Polynomial Models

	Model	Number of data points	Number of model parameters	Posterior mean residual deviance	pD	DIC
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Please also provide details of how the clinical plausibility of the fitted fractional polynomial models was assessed.

Response:

In determining the suitability of a fractional polynomial model, the nature of the survival data was considered. Network meta-analysis of survival data is often based on the reported hazard ratio at one time point. However, the studies included in the current analysis report data at multiple time points. Furthermore, not all studies assessed the outcomes at the same time points. The advantage of using fractional polynomial models is that it allows for the simultaneous analysis of outcomes at multiple time points. Furthermore, fractional polynomial models do not rely on the proportional hazards assumption and as a result the model used can be more closely fitted to available survival data. [1,2]

For each model, plots of the estimated hazard ratio for the comparators relative to the reference treatment (sunitinib) were conducted over time. Study-specific fractional polynomial models were visually inspected and compared with the observed trial data to assess internal validity. External validity was assessed by evaluating the plausibility

versus external data of the implied survivor functions (calculated in the cost-effectiveness model from NMA-based input) however, due consideration was given to the established assumption of clinical equivalence between TKI monotherapies in RCC when modelling survival. To determine the model of choice, we identified the least complex model based on the DIC in conjunction with a qualitative assessment of the validity of the model fit to the observed data.

Request for additional indirect clinical effectiveness evidence

A3. <u>Priority question</u>: Please include the CHECKMATE 214 trial data (nivolumab plus ipilimumab versus sunitinib) in all indirect comparisons for the intermediate/poor risk subgroup.

Response:

Nivolumab in combination with ipilimumab (available through the CDF in the intermediate/poor risk group population only) is not a relevant comparator within this appraisal, despite the assertion in the Assessment Group protocol that this combination will be a relevant comparator should it exit the CDF during the course of this appraisal.

Nivolumab plus ipilimumab is not currently available through baseline commissioning and can therefore not be considered established standard of care, nor can the continuing availability of these treatments following the CDF data collection period be predictable. This is supported by a statement made in January 2019 by NICE[4] whereby products recommended for use in the CDF after 1st April 2016 should not be considered as comparators in subsequent relevant appraisals. This position statement does not contain provision for exceptions to this rule to be made in circumstances where potential comparators exit the CDF during the course of an appraisal which has already commenced, such as this one (ID3760).

Furthermore, the appraisal scope lists nivolumab plus ipilimumab as a comparator *"subject to ongoing appraisal"*; the correct interpretation of this note is that, should the nivolumab plus ipilimumab combination enter baseline commissioning prior to the initiation of the current appraisal (ID3760), it is a relevant comparator. This has not happened and therefore nivolumab plus ipilimumab cannot be considered a relevant comparator.

Identification and selection of relevant studies

A4. Quality assessment: The company states (CS, Appendix D1.1) that two reviewers independently screened and extracted data from publications identified by the review. Please confirm whether two reviewers also independently performed the risk of bias assessments of included studies.

Response:

MSD confirm that two reviewers independently conducted the risk of bias assessment.

A5. Search strategy: Please confirm the date limits, if any, that were applied to the searches of the databases and conference proceedings.

Response:

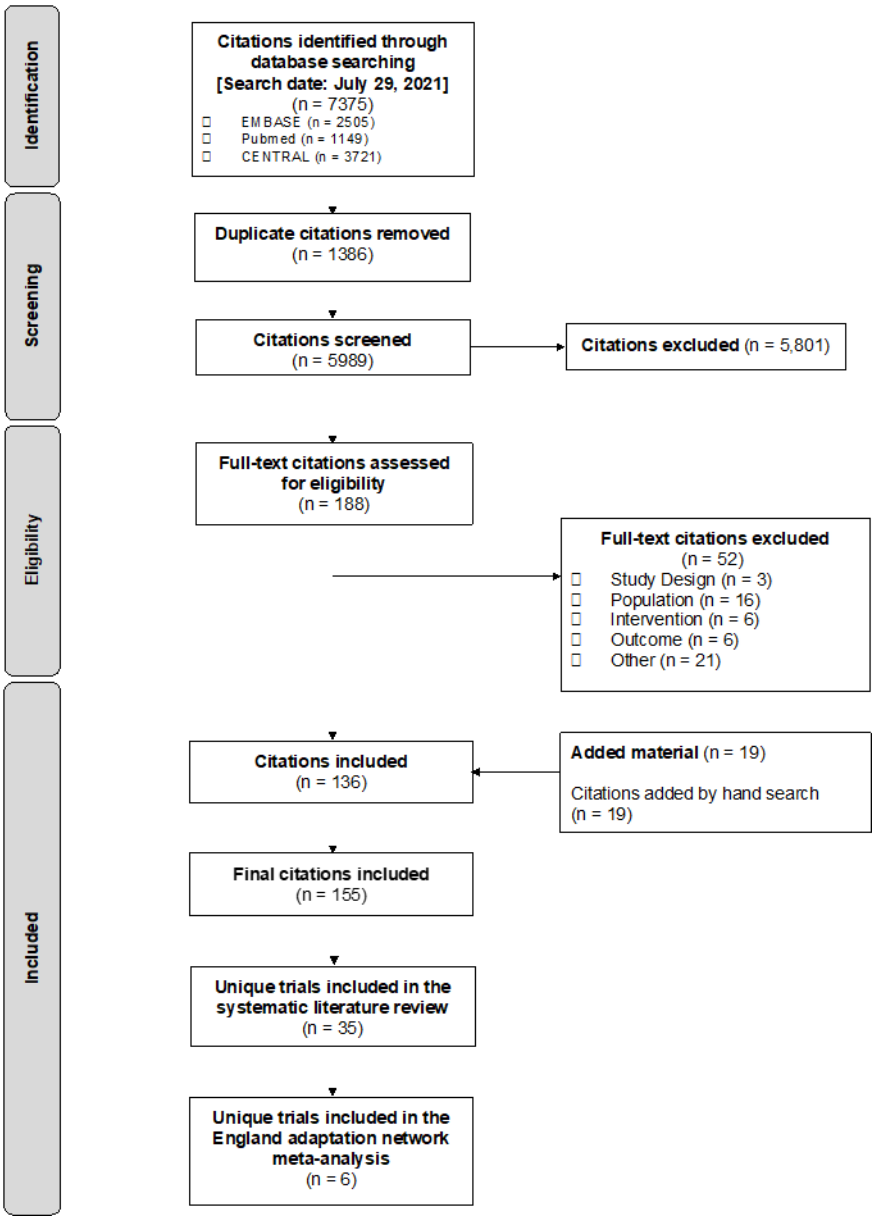
No date limits were applied to the database searches. Relevant conference proceedings between January 2019 to July 2021 were reviewed.

A6. Search strategy: Please provide a PRISMA flow diagram for the clinical systematic literature review.

Response:

The PRISMA flow diagram for the clinical systematic literature review is provided below.

Figure 1. PRISMA Study Flow Diagram for clinical systematic literature review



Section B: Clarification on cost-effectiveness data

B1. <u>Priority question:</u> Please provide cost effectiveness results for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab.

