NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Contents:

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

Pre-meeting briefing

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Abbreviation	In full
AE	Adverse event
BSC	Best supportive care
CI	Confidence interval
CS	Company submission
DIC	Deviance information criterion
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERG	Evidence Review Group
FDA	Food and Drug Administration
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health related quality of life
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan-Meier
NMA	Network Meta-Analysis
mTOR	Mammalian Target of Rapamycin
ORR	Objective response rate
OS	Overall survival

Abbreviation	In full
PD-1	Programmed cell death protein 1
PH	Proportional hazards
PFS	Progression-free Survival
PMB	Pre Meeting Briefing
QALY	Quality-adjusted life year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
TA	Technology Appraisal
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
VEGF(R)	Vascular endothelial growth factor (receptor)

Disease background and management

Kidney cancer

- Seventh most common cancer in UK
- More common in men than women
- Five-year survival is 56%, varying with age
- 86% of renal cancers are renal cell carcinoma

Renal cell carcinoma

- Estimated 9,045 new diagnoses in England per year
- Disease is often locally advanced or metastatic at point of diagnosis
- Early stage disease can be treated surgically – half of patients who have surgical treatment will develop metastatic disease
- Overall survival for people with metastatic disease is 8 months to 3.6 years

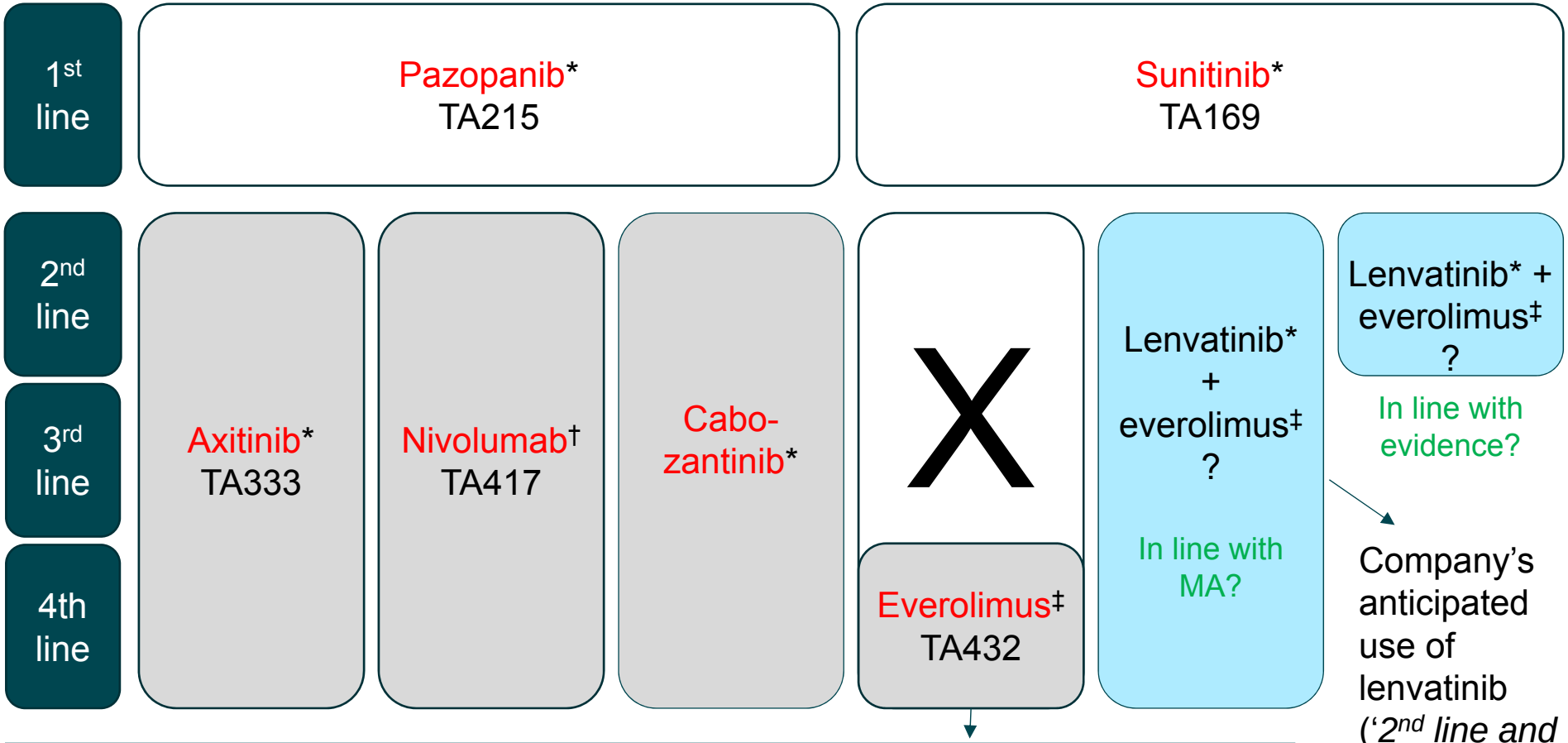
Current NICE guidance for advanced RCC

	Treatment	NICE recommendation
1st line	Sunitinib (TA169)	**Recommended: only if** person suitable for immunotherapy and ECOG performance status 0 or 1
	Pazopanib (TA215)	**Recommended: only if** ECOG performance status 0 or 1
	Bevacizumab, sorafenib, temsirolimus (TA178)	**Not recommended**
2nd and later lines	Axitinib (TA333)	**Recommended:** after failure of 1st-line tyrosine kinase inhibitor (TKI) or cytokine
	Nivolumab (TA417)	**Recommended:** previously treated advanced RCC
	Everolimus (TA432)	**Recommended:** when disease progressed during or after VEGF-targeted therapy
	Cabozantinib (FAD)	**Recommended:** after VEGF-targeted therapy
	Sorafenib, sunitinib (TA178)	**Not recommended**

Lenvatinib (Kisplyx®)

Marketing authorisation (granted August 2016)	Indicated in combination with everolimus for adults with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted therapy
Administration	Oral
Recommended dose	18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg of everolimus
Dosing frequency	Once daily
List price (excluding VAT)	• Lenvatinib: £1,437.00 for 4 mg and 10mg packs (30 capsules) • Everolimus: £2,250.00 for 5 mg pack (30 tablets) • Company is offering lenvatinib with a simple discount patient access scheme

Potential place of lenvatinib + everolimus in current treatment pathway



Recommended for advanced RCC that has progressed during or after treatment with VEGF-targeted therapy (i.e. 2nd or later line), but in clinical practice used as 4th line treatment based on clinical feedback during cabozantinib STA

*Oral tyrosine kinase (TKI) inhibitor
†Programmed cell death protein 1 (PD-1) inhibitor
‡Oral Mammalian target of rapamycin (mTOR) inhibitor

Decision problem (final scope)

Population	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy
Intervention	Lenvatinib in combination with everolimus
Comparators	• Axitinib • Nivolumab • Everolimus • Cabozantinib • Best supportive care (BSC)
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life
Subgroups	None

BSC was not considered as a comparator in the company submission

- ERG agrees with the company that BSC is a comparator of limited importance

Patient and professional feedback

- Impact of this disease on physical and mental health of patients as well as friends and family is significant
- Patient organisations note that there is a significant unmet need for second and third line therapies
- Aim of treatment is tumour reduction or stabilisation of disease while maximising quality of life
- Patients place significant value on having a choice of treatments
  - Particularly given the side effect profiles of the available drugs
- Lack of ability to target treatments means that there has to be a ‘trial and error’ approach to find the best option
- Noted that this combination has more side effects than the individual treatments but were considered manageable

Clinical-effectiveness evidence

Key clinical issues for consideration

- Does the committee consider the results of HOPE 205 valid/generalisable given its:
  - Open-label design and PFS assessed by unblinded assessors?
  - Small sample size?
  - Uncertainties around the observed efficacy and safety of lenvatinib combination therapy?
  - Comparator treatment of everolimus alone?
  - Patient population?
  - Better prognosis for the lenvatinib + everolimus group than for the everolimus group?
  - How reliable is the estimate of efficacy? Fractional polynomial curves showed a potential overestimate of PFS in the lenvatinib + everolimus group
- The evidence base is overwhelmingly 2nd-line treatment. Would lenvatinib + everolimus therapy be used only as 2nd-line or 3rd-line treatment?

Clinical trial evidence

1 key clinical trial: HOPE 205

<table>
<tr><th>Trial</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Outcomes</th></tr>
<tr><td rowspan="2">HOPE 205

Randomised, phase II, open-label, multicentre study (n=153)

11/35 UK sites</td><td rowspan="2">• ≥18 years
• Unresectable or advanced RCC, predominant clear cell RCC
• Only 1 prior VEGF-targeted therapy
• Disease progression on or within 9 months of stopping prior therapy
• ECOG performance status 0 or 1</td><td>• Lenvatinib 18 mg/day + everolimus 5 mg/day (n=51)
• Lenvatinib 24 mg/day (n=52) – not licensed</td><td>Everolimus 10 mg/day (n=50)</td><td rowspan="2">1°
• Investigator-assessed progression-free survival

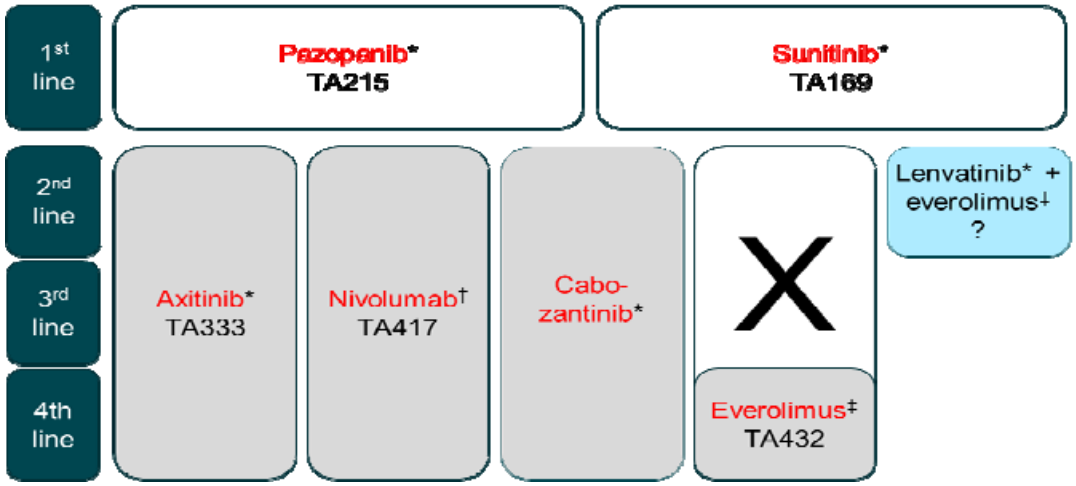
2°
• Overall survival
• Disease response (e.g. objective response rate)
• Tolerability and safety</td></tr>
<tr><td colspan="2">Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent</td></tr>
</table>

Source: Figure 17 of the company submission

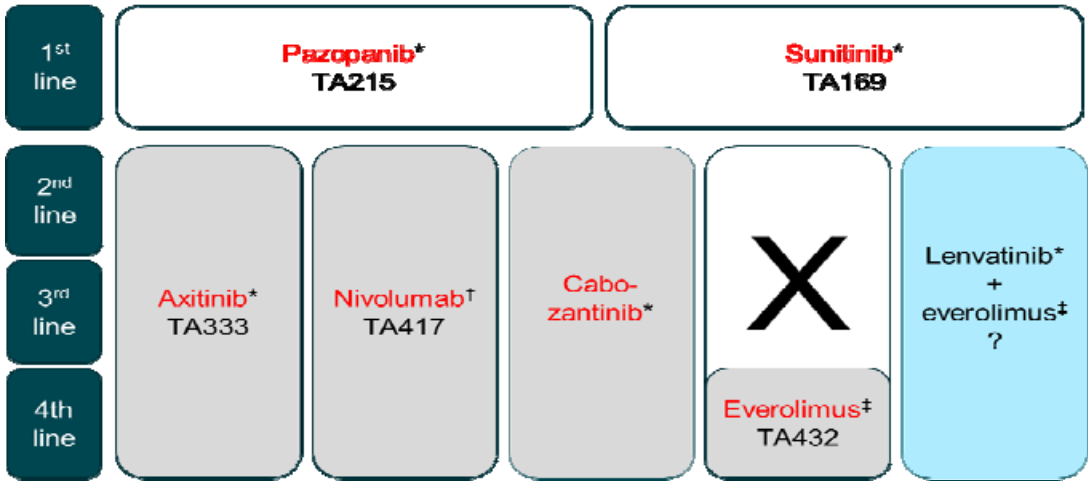
Evidence limited to 2nd-line treatment

Evidence and scope narrower than marketing authorisation

Position supported by clinical evidence and scope



Position suggested by marketing authorisation



ERG critique of trial design

- Small sample sizes means uncertainty around the observed efficacy and safety
- Open-label design introduces bias
  - PFS assessed by unblinded investigator
- Trial did not collect data on HRQoL