Response:

MSD will not be providing cost-effectiveness results for an irrelevant comparator. Please refer to the response to question A3.

B2. Priority question: Please provide cost effectiveness results (lenvatinib plus pembrolizumab versus all relevant comparators) for the favourable risk subgroup of patients.

Response:

Please see the results of the analyses below. These analyses used the same distributions for OS and PFS data extrapolation as those in the ITT population.

Table 1: Cost-effectiveness results for favourable risk subgroup (list price)

	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£)
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	-
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	428,832
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	433,043
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	424,709

MSD continue to seek reimbursement in line with the pembrolizumab plus lenvatinib label (i.e., all untreated advanced RCC patients) and caution against over-interpretation of subgroup results, noting the lower patient numbers and trial powering.

B3. Priority question: Please provide the following Kaplan-Meier analyses:

A. Time to death from any cause (OS)

B. PFS per Independent Radiologic Review (IIR) [FDA censoring rule]

C. PFS per Independent Radiologic Review (IIR) [EMA censoring rule]

D. Time to study treatment discontinuation (TTD)

    a. Please provide TTD data for lenvatinib, pembrolizumab and sunitinib separately

Please use the following specifications:

Trial data set: CLEAR

Format: Please present analysis outputs using the format used in the sample table below

Populations: (i) The ITT population of the CLEAR trial

(ii) The population with favourable risk including all patients lost to follow-up or withdrawing from the trial

(iii) The population with intermediate/poor risk including all patients lost to follow-up or withdrawing from the trial

Trial arms: (i) Lenvatinib plus pembrolizumab

(ii) Sunitinib

Response:

Please see .csv files that have been uploaded in addition to this response document, and a memo from MSD Biostatistics department.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B4. Please provide the data and details of the calculations used to estimate RDI for each of the treatments in the NICE scope. Please provide estimates by risk group.

Response:

The relative dose intensity (RDI) for pembrolizumab was calculated using data form KEYNOTE-581, according to the following formula: mean number of doses/(mean treatment duration days/days per treatment cycle) i.e., [redacted] Note one dose of pembrolizumab is administered per treatment cycle i.e., number of doses = number of treatment cycles.

The RDI for pembrolizumab per IMDC risk group were estimated using the formula above and are presented in **Table *2*** below. The results did not differ markedly by risk group.

Table 2: Pembrolizumab relative dose intensity according to IMDC risk group

	Fav	Int	Poor	Int+Poor	ITT
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Days of treatment duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean dose number administered	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup-specific RDI data was not available for the comparators, so the ITT RDI data was used across all comparators for consistency, and is assumed to be representative of all patients, irrespective of IMDC risk group.

For sunitinib, the RDI (83.2%) was reported in the trial pivotal publication[4]. Data for other non-trial comparators reflected those reported in their relevant appraisals, as outlined below. Details of the calculations were unavailable, so the data submitted as part of the NICE TA was assumed to have been subject to validation by the relevant ERG/Technical team.

- Pazopanib = 86.0% (TA215)
- Tivozanib = 94.0% (TA512)
- Cabozantinib = 94.3% (TA542)

B5. Please provide the details of the subsequent anticancer therapies received by patients in the CLEAR trial by treatment arm. Please provide estimates by risk group. [Note: during the clarification call on Monday December 06 2021, this request was clarified to include favourable risk patients only]

Response:

The details of the subsequent anticancer therapies received by patients in the CLEAR trial by treatment arm for favourable risk group are provided below. For the ITT and intermediate + poor risk groups details of the subsequent anticancer therapies are provided in the appendix N of the submission.

Table 3: Duration of Subsequent Oncologic Therapies (Days) after Discontinuing from Study Treatment Subpopulation of Participants with IMDC Risk Favourable Safety Analysis Set

	LENVATINIB + PEMBROLIZUMAB		SUNITINIB		Pooled	
	(N=109)		(N=117)		(N=226)	
	n (%)	Mean (SE)	n (%)	Mean (SE)	n (%)	Mean (SE)
With one or more Subsequent Oncologic Therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First Subsequent Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AXITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMS 986205	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CABOZANTINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CIFORADENANT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DURVALUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPILIMUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LENVATINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAVOLITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SORAFENIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUNITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEMSIROLIMUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TREMELIMUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second Subsequent Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AXITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CABOZANTINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CEMIPLIMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IBRUTINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPILIMUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LENVATINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAZOPANIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SORAFENIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Third Subsequent Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AXITINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CABOZANTINIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fourth Subsequent Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EVEROLIMUS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent therapy duration is defined as the days from start date of the treatment until the stop date of treatment, or until censoring date of overall survival if the stop date is not available.
Every subject is counted a single time for each applicable row and column
Database Cutoff Date: 28AUG2020

Section C: Textual clarification and additional points

C1. Please provide the October 2021 Advisory Board report (data on file) (reference 54 in the CS).

Response:

Upon revisiting the terms of the agreement with the clinicians who participated in the Advisory Board, MSD are not in a position to share the report of the discussions. The clinicians participated on the terms that the content would be used for internal purposes only, and their details and statements cannot be shared externally without their explicit consent. MSD remain of the position that the statements made in the dossier are true and relevant. However, MSD understand that the Data on File reference is regarded as unverifiable.

Additional request received during clarification call on Monday December 06 2021: *please supply utility values estimated by subgroup.*

Response:

The utility values for the time-to-death approach (base case) and health state-based approach (scenario analysis) are presented in Table 4 and Table 5 below. The poor risk subgroup was deemed to have too low a sample size (n=33) for meaningful conclusions to be drawn, so the values for these patients were pooled with the intermediate risk patients.

Table 4: Time-to-death utility values according to IMDC risk subgroup (base case)

Time-to-Death Utility Values						
TTD (days)	**360+ Days**	**270 - 359 Days**	**180 - 269 Days**	**90 - 179 Days**	**30 - 89 Days**	**0 - 29 Days**
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fav	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Int+Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Health state utility values according to IMDC risk subgroup (scenario analysis)

Health state	ITT	Fav	Int+Poor
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]

Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]
Progressed (on treatment)	[redacted]	[redacted]	[redacted]
Progressed (off treatment)	[redacted]	[redacted]	[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

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

MSD response to additional clarification questions

January 2022

File name	Version	Contains confidential information	Date
MSD response to additional clarification questions [ACIC]	Final	Yes	10/01/2022

Please provide utility estimates for the intermediate/poor risk group and the favourable risk group of patients.

MSD response:

The utility values for the time-to-death approach (base case) and health state-based approach (scenario analysis) are presented in Table 1 and Table 2 below.