Baseline characteristics in HOPE 205 (1)

Baseline characteristic	Lenvatinib + everolimus (n=51)	Single-arm everolimus (n=50)
Age (years)	61 (44–79)	59 (37–77)
Sex		
Men	35 (69%)	38 (76%)
Women	16 (31%)	12 (24%)
ECOG Performance status		
0	27 (53%)	28 (56%)
1	24 (47%)	22 (44%)
Number of metastases		
1	18 (35%)	5 (10%)
2	15 (29%)	15 (30%)
≥3	18 (35%)	30 (60%)
Sites of metastasis		
Bone	12 (24%)	16 (32%)
Liver	10 (20%)	13 (26%)
Lung	27 (53%)	35 (70%)
Lymph nodes	25 (49%)	33 (66%)

Baseline characteristics in HOPE 205 (2)

Most patients had received either sunitinib (56-71%) or pazopanib (18-26%) as their 1st VEGF-targeted therapy
All patients had received only 1 prior therapy

Baseline characteristic	Lenvatinib + everolimus (n=51)	Everolimus only (n=50)
Previous nephrectomy†	44 (86%)	48 (96%)
Previous VEGF therapy‡		
Pazopanib	9 (18%)	13 (26%)
Sunitinib	36 (71%)	28 (56%)
Axitinib	1 (2%)	0
Bevacizumab	0	4 (8%)
Sorafenib	1 (2%)	2 (4%)
Tivozanib	3 (6%)	2 (4%)
Duration of previous VEGF therapy (months)	9.8 (2.0–66.2)	8.9 (1.6–57.8)
Previous checkpoint inhibitor therapy	1 (2%)	2 (4%)
Previous interferon therapy	4 (8%)	7 (14%)
Previous radiotherapy	6 (12%)	11 (22%)

1st line in NHS

ERG critique of participant flow and baseline characteristics

- Trial population is in line with final scope
- Baseline characteristics generally similar to population in clinical practice
  - However, patients may be healthier in the trial than in clinical practice
    - ECOG performance status limited to 0 or 1 in trial; more than 50% of patients had a status of 0
- Baseline characteristics generally well balanced between the trial arms
- Some differences potentially indicate a better prognosis for the lenvatinib + everolimus group
  - A smaller proportion of patients had >1 metastases
  - The duration of prior VEGF-targeted therapy was longer
  - More patients had complete or partial response to prior therapy

Median follow-up in HOPE 205

1 data cut for PFS, 3 data cuts for OS

Data cut	Description	Progression-free survival		Overall survival	
		Median follow-up (months)	*Events**	*Median follow-up (months)*	*Events**
Jun 2014	Protocol-specified primary analysis	**LEN+EVE 13.9** **EVE 17.5**	**62%**	LEN+EVE 18.5 EVE 16.5	45%
Dec 2014	Protocol-specified updated analysis	-	-	LEN+EVE 24.2 EVE 25.0	56%
Jul 2015	Analyses requested by regulators: • EMA: increase follow-up for OS • FDA: change calculation of stratification variables 2 analyses but same data-cut	-	-	**LEN+EVE 32.0** **EVE 32.7**	**68%**

Data-cut used for modelling

*Weighted average across the LEN+EVE and EVE groups

Source: Figure 29 of the company submission

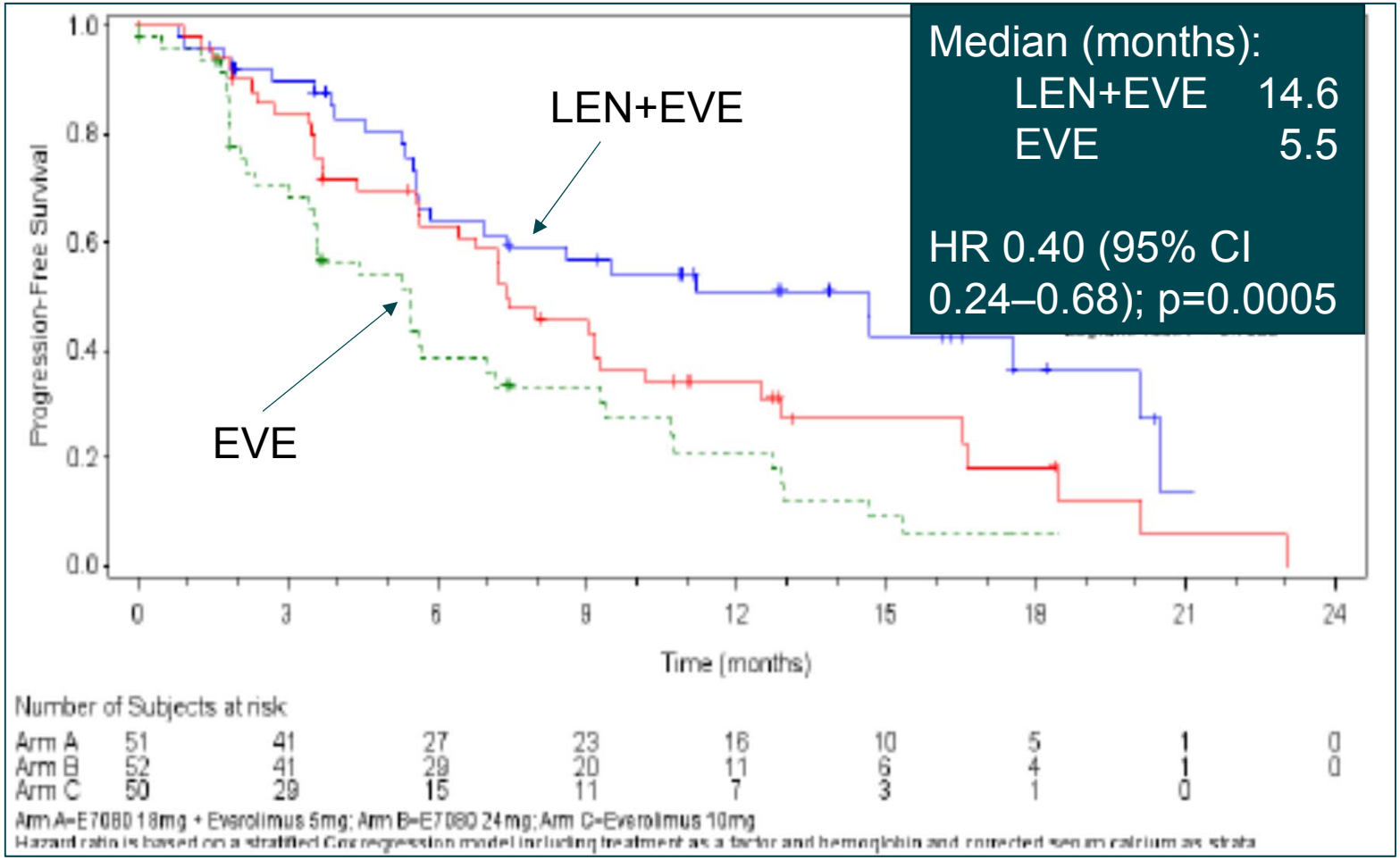
Summary of results across analyses

	Progression-free survival			Overall survival (July 2015 data-cut)		
	Diff. in median between LEN+EVE and EVE (months)	*HR (95% CI)*	*p*	*Diff. in median between LEN+EVE and EVE (months)*	*HR (95% CI)*	*p*
Primary (investigator)	9.1	0.40 (0.24–0.68)	0.0005	8.0	0.55 (0.30–1.01)	0.0623
Primary (independent review)	7.2	0.45 (0.26–0.79)	0.003			
Updated	-	-	-	10.1	0.51 (0.30–0.88)	0.02
EMA	-	-	-	10.1	0.59 (0.36–0.96)	0.06
FDA		0.37 (0.22– 0.62)	NR		0.67 (0.42–1.08)	NR

Source: Section A4, Clarification response

Investigator-assessed PFS (1° outcome)

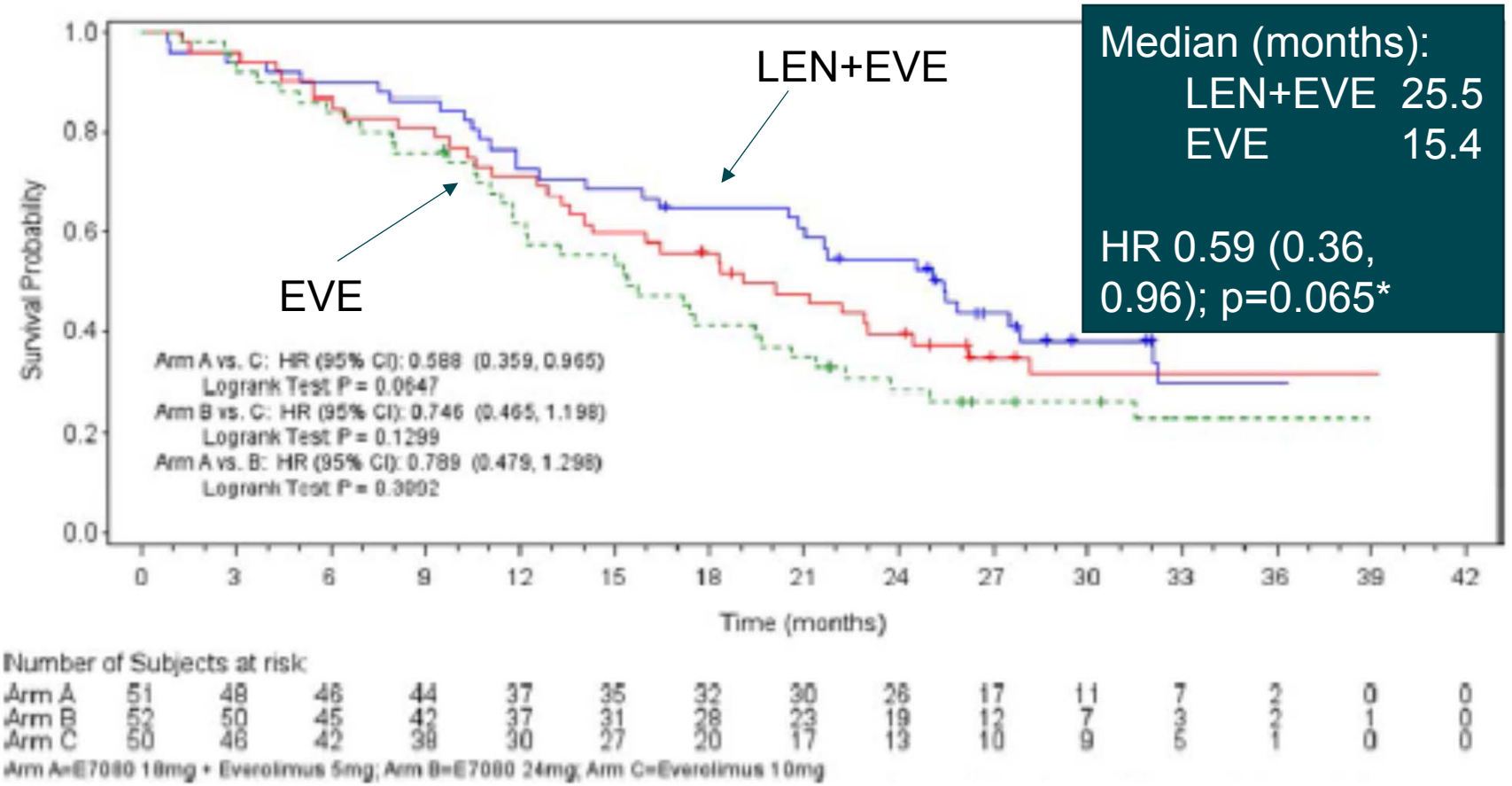
Lenvatinib plus everolimus significantly increases PFS



Source: Figure 24 of the company submission

Overall survival (July 2015 cut-off)

OS is statistically significantly longer for patients treated with lenvatinib combination therapy (95% CI does not cross 1)



*p-value for the log rank test did not reach statistical significance

Source: Figure 31 of the company submission

Adverse events

Serious AEs occurred at a slightly higher incidence in the combination group (54.9%) than in the everolimus group (42%)

- All patients in the trial had at least 1 Treatment Emergent Adverse Event (TEAE)
- *Serious AEs occurred at a slightly higher incidence in the combination group (54.9%) than in the everolimus group (42%)*
- Fatal AEs were rare; 1 patient died due to cerebral haemorrhage in the combination group (2.0%) and 2 patients in the everolimus group (respiratory failure and sepsis, 4.0%)
- The most frequently reported TEAEs (>30% of patients in either treatment group) in the combination group were diarrhoea (84.3%), decreased appetite (51.0%), fatigue (47.1%), vomiting (45.1%), nausea (41.2%), hypertension (41.2%), cough (37.3%), hypertriglyceridemia (35.3%), hypercholesterolemia (33.3%), and weight decreased (31.4%)
- *More patients treated with lenvatinib combination were reported to have grade 3 TEAEs than in the everolimus monotherapy group*

Adverse events (cont.)

Source: Table 22 of ERG report

No direct evidence comparing LEN+EVE with comparators available

Company performed indirect comparisons

	Original submission	Company's clarification
Method	Traditional indirect treatment comparison using everolimus as common comparator	Bayesian network meta-analysis (NMA) using fractional polynomials
Reference	Bucher et al. (1997)	Jansen et al. (2011)
Network	Includes all treatments separately	Simplified assuming everolimus = axitinib
Included trials	HOPE 205, AXIS, CHECKMATE-025, METEOR, RECORD-1, TARGET	HOPE 205 CHECKMATE-025 METEOR
Assumes proportional hazards?	Yes	No
Use in economic analyses	• Company base case	• ERG alternative base case and scenario analyses • Company scenario analysis

Company's original indirect treatment comparison

Original submission

- For PFS and OS, the company used the published HRs and associated 95% CI which requires the proportional hazards (PHs) assumption being fulfilled within trial and between trials

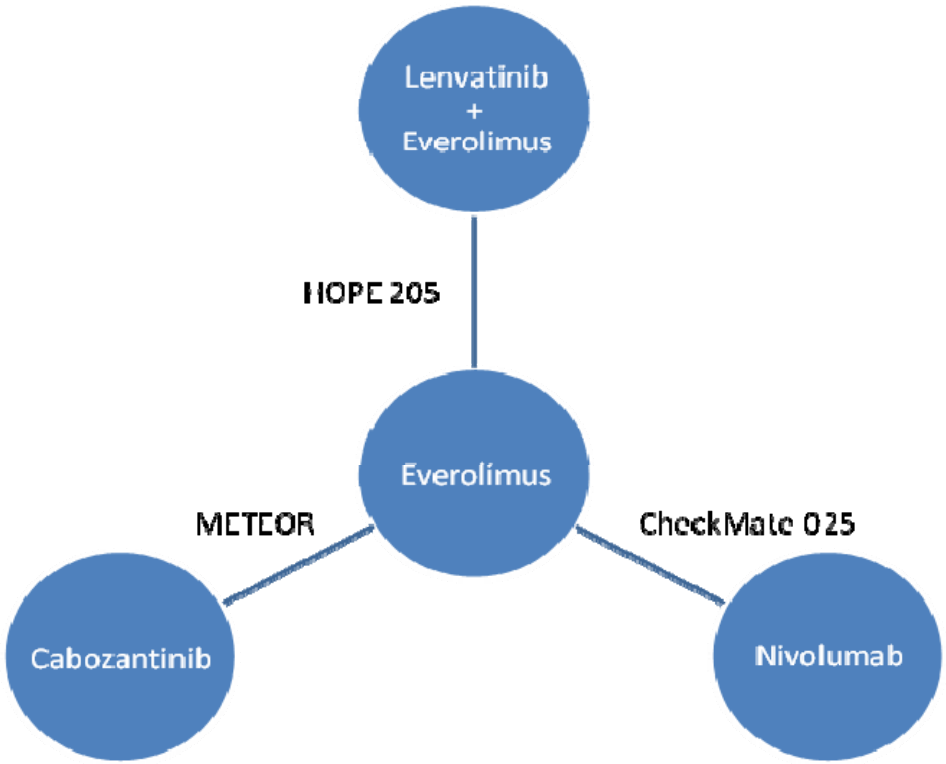
- ERG noted that CheckMate 025 and TARGET (for PFS and OS) and potentially METEOR (for PFS) did not show proportional hazards
- ERG considers it inappropriate for company to use methods for the indirect treatment comparison which relies on proportional hazards

This pre-meeting briefing therefore focuses on the alternative network meta-analysis using fractional polynomials presented by the company in response to the ERG's feedback at clarification stage.

Network meta-analysis using fractional polynomials

Response to clarification letter

- The efficacy of lenvatinib plus everolimus was compared with cabozantinib and nivolumab using a NMA with parametric fractional polynomial survival functions



- Company digitally extracted survival data from the relevant KM curves for CheckMate 025 and METEOR
- This included, for each treatment, survival time, censored events, total number of events, and numbers at risk
- Only fixed-effect model

Source: Figure 12 of ERG report

Summary of trials included in the NMA

Study	Study design	Treatments	N	Prior therapies permitted
CheckMate 025	Phase III open label RCT	Nivolumab	410	1 or 2 prior antiangiogenic; no prior mTORi permitted
		Everolimus	411	
HOPE 205	Phase II open label RCT	Lenvatinib combination therapy	51	1 prior TKI; other prior therapies permitted
		Everolimus	50	
METEOR	Phase III open label RCT	Cabo-zantinib	330	1 or more prior TKIs; no prior mTORi permitted
		Everolimus	328	

Abbreviations: RCT, randomised control trials; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamaycin inhibitor

Source: Table 23 ERG report

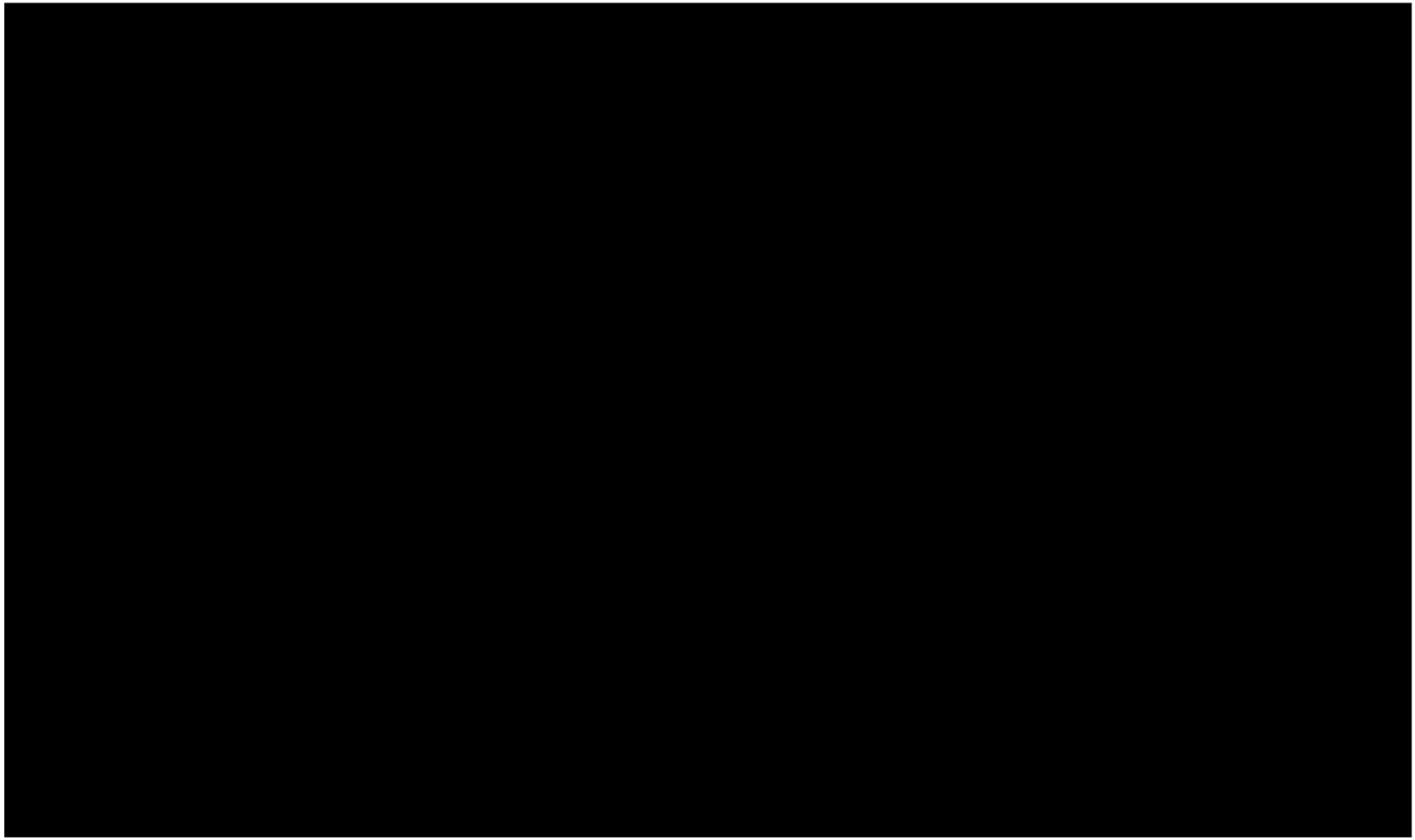
Clinical effectiveness results – PFS (investigator)

Hazard ratio over time

Source: Late clarification response, Appendix, Figure 2.3.2

Clinical effectiveness results – PFS (investigator)