Table 1: Time-to-death utility values according to IMDC risk subgroup (base case)

Time-to-Death Utility Values						
TTD (days)	**360+ Days**	**270 - 359 Days**	**180 - 269 Days**	**90 - 179 Days**	**30 - 89 Days**	**0 - 29 Days**
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fav	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Int+Poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Health state utility values according to IMDC risk subgroup (scenario analysis)

Health state	ITT	Fav	Int+Poor
Pre-progression (on treatment)	[redacted]	[redacted]	[redacted]
Pre-progression (off treatment)	[redacted]	[redacted]	[redacted]
Progressed (on treatment)	[redacted]	[redacted]	[redacted]
Progressed (off treatment)	[redacted]	[redacted]	[redacted]

Please include the utility values by risk group into your cost effectiveness estimates for lenvatinib plus pembrolizumab versus all relevant comparators.

MSD confirm that the cost effectiveness estimates provided by risk group use the relevant utility values presented in the tables above. Therefore, the results for the ITT population and intermediate + poor risk subgroup provided in the Company Submission, and the results for the favourable risk subgroup provided as part of the clarification questions response, serve as responses to this question. This can be verified in the model versions provided; changing the population setting in the Controls sheet will produce the utility values estimated in the Utilities sheet that are reported in the tables above.

The ERG is grateful for the cost-effectiveness results for the favourable risk group but have requested two additional documents:

1. A version of the model in Excel –

   MSD Response: This model version has been provided on December 23rd 2021.

2. Supporting documentation for the favourable risk population to outline the parameters and assumptions used in the model with accompanying justification i.e., in narrative form, in the same way as the other populations modelling is described within the submission.

MSD Response:

As with the ITT population, compliance with the proportional hazards assumption (i.e., that the treatment effect is proportional for all time points between the treatment arms) was investigated in the favourable risk subgroup of patients. The log-cumulative hazards plot presented in Figure 1 below suggests that the assumption does not hold over the full time period, as indicated by the non-parallel and intersecting lines. This suggests that the instantaneous mortality risk varies over time inconsistently between the treatment arms.

Figure 1. Cumulative hazards and log-cumulative hazards plots (Overall Survival, Updated Analysis); favourable risk subgroup

Abbreviations: OS, overall survival
Key: Cumulative hazards (left) and log-cumulative hazards (right) of overall survival over time between pembrolizumab plus lenvatinib versus sunitinib; favourable risk subgroup

Furthermore, the Schoenfeld residual plot presented in Figure 2 suggests that the relative hazards are likely to vary over time, which also indicates the proportional hazards assumption is not likely to hold. Therefore, as with the ITT population, parametric curves have been fitted independently for each treatment arm in this subgroup.

Figure 2. Kaplan-Meier graph and Schoenfeld residual plot (Overall Survival, Updated analysis); favourable risk subgroup

Note: P-value in this figure is corrected to p = 0.1546

Sunitinib OS

As with the overall population, survival of patients receiving sunitinib in KEYNOTE-581 appears superior among the favourable risk patients, relative to external references. The 2-year survival rate of favourable risk patients in KEYNOTE-581 (approximately 87%) exceeds that reported in the study by Savard et al[1]; 80.7%. The differential administration of subsequent therapies between treatment arms may have played a role in the improved efficacy in this subgroup. Over twice the proportion of sunitinib favourable risk patients received a subsequent treatment compared with pembrolizumab + lenvatinib (vs.), an even greater differential than in the

overall population. Furthermore, [redacted] received nivolumab as a second-line treatment, the clinical profile of which is expected to contribute to longer OS, compared to [redacted].

The same standard independent parametric models as for the overall population were fitted to the observed survival data for each favourable risk treatment arm of the KEYNOTE-581 trial. The longer-term survival estimates with all distributions is presented in Figure 3 below. The associated statistical goodness-of-fit measures are presented in Table 3 and the predicted 5-, 10-, and 20-year survival probabilities for each distribution are presented in Table 4.

Figure 3. Long-term sunitinib survival estimates; favourable risk subgroup

[redacted]

Table 3. Statistical goodness-of-fit measures for sunitinib OS curves; favourable risk subgroup

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

Table 4. Predicted 5-, 10- and 20-year survival for sunitinib fitted OS curves; favourable risk subgroup

Distribution	5-year OS	10-year OS	20-year OS
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival

All of the fitted distributions show an estimated 5-year survival probability that is [redacted] than has been observed in a historical trial[1] (49.22%), so for clinical plausibility the most optimistic estimates (those of Exponential, Log-normal, log-logistic, generalized gamma) were excluded from the base case. Furthermore, it is considered plausible that certain favourable risk advanced patients can survive for up to 20 years with sunitinib treatment. Hence, the Gompertz distribution, which [redacted], was also excluded. This left a choice between the Gamma and Weibull distributions as base case candidates.

Pembrolizumab plus lenvatinib OS

The same standard survival distributions have been fitted to the survival data for the favourable risk patients who received pembrolizumab plus lenvatinib within the KEYNOTE-581 trial. A graph showing the longer-term survival estimates per fitted survival curves for patients receiving pembrolizumab plus lenvatinib is presented in Figure 4. Statistical goodness-of-fit measures are presented in Table 5. The predicted 5-, 10-, and 20-year survival probabilities for each distribution are presented in Table 6.

Figure 4. Long-term pembrolizumab + lenvatinib survival estimates; favourable risk subgroup

[redacted]

Table 5. Statistical goodness-of-fit measures for pembrolizumab + lenvatinib OS curves; favourable risk subgroup

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

Table 6. Predicted 5-, 10- and 20-year survival for pembrolizumab + lenvatinib fitted OS curves; favourable risk subgroup

Distribution	5-year OS	10-year OS	20-year OS
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival

Consideration was given to clinical plausibility when selecting the base case choice of distribution for the pembrolizumab + lenvatinib arm in the favourable risk subgroup, including the relative survival compared to the sunitinib arm. The 2-year survival rate observed in the KEYNOTE-581 trial for this arm was approximately 91% (i.e., superior to that of sunitinib). As with the overall population, low number of events and a high level of censoring drives uncertainty in the extrapolations, but MSD believe that a base case analysis where the addition of an immunotherapy such as pembrolizumab to a TKI results in substantially reduced survival relative to TKI monotherapy lacks clinical plausibility. As presented previously, the most suitable candidates for the sunitinib choice of distribution predict 5-year OS of approximately [redacted] and the only distribution which predicts a similar OS rate at this time point is the exponential, which MSD

consider to be a plausible predictor of the pembrolizumab + lenvatinib OS and aligns with the base case survival curve for the overall population.

Pazopanib and tivozanib OS

As for the overall population, OS for pazopanib and tivozanib was assumed equal to sunitinib, therefore a hazard ratio of 1 was applied for all time points, with sunitinib acting as the reference arm.

Progression-free survival (PFS)

As for the ITT population, compliance with the proportional hazards assumption was investigated in the favourable risk subgroup of patients, and based on the log-cumulative hazard plots (Figure 5) and Schoenfeld Residual plot (Figure 6), the assumption was considered to not hold. Therefore, parametric models without treatment effect parameters were explored independently for the pembrolizumab + lenvatinib and sunitinib treatment arms.

Figure 5. Cumulative hazards and log-cumulative hazards plots (Progression-free Survival, IA3); favourable risk subgroup

Abbreviations: OS, overall survival
Key: Cumulative hazards (left) and log-cumulative hazards (right) of progression-free survival over time between pembrolizumab plus lenvatinib versus sunitinib; favourable risk subgroup

Figure 6. Kaplan-Meier graph and Schoenfeld residual plot (Progression-free Survival, IA3); favourable risk subgroup

Note: P-value in this figure is corrected to p = 0.4992

Sunitinib PFS

The standard survival functions were fitted to the PFS data for patients receiving sunitinib from the KEYNOTE-581 trial. Plots of the fitted survival curves are presented in Figure 7. The associated statistical goodness-of-fit criteria are presented in Table 7.

Figure 7. Sunitinib PFS fitted survival curves; favourable risk subgroup

Table 7. Statistical goodness-of-fit criteria for Sunitinib PFS data; favourable risk subgroup

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma[†]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Given the maturity of the PFS dataset, comparisons between the observed trial outcome and that predicted by the model were made to investigate the clinical plausibility of the modelled outcomes for the favourable risk patients, as well as consideration of the goodness-of-fit. When the model employs the log-normal distribution (i.e., the best fitting), it estimates median PFS of [redacted] for the sunitinib arm in this subgroup. This aligns most closely with the favourable risk median PFS from KEYNOTE-581 i.e., 12.9 months.

Pembrolizumab plus lenvatinib PFS

The standard survival functions were fitted to the PFS data for pembrolizumab plus lenvatinib patients in the KEYNOTE-581 study. Plots of the fitted survival curves are presented in Figure 8. The associated statistical goodness-of-fit criteria are presented in Table 8.

Figure 8. Pembrolizumab + lenvatinib PFS fitted survival curves; favourable risk subgroup

[redacted]

Table 8. Statistical goodness-of-fit criteria for pembrolizumab + lenvatinib PFS data; favourable risk subgroup

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion		

Similar consideration regarding clinical plausibility of the model outcomes compared to those observed in KEYNOTE-581 was made for the pembrolizumab + lenvatinib arm. The median PFS for the favourable risk subgroup in the trial (28.1 months) was most closely replicated in modelled median PFS by the generalized gamma distribution i.e., [redacted]). The distribution also exhibits a good statistical fit, with AIC/BIC scores forming a narrow range across the models.

Pazopanib and tivozanib PFS

As for the overall population, PFS for pazopanib and tivozanib was assumed equal to sunitinib, therefore a hazard ratio of 1.0 was applied to the sunitinib arm for all time points.

Time to treatment discontinuation

Time-on-treatment (TOT) (or time to discontinuation (TTD)) data was recorded as part of the KEYNOTE-581 study for pembrolizumab and lenvatinib separately.

As for the overall population, pembrolizumab KM data is used directly to model TTD without the need for parametric extrapolation. This is due to the maturity of the pembrolizumab TTD data and the 2-year stopping rule, which survival models struggle to appropriately account for due to the sudden change in the shape of the curve at the point of the stopping rule.

Parametric models were explored for lenvatinib and sunitinib. The standard survival functions were fitted to the TTD data for each arm. The associated statistical goodness-of-fit criteria are presented in Table 9 and Table 10.

Table 9. Lenvatinib TTD AIC/BIC; favourable risk subgroup

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table 10. Sunitinib TTD AIC/BIC; favourable risk subgroup

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gamma†	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

As for the overall population, given the maturity of the TTD data, the curve selection is based on visual inspection and statistical goodness-of-fit to the data (AIC). For both the lenvatinib and sunitinib treatment arms, the exponential distribution was selected.

A summary of the selected TTD data for each treatment arm in the favourable risk subgroup is presented in Figure 9. The selected curve for pembrolizumab is the KM combined with the two-year stopping rule. For both lenvatinib and sunitinib treatment arms, the exponential distribution was selected. Time-on-treatment equivalence between sunitinib and pazopanib/tivozanib is assumed in line with the ERG preference in TA581[2].

Figure 9. TTD extrapolations for Pembrolizumab, Lenvatinib and Sunitinib independently; favourable risk subgroup

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation
Key: Selected time to treatment discontinuation extrapolation for each treatment arm, compared to general population.

Summary of favourable risk subgroup analysis survival inputs

Table 11. Summary of favourable risk subgroup analysis survival inputs

Parameter	Pembrolizumab + lenvatinib	Sunitinib	Pazopanib, Tivozanib
Curve fitting	Curves were fitted independently for each treatment arm		
OS distribution	Exponential	Gamma or Weibull	Hazard ratio = 1 vs. sunitinib for all time points
PFS distribution	Generalized gamma	Log-normal	Hazard ratio = 1 vs. sunitinib for all time points
TTD distribution	Exponential	Exponential	Hazard ratio = 1 vs. sunitinib for all time points

Abbreviations: OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Summary of favourable risk subgroup cost-effectiveness analysis results

As discussed above, MSD consider the Gamma and Weibull distributions to be base case candidates for the extrapolation of sunitinib OS in favourable risk patients, based on an assessment of clinical plausibility. Results for both scenarios are presented in the tables below, using list prices of all treatments. Please note the results with the Gamma distribution have been updated from the Clarification Questions response in December 2021, following additional quality control. The results were estimated using the model version shared in December 2021.

Table 12. Cost-effectiveness results for favourable risk subgroup (list price) – scenario with Gamma distribution for sunitinib OS

	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Pembrolizumab + Lenvatinib	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	354,839
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	359,052
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	350,580

Table 13. Cost-effectiveness results for favourable risk subgroup (list price) – scenario with Weibull distribution for sunitinib OS

	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Pembrolizumab + Lenvatinib	[redacted]	[redacted]			
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	225,227
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	227,898

Tivozanib		[redacted]			[redacted]			[redacted]			[redacted]	222,527

MSD seek reimbursement in line with the pembrolizumab plus lenvatinib marketing authorisation (i.e., all untreated advanced RCC patients). MSD note that the results of subgroup analyses should be interpreted with caution because of the lower patient numbers in both treatment arms and lack of trial powering for the subgroup analyses.