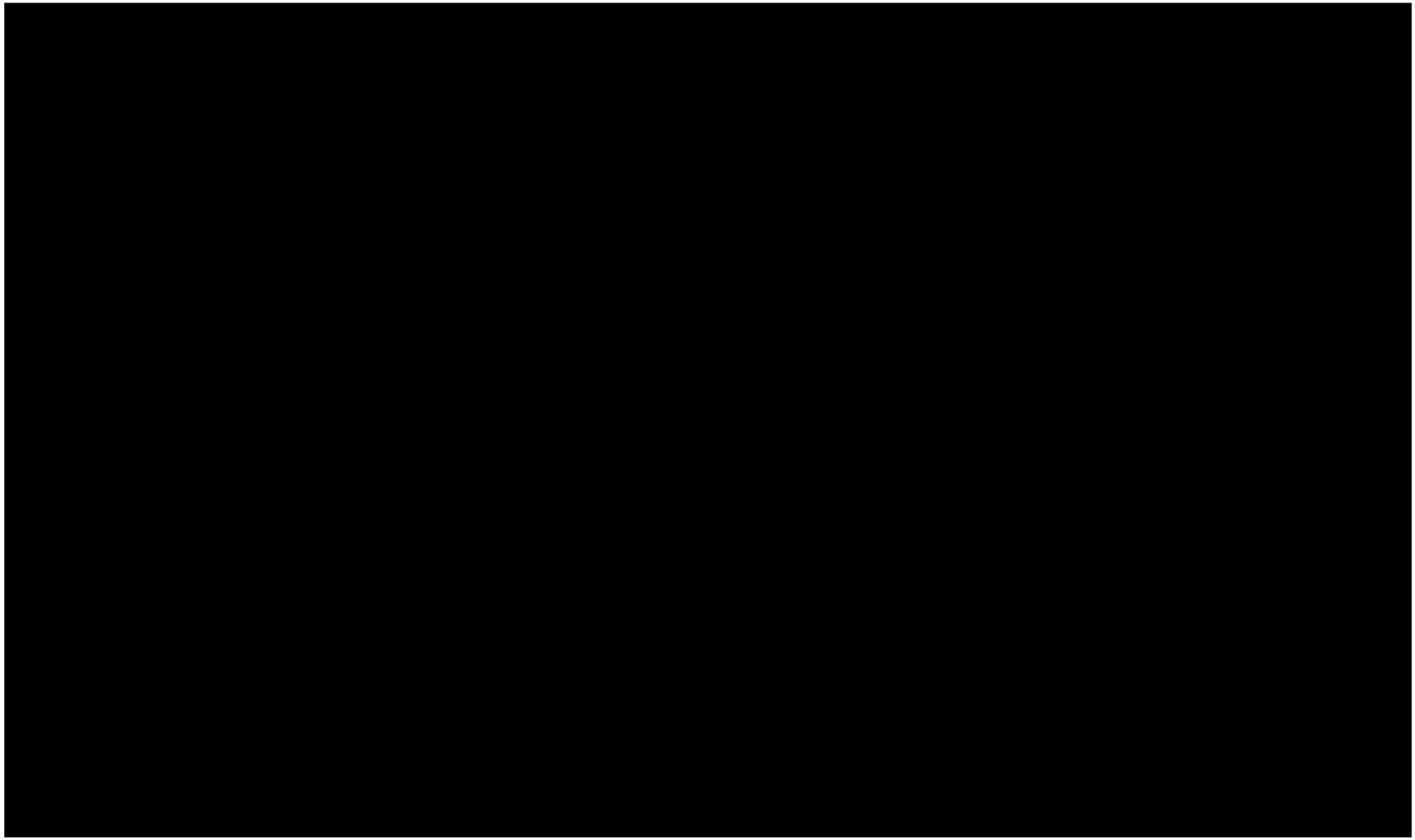
Survival curves used in company's model



Source: Late clarification response, Appendix, Figure 2.3.3

Clinical effectiveness results - OS

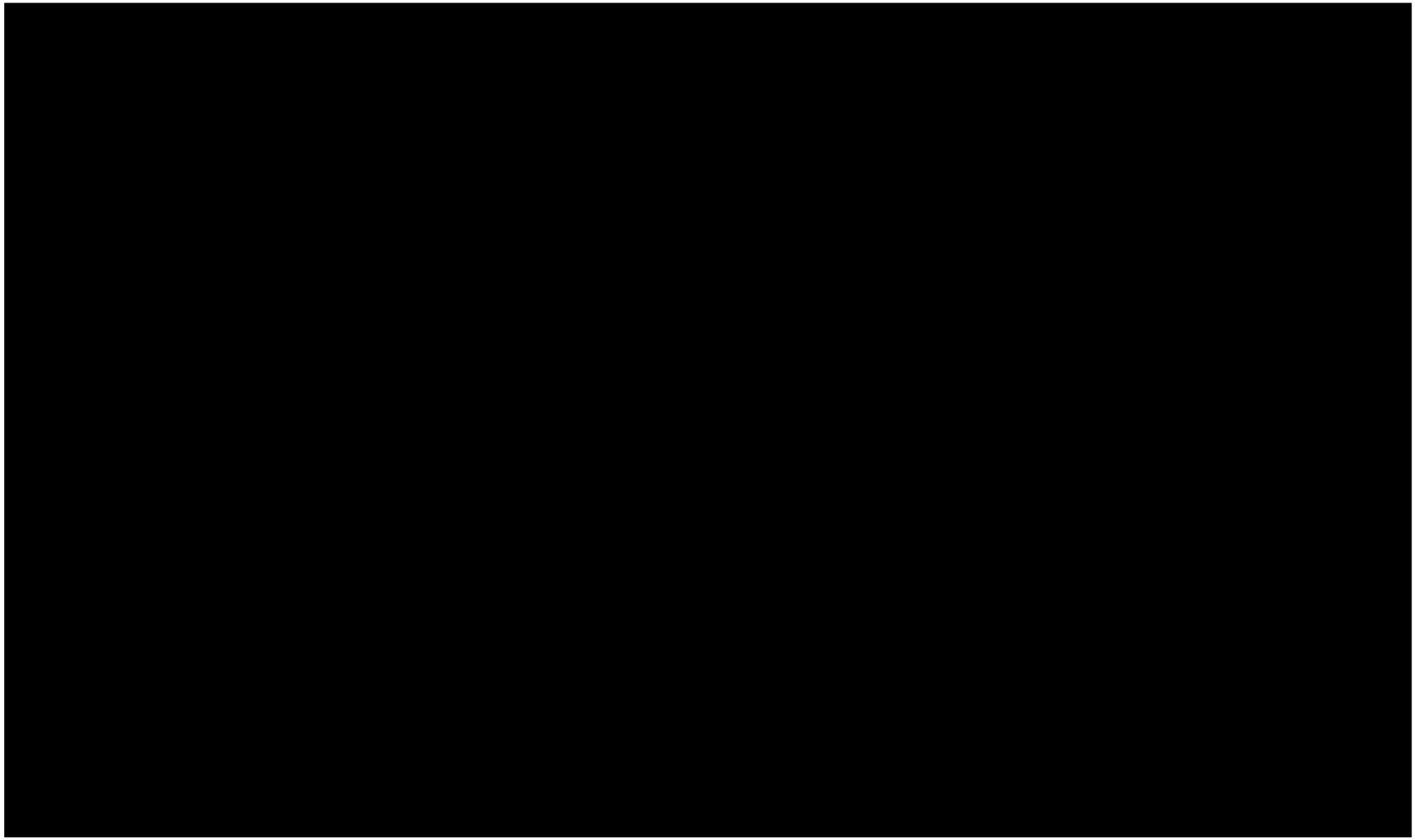
Hazard ratio over time



Source: Late clarification response, Appendix, Figure 2.4.2

Clinical effectiveness results - OS

Survival curves used in company's model



Source: Late clarification response, Appendix, Figure 2.4.3

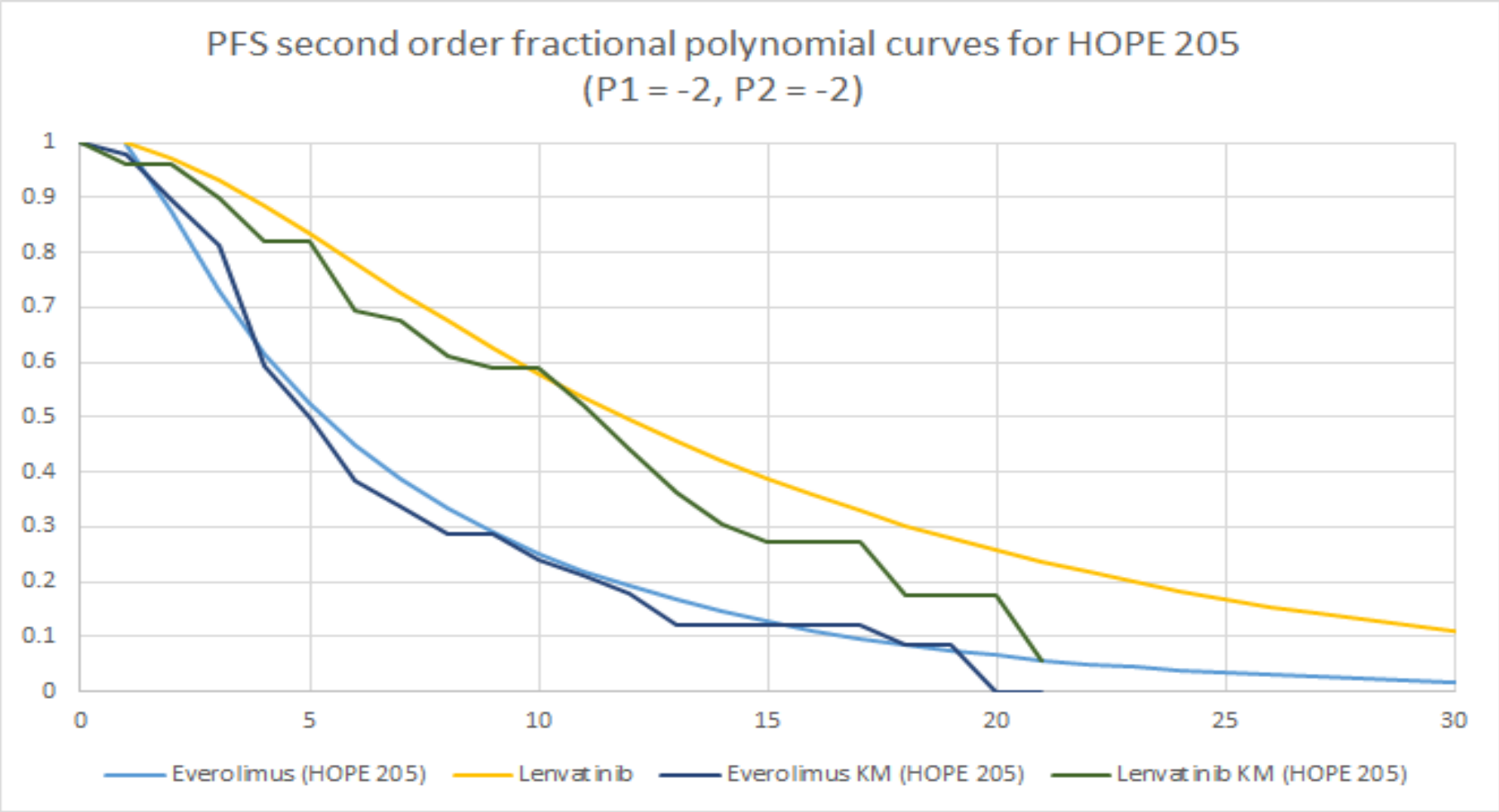
ERG's critique of company's network meta-analysis to estimate PFS/OS between treatments

- Company's 'best' model fit for PFS was a '2nd order fractional polynomial model'; P1=-2 and P2=-2. No other curves provided a plausible fit
- Company's 'best' model fit for OS was a '1st order fractional polynomial model; P1=-1, DIC 640.3
  - 1 other curve provided a plausible fit (1st order fractional polynomial with P = -0.5)
  - ERG explored this curve in a scenario analysis within ERG's preferred base case
- Fractional polynomial method implemented appropriately, however:
  - Company's plots of limited value to validate model fit
- ERG tested how well fractional polynomials fit trial Kaplan-Meier survival curves for PFS and OS for each treatment
- ERG digitised only the KM curves for CheckMate 025 and used individual patient-level KM data for HOPE 205 supplied by the company (see next slides)