References:

1. Savard M-F, Wells JC, Graham J, Dudani S, Steinharter JA, McGregor BA, et al. Real-World Assessment of Clinical Outcomes Among First-Line Sunitinib Patients with Clear Cell Metastatic Renal Cell Carcinoma (mRCC) by the International mRCC Database Consortium Risk Group. Oncologist. 2020 May;25(5):422–30
2. NICE. TA581 | Recommendations | Nivolumab with ipilimumab for untreated advanced renal cell carcinoma | Guidance | NICE [Internet]. NICE. Available from: https://www.nice.org.uk/guidance/ta581/chapter/1-Recommendations

NICE National Institute for Health and Care Excellence

Patient expert statement

NICE MTA Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma - ID3760

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Action Kidney Cancer**

2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Action Kidney Cancer
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Pre diagnosis is difficult – often you feel unwell, symptoms are common things that you could put down to other more common health issues. Until the stage where you start to present more serious issues such as chronic abdominal pain, sickness, confusion, brain-fog etc. Post diagnosis chronic fatigue is common and seems a very unsupported aspect from the medical profession. I suffer with tiredness too. Mental Health challenges worries of recurrence, anxiety around annual check-ups and scan results etc. As a sufferer of RCC but also having previously cared for my father who had the condition, the lack of information available around treatment options is difficult. Not knowing what the implications or side effects might be. Those things stop a supporting discussion happening with the diagnosed person, to then decide on actions for treatment. There is also a lack of moral support and structured support for carers who often have to find their own way through supporting their loved ones.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Generally I think the overall aspects of treatments from a patient perspective is things have improved, I know personally that in the past 8 years the options since my father's diagnosis had improved. Plus, since my own diagnosis 5 years ago, more lines of treatment and different options are now available. The difficult thing as a patient is working out what options are available and in what steps you can take for the different lines of treatment. Taking one drug may preclude you from taking another drug of choice for the next line of treatment. That's a crucial thing to understand as a patient.
10. Is there an unmet need for patients with this condition?	The critical issue for me is screening and possible genetic links for patients with a family history of cancer and/or Kidney Cancer.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Technology makes it easier to keep in touch, peer support, professional support etc. Advances in operation such as partial and full robotic nephrectomy was helpful and meant a shorter recovery period for me personally.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	It doesn't suit everyone and lots of older patients struggle to keep up with the technology advances.
Patient population	
13. Are there any groups of patients who might benefit	I think if we were to enhance technology it would be to generate some kind of treatment pathway for the cancer stages and map that out so patients can see what their options are and what to expect and

more or less from the technology than others? If so, please describe them and explain why.	when. There are so many options and choices at each stage which impact on future stages it's important to understand that from Day 1. I'm not certain we have that clarity as patients and it's very difficult to understand the options being given to you verbally when often you are reeling from the diagnosis and trying to process a lot of detail and information. It's very stressful with heightened levels of anxiety and mental health challenges that I just don't think the medics appreciate enough.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	I think when agreeing to provide a new combination, we have to give thought to access for all. Postcode lottery with commissioning providers issues need to be considered. Everyone should be able to access these combinations regardless of where they are in the country.
Other issues	
15. Are there any other issues that you would like the committee to consider?	None
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • We have to consider better the position of individuals diagnosed and the mental and physical strain that has on a patient	

- Stages of cancer are complex and treatment options are varied and often more complex. It's imperative that we find a way to explain decision making processes and the impact these can have on future treatment options. If you make a choice at any stage what do this open doors to or close doors to in future drug choice wise.
- Have to ensure that any new choices are equally available to all, regardless of localities and provider/commissioning arrangements.
- Any technology enhancements to help with patient choice are developed sympathetically and collaboratively to help decision making.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

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

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

About you and your organisation

Your name: Sharon Deveson Kell

Name of your organisation: Kidney Cancer Support Network

Your position in the organisation: Medical Affairs

Brief description of the organisation:

Kidney Cancer Support Network (KCSN) was founded in 2006 by cancer patients/survivors Rose Woodward and Julia Black, who started by providing practical and bespoke support to individual patients for access to life-extending cancer drugs to treat metastatic kidney cancer.

Empowering patients to take an active role in their own health care, and in decisions affecting the choice, provision, and quality of cancer services throughout the UK, remains the top priority for KCSN. Over the years, KCSN has grown considerably, with a membership of over 1400 kidney cancer patients and carers on its confidential community forum. In addition, our website regularly has over 300 visits per day from people looking for information about kidney cancer, advice, and support.

KCSN is unique; originally it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Although KCSN remains patient-led, the group is now a registered charity, which enables it to better meet the growing needs of the kidney cancer community in the UK.

Before the COVID-19 pandemic, funding came from trusts, foundations, and the pharmaceutical industry (around 55%), as well as fundraising activities/events organised by the public and kidney cancer community (45%). Since the pandemic, the latter has dropped off by almost 100%.

Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?

If so, please state the name of manufacturer, amount, and purpose of funding.

Yes, we have received £15,000 from Merck Sharp and Dohme (MSD) towards our multi-funded community outreach programme consisting of clinician webinars, a community map on our website, and regular patient and carer Click & Chat sessions via Zoom. MSD were not involved in the planning, production, or implementation of the project.

We have also received £4,725 from Eisai towards our multi-funded 2021 World Kidney Cancer Day campaign to raise awareness of the psychosocial issues facing kidney cancer patients. Again, Eisai were not involved with the planning or execution of this campaign.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

KCSN is a patient-led kidney cancer charity with the largest and most active patient and carer membership across the UK. As such, we feel we are in the strongest position to feedback how metastatic renal cell carcinoma (RCC) affects the day-to-day lives of people living with this disease.

Between 2016-2018, there were around 13,300 new cases of kidney cancer diagnosed annually in the UK (36 cases diagnosed every day) and kidney cancer is the seventh most common cancer affecting British people. Kidney cancer accounts for 4% of all new UK cancer cases (2016-2018). In 2016-2018, nearly 5,000 people died from the disease and about a third of kidney cancer patients were diagnosed with late-stage disease. In these cases, it is estimated that only 12% of people will survive for five years or more (Cancer Research UK). It is difficult to remain positive in the face of figures like this.

Metastatic RCC is a devastating disease and is currently incurable. The majority of metastatic RCC patients are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings enormous financial pressures for the patient and their family (and additional costs to the state), and can precipitate psychological problems, depression, loss of confidence and self-worth.

Patients may suffer constant pain from metastatic tumours in the brain, bones, lungs, liver, and other rarer sites. Patients with bone metastases are at risk of bone breaks and spinal cord compression. Metastases in the lungs can lead to breathlessness, and persistent coughing. Spread of the cancer to the brain can lead to severe and debilitating headaches, confusion and, in some cases, paralysis. Kidney function is often compromised, and patients find daily living difficult, regularly needing periods of rest during the day.

Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental as well as physical clinical situation. Sexual function is affected for both male and female patients, and family life suffers as a result.

The impact of a terminal diagnosis on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one is diagnosed with a terminal disease.

Patients diagnosed with hereditary kidney cancer or rare RCC subtypes currently have very limited treatment options, exacerbating feelings of depression, fear, and low self-worth.

Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period.

Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, a process of elimination is used to select the most effective treatment for individual patients. Clinicians in the UK should have the ability to choose the optimal treatments for individual patients from those available.

Without a choice of treatment alternatives, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue, and shortness-of-breath. Patients need to be able to choose their therapy to continue managing their disease, and to maintain quality of life. An increase in the choice of treatments will eventually lead to more personalised therapy, enabling patients and clinicians to tailor care plans to suite individual patient needs.

Kidney cancer cases are rising year-on-year and there is a need for first-line treatment with better overall survival rates than currently exist, especially for difficult-to-treat rare subtypes of RCC.

Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

For the majority of patients, the most important treatment outcome would be no evidence of disease, i.e., a potential cure for their kidney cancer. The hope of achieving this outcome spurs patients on to continue to take current medication, despite significant toxicity, and to search for alternative, more effective treatments that can extend overall survival. Failing to achieve no evidence of disease, tumour shrinkage or disease stability would be the next best outcome for patients.

In addition to treatment outcomes, quality of life is also an important consideration for many patients. Most patients would prefer a treatment that allows them to continue to lead as normal a life as possible, and to contribute both socially and economically to their communities:

> *"The extra years which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various ……. enterprises which I manage……. I'm making a hugely positive contribution to society, and the wider economy, and I wish to be able to carry on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities".*
>
> *"……has enabled me to enjoy every day, do 3- or 4-days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths……".*

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

The current treatment pathway for metastatic RCC is surgery (either radical or partial nephrectomy), followed by either sunitinib, pazopanib or tivozanib in the first-line setting, and lenvatinib, everolimus, cabozantinib or lenvatinib plus everolimus in the second-line setting, all of which are oral medicines and have similar modes of action (vascular endothelial growth factor receptor (VEGFR) inhibitors or mTOR inhibitors that block angiogenesis).

Nivolumab is also recommended for use within NHS England for second- or third-line treatment of metastatic RCC and is the first third-line treatment in use by the NHS. Nivolumab is an immune checkpoint inhibitor (anti-PD-1), which is administered as a biweekly intravenous infusion, requiring outpatient hospital treatment (chemotherapy chair resources), and the associated travel time and expense for the patient and carer.

We have extracted the following details from statements submitted to KCSN by patients living with metastatic RCC. Using currently available drugs, many patients suffer with the following side effects, all of which severely affect quality of life:

- Extreme fatigue
- Rash and itching
- Severe hand and foot syndrome which can leave patients unable to walk
- Intestinal problems (chronic diarrhoea)
- Pneumonitis requiring hospital treatment and cessation of treatment
- Severe mouth ulcers causing problems eating and drinking
- Nausea and vomiting, which can also cause problems taking the medication
- High blood pressure (hypertension)

- Hyperthyroidism
- Immune-related adverse events
- Muscle pain/joint pain
- Constipation
- Diarrhoea

All the above side effects require additional medicines to help patients manage the drugs and/or tumour pain, which require opioid prescriptions. Costs for additional medicines to mitigate the side effects of these therapies should be considered.

Other less serious side effects, which still affect the patient's quality of life, are headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment because of severe side effects. Patients are aware that these treatments are life-extending drugs, but they continue to look for drugs with different modes of action, which can give improved overall survival with better quality of life.

For patients that have been on standard first-line treatment with VEGFR inhibitors and experienced severe side effects, a combination of an immune checkpoint inhibitor with a VEGFR inhibitor could see a dramatic change in quality of life:

> *"No GI issues at all like I had with Sutent. Some knee and shoulder pain, but I am used to that from arthritis. Food is great, energy is great... I feel cured!! I realise I am not... but I never knew I had kidney cancer until they told me I did... and I never was sick. Start Sutent, and that is all I felt... sick. The surgery to remove my kidney, took me about 8 or 10 months to feel good again... brain met surgery... easy... my hard part was the Sutent side effects."*

> *"When I began treatment, I was in a state of helplessness. The abdominal tumour was located in such a position that it was growing so fast and caused so much pain I was unable to function. I was taking very high doses of Opiate pain medication with the result that I had no appetite and combined with side effects of Sutent my weight dropped to 139 pounds from 210 pounds. I lost large amounts of muscle. As a result, I was eventually confined to a wheelchair. I was unable to carry out even basic tasks and from being a very physically strong man who was very active and worked on my small ranch, I could do nothing for myself. I was very ill; I was told I had about 12 months to live. Tumours were growing aggressively."*

> *"I have had three infusions of Nivolumab, and I feel great. So far only minor SE. There was some shoulder, neck, and headaches at first, but none in the past week after my last infusion. I was on Votrient for almost year, and I am so glad to be rid of the GI side effects. My energy is good, my taste buds are back, no more tingling in hands and feet and my hair colour is slowly returning."*

Although less serious than some of the side effects to current first-line treatments available via NHS England, some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients. Some of the current first-line treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels.

From a psychological point of view, knowing that you have stage 4 cancer and knowing that there are possibly more effective treatments that you are not able to access is very difficult for patients. Carers seem to find this even harder, as they live with a guilt of not being able to do all they can for their loved one. Access to a choice of treatments in the first line would enable patients and their families to know that they had tried their best to beat the cancer, leading to better family relationships and a subsequent improvement in quality of life and wellbeing for the patient.

Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities. International discussion forums exist where patients talk to one another daily. Patients are more aware of the experiences of others, including their access to

innovative treatments, quality of life, and treatment successes and failures. News about lack of access to effective medicines ripples out to other patients and families, destroying their hope and positivity. Information about combination treatments is readily available to patients around the world on websites. Patients and clinicians expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so that patients in England have the same choices as patients in other countries and to improve outcomes.

What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

The lenvatinib plus pembrolizumab combination has been proven to be a clinically effective and well-tolerated treatment and has recently been approved by the US Food and Drug Administration (FDA) for the first-line treatment of people with advanced RCC.

Patients and carers are hopeful that the combination of an immune checkpoint inhibitor with a VEGFR inhibitor will improve response to treatment and subsequent survival, with minimal side effects and little impact on quality of life.

This is borne out by the results from the phase 3 CLEAR/KEYNOTE-581 trial with over 1000 patients, in which the lenvatinib plus pembrolizumab combination showed significant improvement in survival and response to treatment compared to the standard of care with sunitinib in patients with previously untreated advanced RCC.

Lenvatinib plus pembrolizumab reduced the risk of the cancer getting worse by 61%. Progression-free survival was an average of 23.9 months with the combination compared to 9.2 months for sunitinib. Overall survival data are not yet mature. The improvement in progression-free survival could be due to the additive effect of combining an immune checkpoint inhibitor with a VEGFR inhibitor, both of which have different modes of action to currently available treatments. Patients are optimistic that this synergistic effect will result in improved overall survival.

The combination reduced the risk of death by 34% versus sunitinib. Seventy-three percent (73%) of patients responded to treatment and their cancer reduced in size versus 36% with sunitinib. Sixteen percent (16%) of people had a complete response and 55% had a partial

response to treatment with lenvatinib plus pembrolizumab, compared to 4% and 32% for those on sunitinib.

In addition, the safety profile of the lenvatinib plus pembrolizumab combination is no worse than that for the individual drugs alone, and is, therefore, seen as being better tolerated than standard first line VEGFR inhibitor treatments, such as sunitinib and pazopanib. This results in improved quality of life to enable patients to contribute both socially and economically to society. Pembrolizumab can cause immune-related adverse events, which may be severe or fatal and can affect any organ or tissue in the body. However, if identified early they can be managed to ensure the safe use of pembrolizumab.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

The results from the phase 3 CLEAR/KEYNOTE-581 trial with 1069 people with advanced RCC showed significant improvement in survival and response to treatment with the lenvatinib plus pembrolizumab combination compared to the standard of care with sunitinib.