ERG's fractional polynomial curve fit

Progression-free survival, HOPE 205

Curves fit data well but overestimate PFS for LEN+EVE

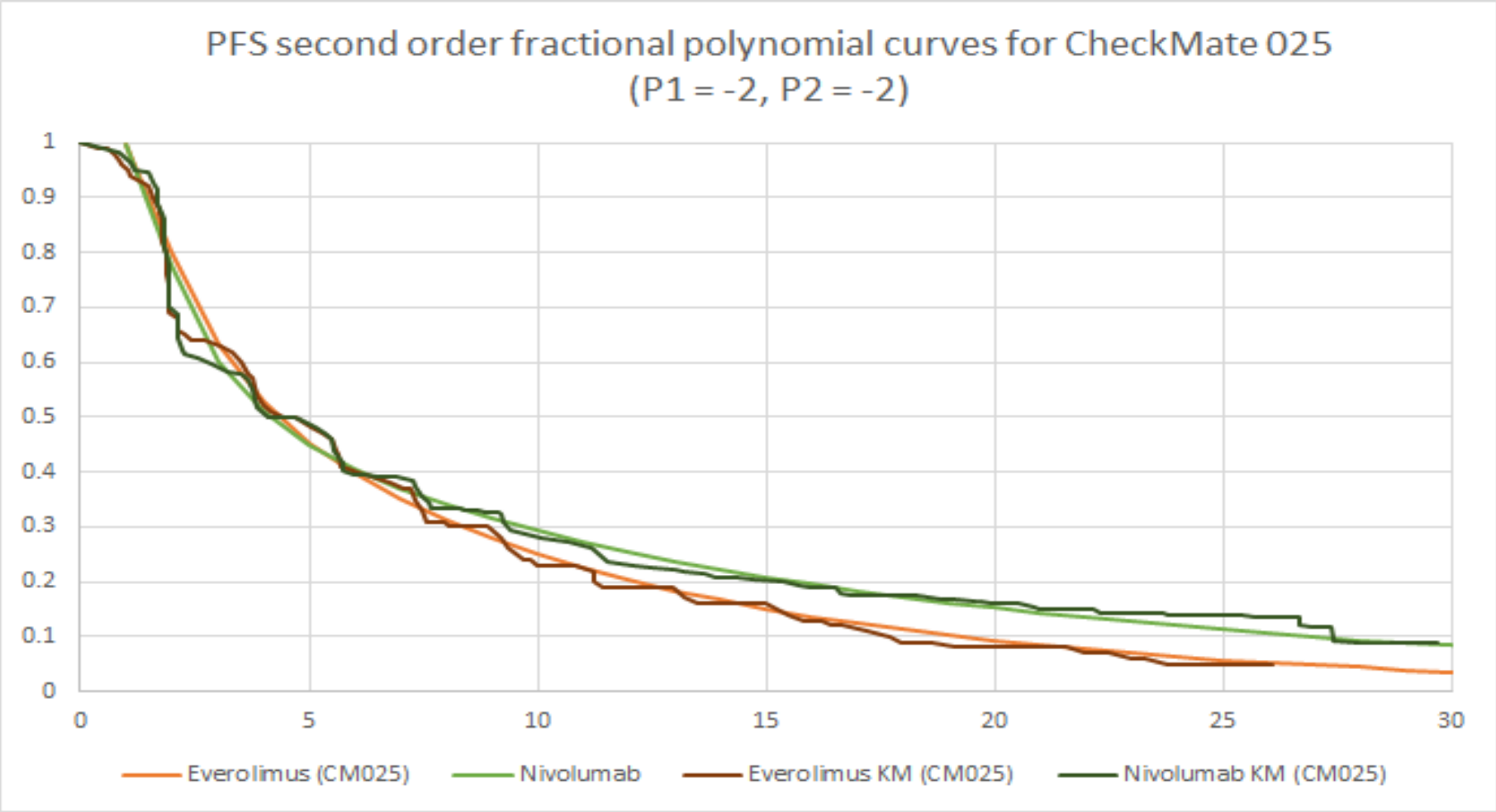


Source: Figure 13 ERG report

ERG's fractional polynomial curve fit

Progression-free survival, CheckMate 025

Curves fit data well

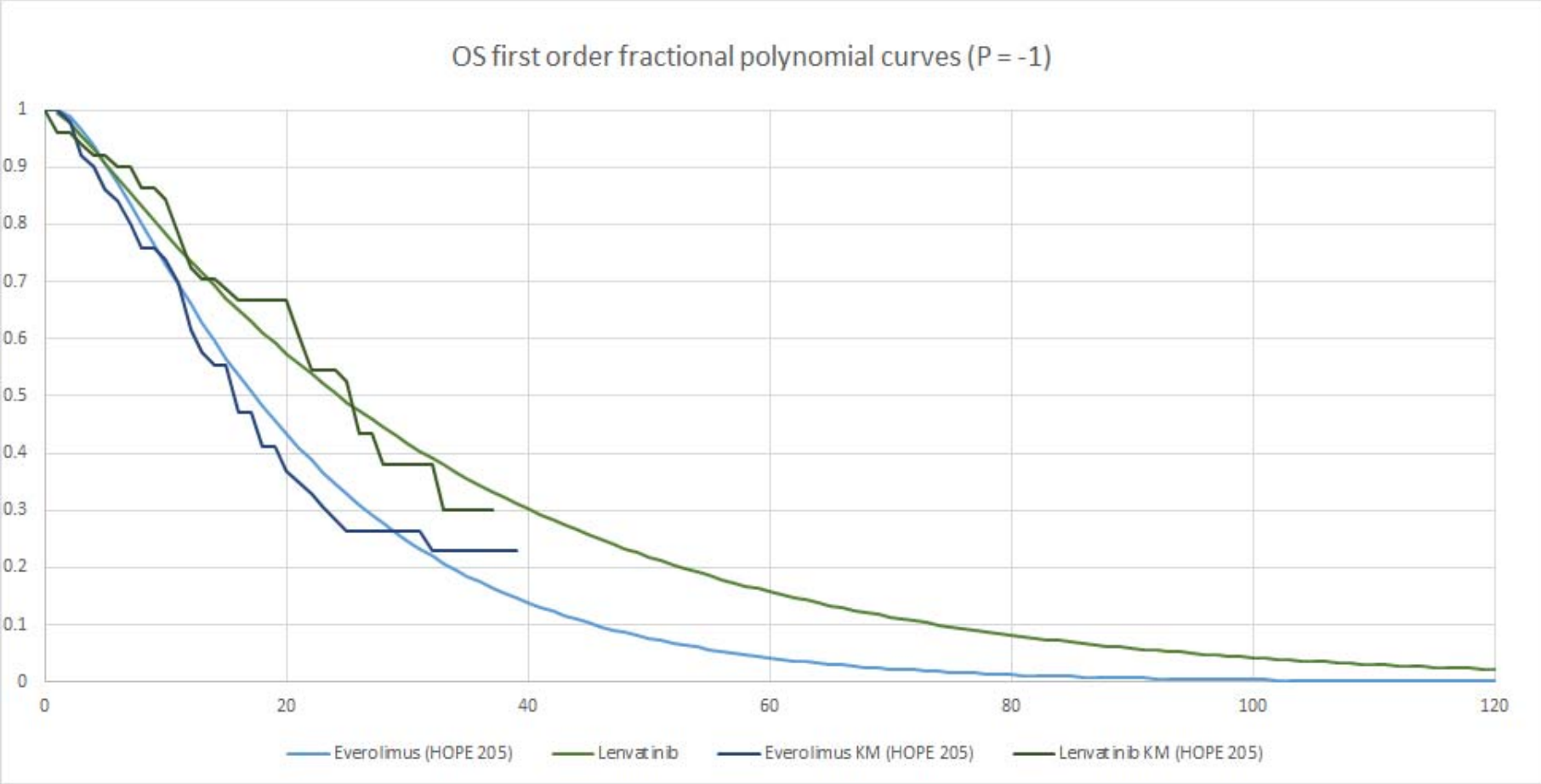


Source: Figure 13 ERG report

ERG's fractional polynomial curve fit

Overall survival, HOPE 205

Visual inspection of these curves overlaid on the underlying KM data shows a good fit for both trial arms in HOPE205

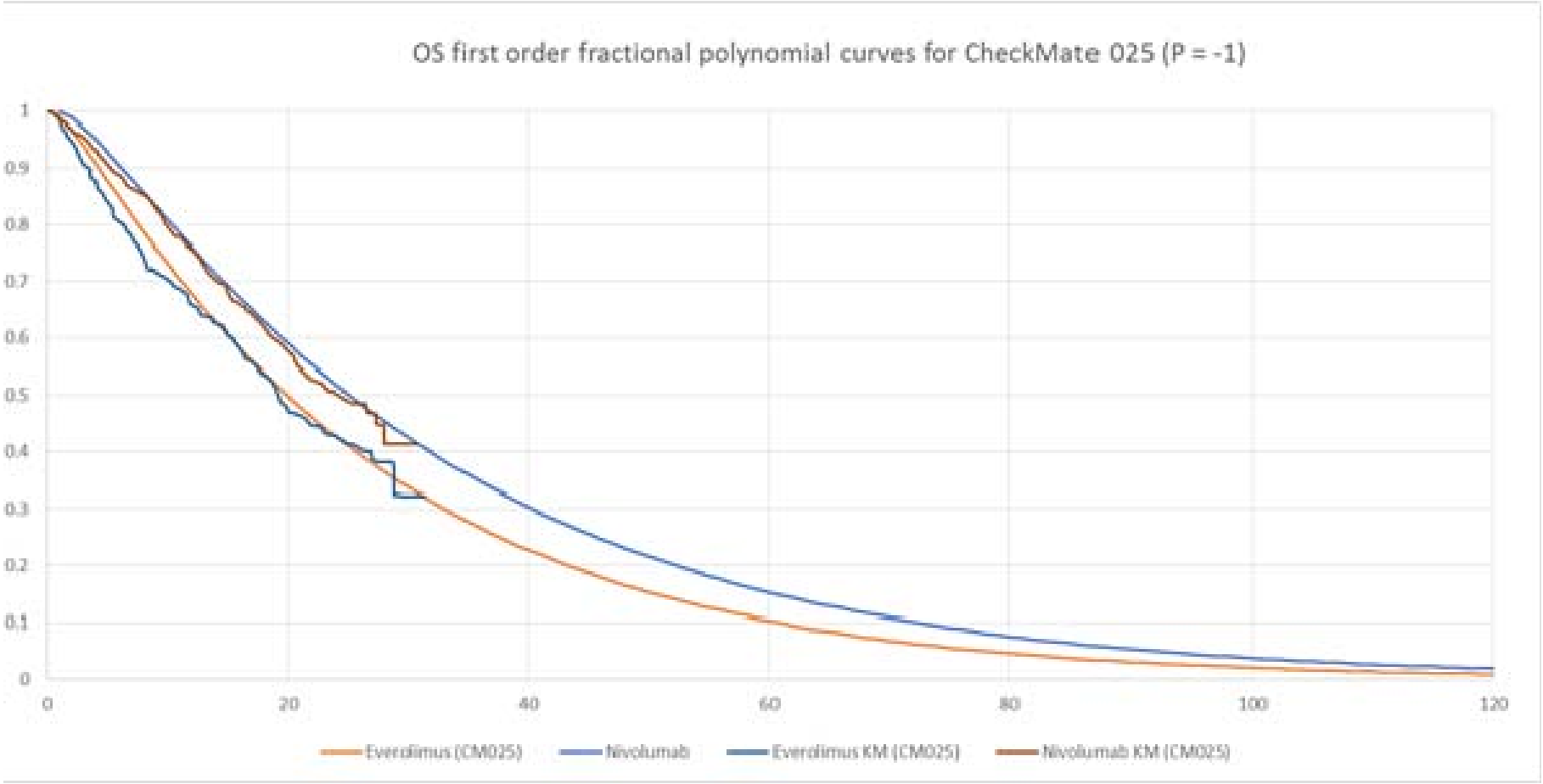


Source: Figure 16 ERG report

ERG's fractional polynomial curve fit

Overall survival, CheckMate 025

Visual inspection of these curves overlaid on the underlying KM data shows a good fit for both trial arms in HOPE205



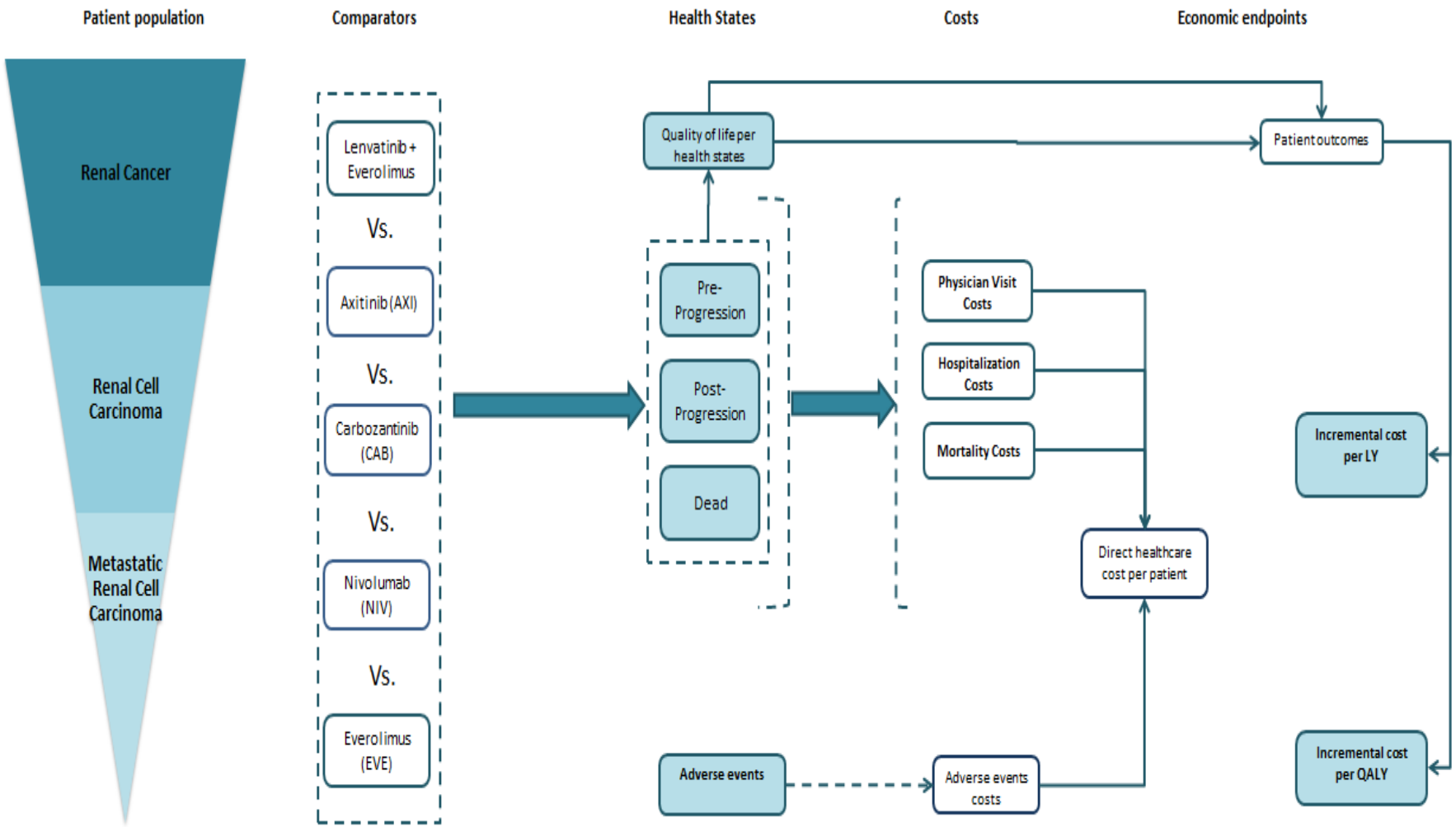
Source: Figure 16 ERG report

Cost-effectiveness evidence

Key economic issues for consideration

- Is the company's model which includes only 1st- and 2nd-line therapy fit for purpose?
- Did the company correctly implement its scenario analysis based on fractional polynomials beyond 5 years?
- The company included the benefits but not the costs of subsequent treatments that patients received in all the trials. What is the appropriate approach?
- Does LEN+EVE extend life by 3 months compared with the comparators?
- Utility: The HOPE trial did not measure quality of life. Does the committee consider the data from the AXIS trial appropriate?
- Is it appropriate to correct utilities to account for patients who remain on treatment after progression?
- Drug costs: What is the appropriate way to estimate and model treatment duration?

Conceptual Model Framework



Source: Figure 55 of the company submission

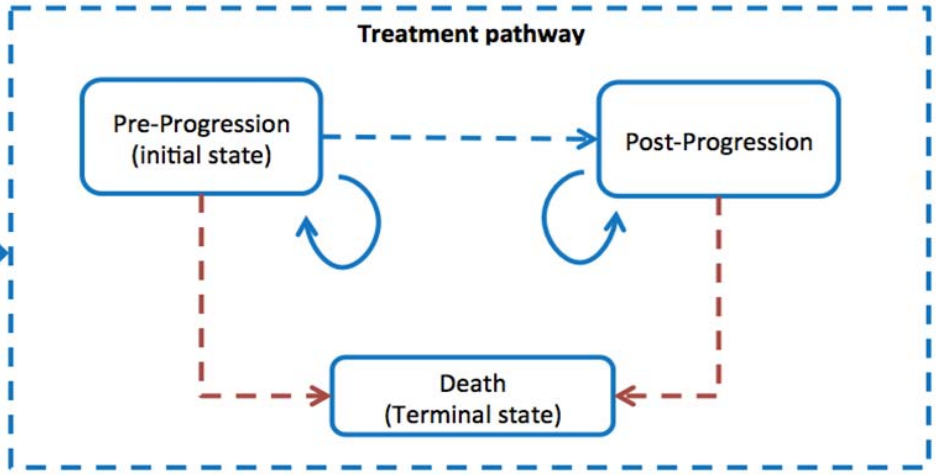
Company's model structure

Partitioned-survival (area-under-the-curve) model

Population
Same as HOPE 205 trial, ITT population, adults with 1 prior VEGF-targeted therapy

Intervention
Lenvatinib + everolimus

Comparators
Axitinib, cabozantinib, everolimus monotherapy, nivolumab



Source: Figure 56 of company submission

4-week cycle length (reflecting frequency of consultant oncologist visits), 20-year time horizon

ERG considered population, comparators and model structure reasonable

Features of the company's model

Element	Chosen values	Justification
Time horizon	Base case: lifetime Sensitivity scenarios: trial-horizon, 5 and 10 years	Lifetime scenario was considered sufficient to capture all meaningful differences in technologies compared
Half-cycle correction	Included	Provide a more accurate estimate for each cycle
Were health effects measured in QALYs; if not, what was used?	Yes (life years gained also assessed)	According to NICE guidelines QALYs were the primary preference-based outcome evaluated
Discount of 3.5% for utilities and costs	Yes	According to NICE guidelines
Perspective (NHS/PSS)	NHS England	No social services or indirect costs were included in the model as considered non relevant.

Source: Figure 57 of the company submission

ERG's comment on company's model structure

Company's base case	ERG comment
Population	Company's analysis reflects population outlined in NICE final scope
Comparators	Company's analysis includes all relevant comparators Excluding best supportive care appropriate
Model structure	• Model 'structure' reasonable, and includes all relevant health states • However, permits only 2nd line therapy – does not reflect clinical practice • 1-month cycle length consistent with frequency of visits to oncologists • Time horizon (20 years) reasonable

ERG critique of company's modelling of effectiveness using fractional polynomials

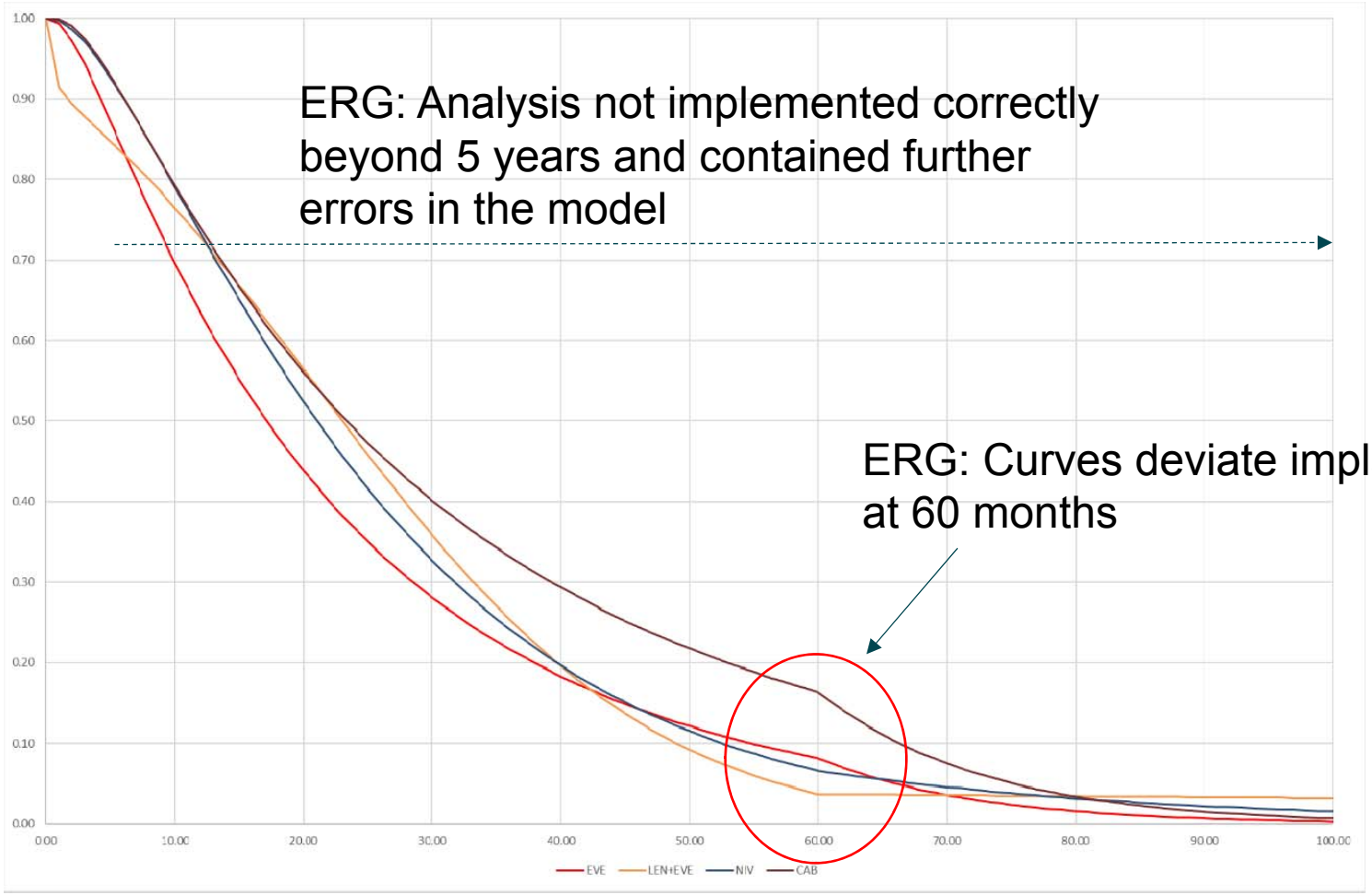
ERG's comment on fractional polynomials

- ERG prefers fractional polynomials to estimate effectiveness
- Key limitation is that the goodness-of-fit is measured globally across all curves, and may not reflect a good fit to individual treatment curves

ERG's comment on company's application of fractional polynomials

- ERG considers that company used fractional polynomials incorrectly
- Company generated survival curves only up to 5 years, beyond which the company estimated survival probabilities by multiplying the previous probability by 1 minus the hazard rate
  - Mathematically incorrect
  - Survival curves deviate implausibly at 60 months (see next slide)
- ERG regenerated curves based on fractional polynomials for the entire time horizon based on the results of the ERG's network meta-analysis
- ERG's curves to 5-year time point deviate slightly company's curves
- ERG prefers its own approach

Company's fractional polynomial curves for overall survival



Source: Figure 24 of the ERG report

Modelling of duration of treatment

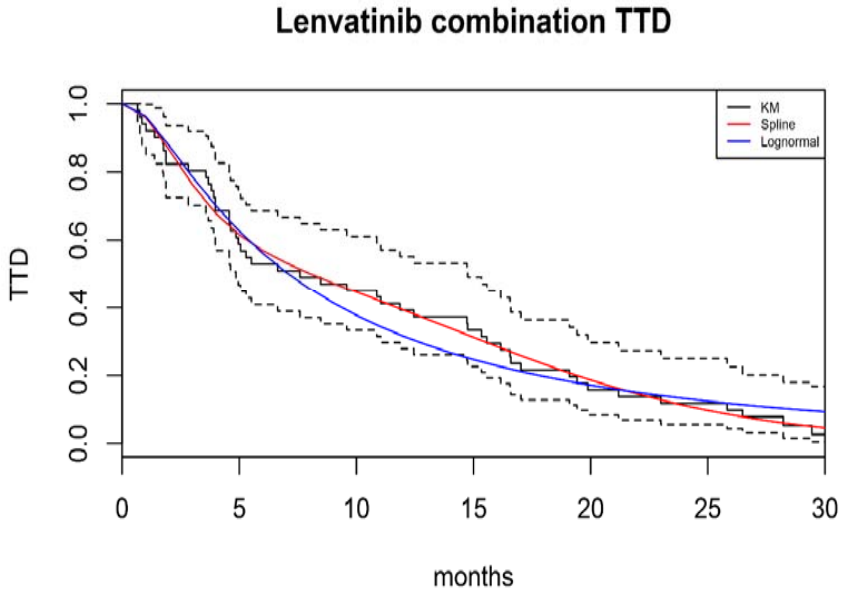
Company's approach	ERG's critique	ERG's preferred approach
<u>For LEN+EVE and everolimus:</u> • Directly used Kaplan–Meier data on time-to-treatment discontinuation (TTD) from HOPE 205 <u>For remaining comparators</u>: • Applied ratio of median TTD relative to LEN+EVE, estimated using data from the respective trials used in the ITC, as powers to the LEN+EVE TTD Kaplan–Meier data	• Approach incorrect as it assumes that ratio of median treatment duration equals a ratio of the hazard rates for TTD for each treatment • Resulted in discrepancies between the modelled median TTD durations and the observed TTD	• Fit parametric curves to digitised Kaplan–Meier data and extrapolate the best-fitting curve beyond follow-up period • Log-normal and '2-knot spline' appeared reasonable, but latter provided a better fit for LEN+EVE • ERG's alternative base case used 2-knot spline, and log-normal explored in scenario analysis