In addition to improvement in survival and response to treatment, patients on the lenvatinib plus pembrolizumab combination reported an improvement in health-related quality of life compared to standard treatment with a VEGFR inhibitor combination or sunitinib.

Patients were put into 3 groups: one group were treated with lenvatinib plus pembrolizumab, another group with lenvatinib plus everolimus, and the third group with sunitinib. Health-related quality of life was assess using three questionnaires, (FKSI-DRS, EORTC QLQ-C30, and EuroQoL EQ-5D-3L), at baseline, on day 1 of each treatment cycle and when the patient came off treatment. Only quality of life information from patients who had been treated with at least one dose of study medication was analysed.

Patients treated with the lenvatinib plus pembrolizumab combination had better physical function and cancer symptoms, such as fatigue, shortness of breath (dyspnoea), and constipation, as well as improved quality of life than patients on sunitinib, and sunitinib scored better than lenvatinib plus everolimus for overall health-related quality of life, pain, appetite loss, and diarrhoea.

The following quotes are taken from patients with advanced RCC being treated with an immune checkpoint inhibitor plus VEGFR inhibitor combination treatment:

> *"…….my experience of [this combination treatment] has been one of positives. I've been able to live pretty much normally, bearable side effects and until my heart issue (not cancer related we don't think) had shrinkage of 51% over a total of 8 months. Now hoping I can get back on it as post 6 months from my heart op [I have] only been on [pembrolizumab] which on its own has shown 17% growth. These new combinations are looking so promising."*
>
> *"I was first diagnosed with a tumour on my right kidney ……. in Summer 2016. A CT scan showed …. a 4cm tumour that went onto the Vena Cava…… opted for a full Nephrectomy…. October of the same year……March 2017 it was noted to be in my lymph nodes in the renal bed. I was offered standard TKI treatment……. but the Oncologist offered to refer me to a London cancer centre to explore more options. I volunteered for the trial ……. June 2017.*
>
> *"……. the side effects of the first [pembrolizumab infusion] was [sic] quite extreme with flu-like symptoms and aches pains, these soon wore off……. I only noted 2 minor side effects of the [VEGFR inhibitor] at this stage and this was spots in my hair and a slight sore throat. However, these were in no way affecting my quality of life. I actually went on a 3-week road trip around Europe without any problems.*
>
> *"September 2017 I was put up to 7mg twice a day. This caused some worse side effects with sore mouth, a worse sore throat, sore feet, and slight diarrhoea. Again,*

this did not affect my quality of life too much and I was put [up] to 10mg twice a day in Feb 2018. I have managed to stay on 10mg twice a day, but the side effects can be extreme. I have daily diarrhoea up to 5 times a day, this has led to other connected effects such as ……. haemorrhoids, my feet can be so sore that I cannot walk, I suffer with sore mouth at times, the most unusual side effect is that my muscles can get really tight and make my body ache. I have suffered with breathlessness, headaches, my thyroid has suffered, and I am now on 150mg of Thyroxine daily. However, I have managed to stay on 10mg twice a day and continue to work and lead a normal life (relatively). I don't really experience tiredness, but I have noticed my memory has suffered slightly.

"…….in the summer I have hardly any side effects, the diarrhoea remains but sore feet, mouth, spots in the hair etc. all clear up. As soon as it gets cold again and I come into contact with bugs and viruses the side effects seem to get worse again.

"The results have been great, so far! [The metastasis in the lymph nodes has reduced from 27mm to 5mm]."

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Metastatic RCC is a devastating disease and is currently incurable. The majority of metastatic RCC patients are forced to give up work because of the disease itself, and current treatments

are very debilitating. This brings enormous financial pressures for patients and their families, sometimes resulting in psychological problems, depression, loss of confidence and self-worth.

Immune checkpoint inhibitor treatments are administered as intravenous infusions, requiring regular trips to hospital and the use of chemotherapy chairs. Some patients may need to travel some distance to regional cancer centres, take time off work, or have a partner travel with them for treatment. The practicality of this is of concern to some patients and carers.

In addition, the side effects of both immunotherapies and VEGFR inhibitors are of particular concern to patients, especially if they impact quality of life. This is especially pertinent with immune-related adverse events from immunotherapies, which can be life-threatening, chronic, and sometimes difficult to treat.

Most side effects require additional medicines to help patients manage their treatment, adding to the cost of treatment overall.

Other less serious side effects can still affect the patient's quality of life, e.g., headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. Some patients find the changes to their appearance caused by these treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and singles people out as cancer patients. Some of the current first-line treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels.

In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment because of severe adverse events.

We understand that combination treatments are expensive, and we appreciate the budgetary constraints of the NHS. Nonetheless, NICE and the manufacturer need to work collaboratively to negotiate an acceptable patient access scheme to ensure RCC patients can benefit from this latest clinically effective drug combination.

Please list any concerns patients or carers have about the treatment(s) being appraised.

Pembrolizumab is given intravenously over 30 minutes every 3 weeks until disease progression or drug intolerance. This requires hospital visits every 3 weeks and the provision of chemotherapy chairs for the infusion. Lenvatinib is an oral drug, which can be taken at home. Standard first-line treatment with oral VEGFR inhibitors only require a monthly hospital visit to replenish supplies of medication.

Patients will typically be travelling some distance to a regional cancer centre for the pembrolizumab infusions and to collect lenvatinib supplies. Some patients may need to take time off work, or have a partner travel with them to treatments, the practical aspects of which can impact the quality of life of both patient and carer.

However, balanced against the extra travel and time is the improved side effect profile and enhanced quality of life. Most patients feel much better able to cope with life, and some return to work. Half a day in hospital is preferable to the debilitating side effects of VEGFR inhibitors.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

No

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

No

Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☐ Yes [x] No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes [x] No

If yes, please provide references to the relevant studies.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality,

ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

The lenvatinib plus pembrolizumab combination is not under consideration for the treatment of non-clear cell RCC, an area of significant unmet need. This puts patients with non-clear cell RCC at a disadvantage when it comes to treatment options.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐ Yes [x] No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Are there any other issues that you would like the Appraisal Committee to consider?

Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that these novel combinations are made available to patients in order that they have the best possible care. If these combinations are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. Poor UK survival rates might possibly be due to the restrictions in clinical choice brought about by UK regulatory authorities.

In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual

patients from those available, and without the lenvatinib plus pembrolizumab combination, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the first line, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.

Current first-line treatment options are not effective for everyone. Undue restrictions in accessing novel combination therapies would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.

Although unproven, the lenvatinib plus pembrolizumab combination could potentially be used for the treatment of patients with rare or hereditary (non-clear cell) subtypes of RCC where there is currently a significant unmet need for and effective and safe treatment strategy.

Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The lenvatinib plus pembrolizumab combination is safe and effective to use for the first-line treatment of people with advanced RCC, and has already been approved for use by the FDA in the USA
- The lenvatinib plus pembrolizumab combination is well tolerated, as well as proven to be more effective at extending progression-free survival and improving overall response rates compared to standard first-line treatment with sunitinib
- Adding the lenvatinib plus pembrolizumab combination as a choice in the first line enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life
- The extended progression-free survival and relative toxicity of the lenvatinib plus pembrolizumab combination enhances quality of life and enables patients to contribute socially and economically to society
- The lenvatinib plus pembrolizumab combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Paula Brown**
2. Are you (please tick all that	☐ a patient with the condition? Y ☐ a carer of a patient with the condition? N

apply):	☐ a patient organisation employee or volunteer? Y ☐ other (please specify):
3. Name of your nominating organisation	Kidney Cancer UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ I don't know Y
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.) I have not seen it

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition Y ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with stage 4 RCC in Nov 2018. I have extensive spread, especially through the bones of my spine & pelvis. Due to spinal mets I have had mobility problems including partial paralysis.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The range of treatment options is good, though some regimens cause a lot of side effects and reduce quality of life. Patients are often scared to reduce dosages (to reduce side effects) in case the drugs fail. Another problem is that treatments fail after just a few months in some cases, or never work at all. It's a source of great concern to patients that we only get 3 or 4 rounds of therapy on the NHS, so for every failure a "lifeline" is gone.

10. Is there an unmet need for patients with this condition?	We need drugs that have fewer side effects and offer longer term control of RCC. I believe this combination should not be restricted to previously untreated patients if it works well. It needs to be an option for those who have been previously treated as well.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	**The possibility of getting longer on a drug regimen before it fails. Also, that it will be more successful across the patient group, controlling cancer in more patients.**
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Younger, fitter patients may benefit more as they potentially have more years to live with RCC. Having effective treatments without severe side effects enables people to keep working while they are able. Also, people who are more mentally motivated to keep fit may benefit as while the cancer sleeps we can re-build ourselves physically. I have found that my body tries to heal around the tumours, even growing new bone in my spine. I was originally told I would be in a wheelchair permanently or only able to walk a few metres on crutches. My persistence at working on my mobility means that I have been able to derive greater benefits and quality of life during the time I have had stable.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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NICE National Institute for Health and Care Excellence

Patient expert statement

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Sophie Scott**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Kidney Cancer UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Being diagnosed with kidney cancer can be incredibly stressful for patients and their families, and the challenges they face greatly depend on the stage of their disease. Most people with kidney cancer will receive surgery at some point, which will require a period of recovery. There will be times when the patient and family/carers will be worried about the future and require information and guidance. Waiting for news, scans and procedures can be emotionally draining. Knowledge that there are a variety of treatment options available to them will give them some comfort. Dealing with side effects of drugs can be equally exhausting as the symptoms of the cancer, so finding the balance of treatment and quality of life that is right for each patient is important. According to our annual survey patients with kidney cancer reported

	feeling anxious, emotionally low, abandoned after surgery and scared about their cancer returning. Knowledge that there are a variety of treatment options available to them will give patients and their carers some hope and comfort. Patients reported having a range of symptoms from their cancer including fatigue, depression, weight loss, anorexia, anaemia and pain which varies in severity according to the stage of their disease, which can be disabling for many and distressing for both patients and carers. This can affect their life in many ways, they may need to take regular pain medication to control their pain, many people report having less energy to carry out their activities of daily living and have needed to take time off work. Side effects from treatment include fatigue, loss of appetite, nausea, night sweats and rashes, some even report being hospitalised with colitis or pneumonitis too. However, some people report that the drugs work for them and they have fewer side effects and they have no further disease spread which helps to improve their quality of life. Finding the balance of treatment and quality of life that is right for each patient is important.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The treatment and outcome are very much dependant on how early the kidney cancer has been caught. Ideally the tumour is of an early stage and is removed by surgery or cryotherapy and the patient enjoys a life after cancer. This would always be the preferred treatment. However, if the tumour has spread patients will rely on targeted therapies and immunotherapy treatments. Current drug treatments for kidney cancer are very limited in number and have plenty of side effects. Kidney Cancer UK feel that there are significant improvements that could be made in this area. A wider range of options with improved efficacy and fewer side effects. The most commonly used Tyrosine kinase inhibitors (Sunitinib and Pazopanib) act to extend life and in some cases they work very well and extend life for many years. For others, the extension of life is a matter of months. However, those months can be invaluable for individuals and their families. The introduction of Nivolumab as a NICE recommended drug was well received by patients and their families. Patients have reported back on how effective this drug has been for them, especially on how it improves their quality of life. I think that having combinations of treatments may give alternate options and even better results as a first line treatment. Giving alternate options for patients can be invaluable especially in an era where personalised medicine may be introduced. It may be found that Pembrolizumab and Lenvatanib combination therapy works for a set of patients where other treatments may fail. A multitude of treatment options is always desirable.
10. Is there an unmet need for patients with this condition?	Yes, there is an unmet need for treatment of advanced RCC, it would most certainly improve some outcomes in patients surviving kidney cancer and to be free of cancer for the foreseeable future. We understand that most drug treatments aim to extend the lives of people with kidney cancer and viewing kidney cancer as a chronic disease that can be lived with would be a desirable outcome. Tolerable side effects of a treatment are important if kidney cancer is to be viewed as a chronic disease and patients are to have a good quality of life.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Advantages of the treatment patients and their carers reported were; • Disease control with no metastatic progression • Prolonged survival rate • Reduction in cancer pain and other cancer symptoms • Improvement in their mental health knowing that their treatment is working • Quality of life- living longer and having more time with family and friends • Family and friends feel reassured that their loved one's treatment is working • Patients felt more in control of their lives on treatment • Some patients report that they feel more reassured taking IV treatment as they feel the drugs are more effective than tablets and like to have the extra monitoring in hospital and contact with medical staff
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Disadvantages of a treatment might include: • Poor disease control and metastatic progression • No difference in survival rate • Side effects such as fatigue, low mood, weight loss, poor appetite, urticaria, bone pain, elevated liver enzymes, and in rarer cases colitis and pneumonitis as reported by patients • The patients would be required to travel to hospital to receive their treatment frequently, it may be far for them and difficult if they have mobility problems or feel unwell

	• IV route of administration – It may be difficult to administer the treatment and distressing for patients who are hard to cannulate and who have needle phobia. • Difficult for carers watching loved ones suffer from side effects of the treatment
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with advanced kidney cancer are likely to require treatment to extend their life. Also, people who have failed prior systemic treatment are likely to need another treatment option.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Patients who have had failed treatments previously require more treatment options and patients with rarer types of RCC should be included.

Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Patients with advanced RCC have limited treatment options and require a variety of drug choices.
- Patients with rarer RCC tumours and those who require another treatment line should be considered.
- Pembrolizumab and Lenvatanib has an acceptable and improved side effect profile compared to other first line drugs, which could potentially improve patient's quality of life and life expectancy.
- In time there will be more development in immunotherapy treatments and there will be better outcomes in survival rates and a better quality of life for patients living with advanced RCC.
- How the treatment works varies for everyone. A particular group of people may respond really well to Pembrolizumab and Lenvatanib where other treatments may fail as a first line treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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