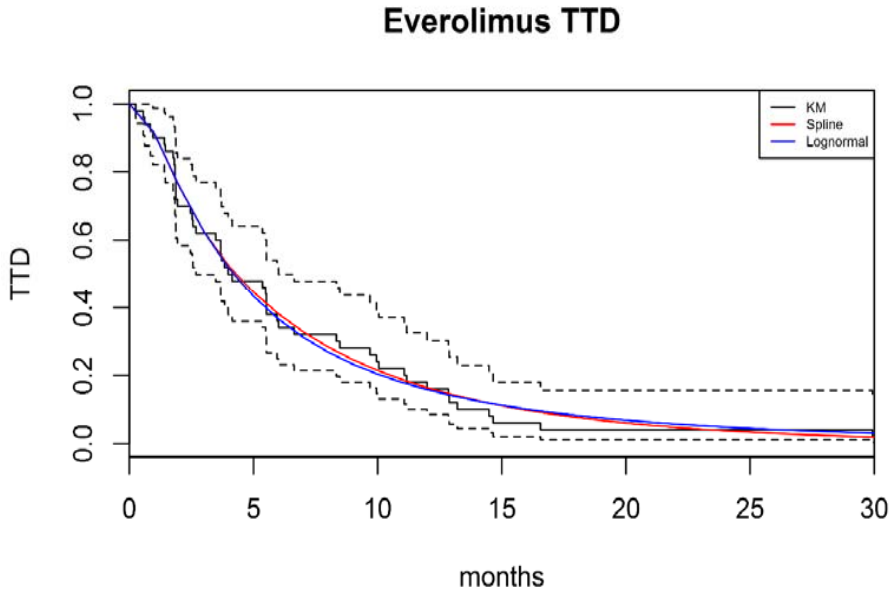
Modelled treatment durations in company's base case

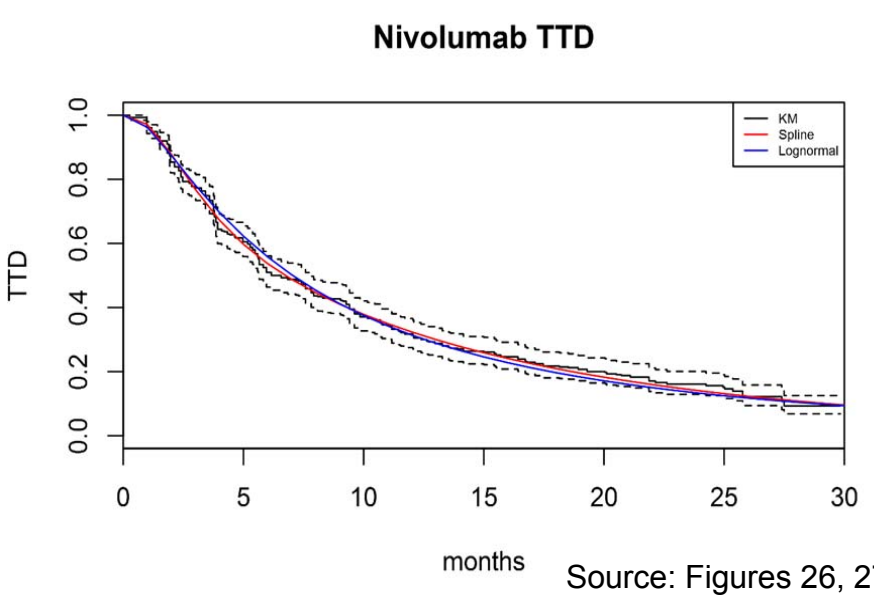
	LEN+EVE	Everolimus	Axitinib	Cabo-zantinib	Nivolumab
Median treatment durations in trials (months)	**8.0**	**4.1**	**8.2**	**8.3**	**6.2**
Estimated median treatment durations in company's base case	<7	<4	~7	~7	<5
ERG analysis: 2-knot spline	8.1	4.3	Assumed equal to PFS	8.9	6.7
ERG analysis: log-normal distribution	7.1	4.2		9.3	7.0

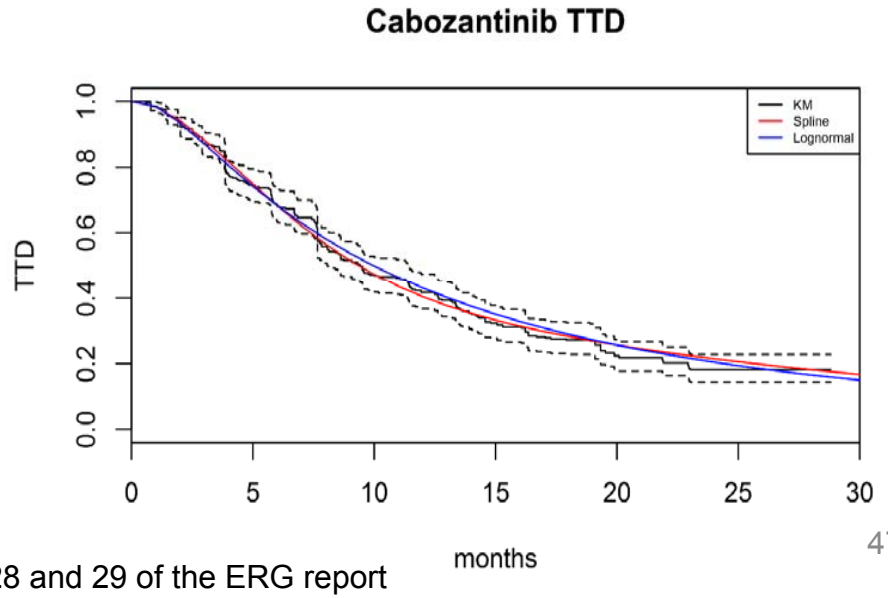
Source: Table 41 of the ERG report

ERG's curve fits for TTD









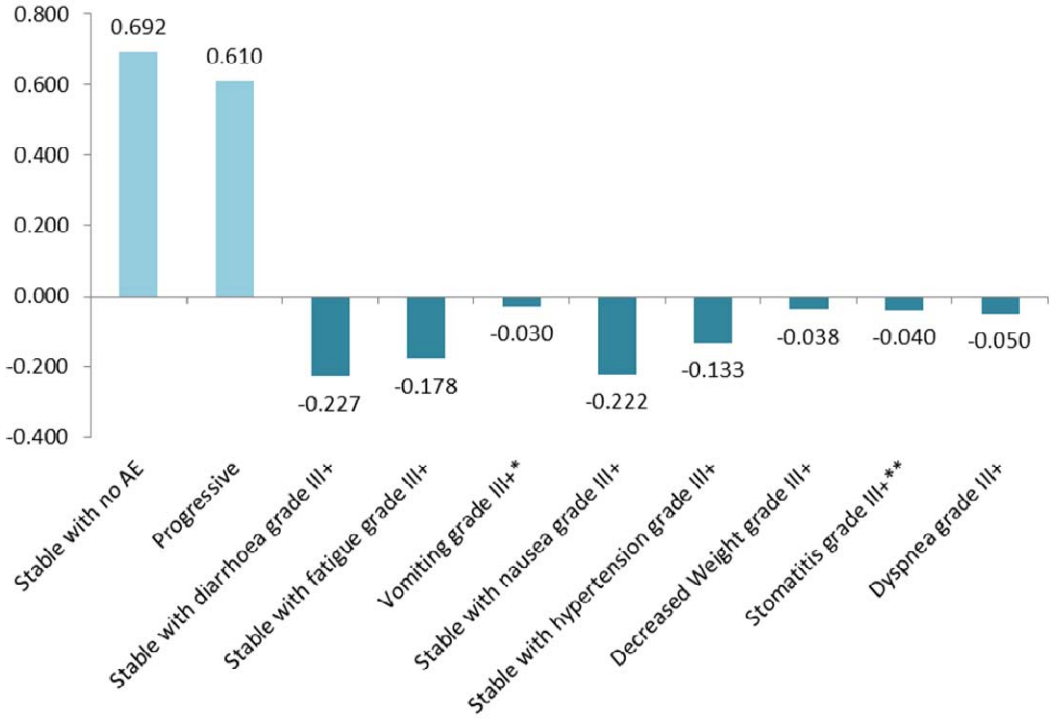
Source: Figures 26, 27, 28 and 29 of the ERG report

Health related quality of life in the model

Model used literature-based values

- No HRQoL data available from HOPE 205
- Utility values sourced from AXIS study (base case) and a separate vignette utility study (scenario analysis)
- Additional disutility values (not included in the AXIS) obtained from other published literature

Unadjusted utility scores used in the model



Source: Figure 84 of the company submission

ERG critique of health-related quality of life in the model

- Reasonable to use AXIS to source utility values as based on previous evaluations the population in AXIS reflects patients seen in UK clinical practice
- The company assumed adverse events cause a utility decrement
  - The utility value of 0.69 already includes the impact of adverse events on QoL and, therefore, there is double counting of the impact of adverse events, for axitinib at least
  - The company's approach in assuming that all patients start with a value of 0.69, and using the proportions of adverse events experienced in the trials is fair and should reflect the difference in safety profiles across the treatments
- Utility decrements for adverse events were obtained from submission for TA333 and two published quality of life studies (Shabaruddin et al. and Shiroiwa et al.)
  - ERG disagrees with the use of values elicited Shiroiwa et al (data collected from members of the general population, estimates were elicited for patients with colorectal cancer and not renal cancer which may not be generalisable to patients with RCC

Resource use and costs

- The company included the following cost categories:
  - Intervention and comparators' costs
  - Drug dosing costs
  - Administration costs
  - Health-state unit costs
  - Routine care unit costs
  - Mortality costs
  - Adverse reaction unit costs
- Based on UK reference costs, literature and expert opinion

Subsequent therapies in HOPE 205

	HOPE 205		CheckMate 025		METEOR	
	LEN+EVE	*EVE*	*Nivo-lumab*	*EVE*	*Cabo-zantinib*	*EVE*
Any	35%	36%	55%	63%	50%	55%
Any VEGF	18%	26%	-	-	24%	47%
Axitinib	12%	24%	24%	36%	17%	27%
Everolimus	10%	4%	26%	-	29%	-
Pazopanib	-	-	9%	16%	-	-
Sorafenib	-	-	-	9%	-	-
Sunitinib	-	-	-	-	-	10%

Source: Table 25 of ERG report

Modelled cost of subsequent therapies

Company's original submission

'… there are currently no treatments approved on the NHS for the third-line treatment of advanced or metastatic RCC. Therefore, in line with recommendations from recent NICE submissions for nivolumab and cabozantinib patients were assumed to switch to secondary therapy, defined as best supportive care (no treatment) in the model.'

Cost of subsequent therapies not included in base case

Modelled cost of subsequent therapies

Company's clarification response

ERG asked company to carry out a scenario analysis using the proportions of subsequent treatments received in the respective trials for all the treatments arms

Company disagreed because:

(1) Data not available for all drugs, including LEN+EVE in the respective clinical trials

(2) Difference in cost could be related to an expensive secondary therapy and would bias the ICER

(3) Secondary therapy would be significantly biased by the availability of drugs at the end of the trial, and not based on clinical practice

Instead, company estimated cost of subsequent therapies estimated based on the UK market share of drugs received as subsequent therapies across the LEN+EVE and everolimus groups of the HOPE 205 trial and applied to all treatment groups

Modelled cost of subsequent therapies

ERG's preferred approach

- ERG disagreed with justification put forward by the company
- Patients in the HOPE 205, METEOR, CheckMate 025, and AXIS trials received a further line of therapy after stopping treatment
- The estimates from these trials included any potential benefits that patients received from these subsequent treatments that are not attributed to the initial drugs received in the trials

Used actual proportion of treatments received in the trials in a manner reflective of what is available in the UK

Additional work undertaken by the ERG

Analyses within the company's base case

- ERG corrected 2 errors in the model:
  - Half cycle correction: company inconsistently applied half cycle correction for costs and QALYs, which overestimated QALYs for all treatments (favours lenvatinib + everolimus)
  - Correction of utilities: company applied pre-progression utility to all patients on treatment, and therefore, did not account for patients who progressed but remained on treatment

<u>Scenario analyses within the company's base case</u>

- Trial-based subsequent treatments
- ITC based HR applied for everolimus PFS and OS
- Utilities used in TA417 (based on CheckMate025) applied to nivolumab
- General population mortality for 50% of nivolumab patients

Additional work undertaken by the ERG

Analyses within the ERG's preferred base case

ERG's preferred base case:

1. ERG's preferred survival curves: Best fitting fractional polynomials for OS and PFS, and 2-knot spline for TTD
2. Subsequent treatment costs based on trials

Scenario analyses within ERG's preferred base case:

- Alternate first order OS fractional polynomial (P = -0.5)
- Alternate TTD curve (Log-normal)
- Utilities used in TA417 (based on CheckMate025) applied to nivolumab
- General population mortality for 50% of nivolumab patients

Innovation

- Lenvatinib in combination with everolimus is considered to provide substantial innovation to current management of second-line mRCC patients who have progressed after one previous VEGF-targeted therapy since this is the first and only TKR inhibitor plus mTOR inhibitor regimen authorised in this setting
- A synergistic effect has been shown for the combination, with higher efficacy levels in terms of PFS and response rate than for each of the individual agents separately
- This benefit has been proved clinically significant for the combination compared to everolimus, which has been very recently recommended by NICE for second line treatment of RCC after TKI failure
- The combination allows the administration of lower doses than those used for each of the individual agents and offers an acceptable safety profile at a convenient once daily oral regimen

End of life

- Company comment
  - Eisai does not believe that the lenvatinib in combination with everolimus is suitable for consideration as a 'life extending treatment at the end of life'

- ERG comment
  - In terms of an extension to life, lenvatinib has a modelled increase in life expectancy of greater than 3 months when compared to the next most effective treatment, cabozanitnib
  - The increase is greater still for the remaining treatments
  - The ERG notes that end of life criteria have been applied in previous NICE technology appraisals for patients with previously treated renal cell carcinoma

Cost-effectiveness results

All the ICERs are reported in PART 2 because they include the PAS discount for LEN+EVE, as well as the comparators axitinib, cabozantinib and nivolumab, unless otherwise specified.

Authors

- **Orsolya Balogh**
  Technical Lead
- **Ahmed Elsada**
  Technical Adviser
- with input from the Lead Team **Ray Armstrong**, **John Cairns and Danielle Preedy**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of lenvatinib with everolimus within its marketing authorisation for previously treated advanced renal cell carcinoma.

Background

Renal cell cancer (RCC) is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer (approximately 80% of the cases).[1] There are several types of RCC. The main ones are clear cell, papillary and chromophobe. Clear cell is the most common form of RCC accounting for approximately 75% of cases.[2]

The tumour node metastases system is used to grade RCC into stages I to IV. Stage III denotes disease that is locally advanced and/or has spread to regional lymph nodes and stage IV denotes that distant metastasis has occurred. Early, small RCC tumours are usually asymptomatic; the diagnosis of early RCC is often incidental after abdominal scans for other indications. The most common presenting symptoms of advanced or metastatic RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss. Nephron sparing surgery may be curative in people with localised tumours. However, around half of those who have curative resection for earlier stages of the disease develop advanced or metastatic disease later on.

In 2014, 9,123 new kidney cancer cases were diagnosed in England.[3] In 2014, approximately 44% of people diagnosed with kidney cancer had stage III or IV disease and 25% had stage IV disease.[4] The 5-year survival rate for metastatic RCC is approximately 10%.[5]

The aim of treatment is to stop the growth of new blood vessels within the tumour. After failure of prior systemic treatment with a cytokine or tyrosine kinase inhibitor NICE technology appraisal guidance 333 recommends axitinib. Because the remit referred to NICE by the Department of Health for axitinib only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors, such as pazopanib (NICE technology appraisal guidance 215) is not subject to statutory funding. Nivolumab is also recommended as an option for previously

treated advanced renal cell carcinoma in adults (TA417). Everolimus is available in England for metastatic RCC through the Cancer Drugs Fund (at the time the scope was written) for people whose disease has progressed during or after treatment with vascular endothelial growth factor targeted therapy. Everolimus is subject to ongoing NICE CDF transition review [ID1015]. Cabozantinib is subject to ongoing NICE appraisal for previously treated advanced RCC.

The technology

Lenvatinib (Kisplyx, Eisai) is a multiple receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors and other receptor tyrosine kinases that are involved in tumour proliferation. It is administered orally.

Lenvatinib has a marketing authorisation in the UK "in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy."

Intervention(s)	Lenvatinib
Population(s)	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy
Comparators	• Axitinib • Nivolumab • Everolimus (NICE guidance is in development, funded by the Cancer Drugs Fund in the interim) • Best supportive care • Cabozantinib (subject to ongoing NICE appraisal [ID931])
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Nivolumab for previously treated advanced renal cell carcinoma' (2016). NICE technology appraisal 417. Review date November 2019. 'Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment' (2015). NICE technology appraisal 333. Review date to be confirmed. 'Everolimus for the second-line treatment of advanced renal cell carcinoma' (2011). NICE technology appraisal guidance 219. Everolimus subject to ongoing NICE CDF transition review [ID1015], expected date of publication February 2017. 'Bevacizumab (first-line), sorafenib (first- and second line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' (2009). NICE technology appraisal guidance 178. Review date to be confirmed. Terminated appraisals 'Pazopanib for the second line treatment of metastatic renal cell carcinoma (discontinued)' NICE technology appraisals guidance [ID70]. Appraisals in development (including suspended appraisals)

	'Cabozantinib for treating renal cell carcinoma'. NICE technology appraisals guidance [ID931]. Publication expected June 2017. 'Tivozanib for the treatment of advanced renal cell carcinoma'. NICE technology appraisals guidance [ID591]. Publication expected December 2017. 'Axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic renal cell carcinoma'. NICE technology appraisals guidance [ID897]. Suspended appraisal. Related Guidelines: 'Suspected cancer: recognition and referral' (2015) NICE guideline 12 'Improving outcomes in urological cancers' (2002). NICE guideline CSGUC. Review date to be confirmed. Related Interventional Procedures: 'Irreversible electroporation for treating renal cancer' (2013). NICE interventional procedures guidance 443. 'Laparoscopic cryotherapy for renal cancer' (2011). NICE interventional procedures guidance 405. 'Percutaneous cryotherapy for renal cancer' (2011). NICE interventional procedures guidance 402. 'Percutaneous radiofrequency ablation for renal cancer' (2010). NICE interventional procedures guidance 353. Related NICE Pathways: Renal cancer (2015) NICE pathway
Related National Policy	NHS England (July 2016) National Cancer Drugs Fund List. https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/ NHS England (May 2016) Manual for prescribed specialised services. Section 15. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health (April 2016) NHS Outcomes Framework 2016-2017. Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Independent Cancer Taskforce (2015) Achieving world-

	class cancer outcomes: a strategy for England 2015-2020 http://www.cancerresearchuk.org/about-us/cancer-strategy-in-england Department of Health (2014) The national cancer strategy: 4th annual report https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report NHS England (2013/14) B14. Specialised Urology. NHS Standard Contract. http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b14/

References

[1] Cancer Research UK Types of kidney cancer. Accessed November 2016.
[2] Cancer Research UK Types of kidney cancer. Accessed November 2016.
[3] Office for National Statistics Cancer Registration Statistics. Access October 2016.
[4] Cancer Research UK Kidney cancer statistics. Accessed October 2016.
[5] GP Notebook Clear Cell Cancer. Accessed October 2016.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Eisai (lenvatinib) Patient/carer groups • Black Health Agency • British Kidney Patient Association • Cancer Black Care • Cancer Equality • Cancer 52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Kidney Cancer Support Network • Kidney Cancer UK • Kidney Research UK • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Muslim Council of Britain • National Kidney Federation • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Association of Urological Nurses • British Association of Urological Surgeons • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society of Urogenital Radiology • British Renal Society • Cancer Research UK	General • Association of Renal Industries • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Kidney Patients Association Possible comparator companies • Bristol-Myers Squibb Pharmaceutical (nivolumab) • Ipsen Pharma (cabozantinib) • Novartis Pharmaceuticals (everolimus) • Pfizer (axitinib) Relevant research groups • Cochrane Urology • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research Associated Public Health Groups • Public Health England

Consultees	**Commentators (no right to submit or appeal)**
• Renal Association • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • Society for DGH Nephrologists • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society • UK Renal Pharmacy Group • Urology Foundation <u>Others</u> • Department of Health • NHS Dudley CCG • NHS Kingston CCG • NHS England • Welsh Government	• Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

Company evidence submission

March 2017

File name	Version	Contains confidential information	Date
		Yes	**March 30th, 2017**

Contents

Figures

List of abbreviations

Abbreviation	
AE	Adverse event
a/m RCC	Advanced /metastatic Renal cell carcinoma
AJCC	American Joint Committee on Cancer
BOR	Best overall response
BP	Blood pressure
CBR	Clinical benefit ratio
CDF	Cancer Drug Fund
CI	Confidence interval
CR	Complete response
DCR	Disease control rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
FGF	Fibroblast growth factor
IFN-α	Interferon-α
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IL-2	Interleukine-2
IMDC	International Metastatic RCC Database Consortium
ITC	Indirect Treatment Comparison
ITT	Intention to Treat
LDH	Lactate dehydrogenase
LY	Life year
MRI	Magnetic Resonance Image
MSKCC	Memorial Sloane Kettering Cancer Centre
mTOR	Mammalian Target of Rapamycin
NCCN	National Comprehensive Cancer Network
ORR	Objective Response Rate
OS	Overall Survival
PDGFR	Platelet-derived growth factor receptor.
PFS	Progression-free Survival
PR	Partial response
PS	Performance Status
QALY	Quality-adjusted life year
QoL	Quality of Life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection tyrosine kinase receptor

Abbreviation	
RTK	Receptor tyrosine kinase
SD	Stable disease
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SY	Subject Years
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
US	Ultrasound
VEGF(R)	Vascular endothelial growth factor (receptor)

1 Executive summary

1.1 Statement of decision problem

The decision problem, as stated in the NICE final scope, is to appraise the clinical and cost effectiveness of lenvatinib with everolimus within its marketing authorisation for previously treated advanced renal cell carcinoma. This company submission provides the clinical and economic evidence to support NICE in making their decision.

The decision problem is presented in Figure 1 overleaf.

Figure 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy	Not applicable
Intervention	Lenvatinib in combination with everolimus	Lenvatinib in combination with everolimus	Not applicable
Comparators	▪ Axitinib ▪ Nivolumab ▪ Everolimus ▪ Best supportive care ▪ Cabozantinib	▪ Axitinib ▪ Nivolumab ▪ Everolimus ▪ Cabozantinib	BSC was not considered as a comparator in the company submission. This is in line with NICE committee draft recommendations based on clinical expert input during the cabozantinib NICE assessment. (GID-TA10075)
Outcomes	▪ Overall survival ▪ Progression-free survival ▪ Response rate ▪ Adverse effects of treatment ▪ Health-related quality of life	▪ Overall survival ▪ Progression-free survival ▪ Response rate ▪ Adverse effects of treatment ▪ Health-related quality of life	Not applicable
Economic analysis	Cost-effectiveness, expressed in terms of QALY. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	Cost-effectiveness, expressed in terms of QALY. Lifelong time horizon In addition, trial-horizon, five and ten year time horizons are provided as sensitivity analysis scenarios	Not applicable
Subgroups to be considered	None	None	Not applicable
Special considerations including issues related to equity or equality	None	None	Not applicable

1.2 Description of the technology being appraised

Figure 2 Technology being appraised

UK approved name and brand name	Lenvatinib mesilate (Kisplyx®)
Marketing authorisation/CE mark status	EMA product number EMEA/H/C/004224 An European Marketing authorisation was granted on Aug 25th, 2016
Indications and any restriction(s) as described in the summary of product characteristics	Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.
Method of administration and dosage	Kisplyx treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. The recommended daily dose of lenvatinib is 18 mg (one 10 mg capsule and two 4 mg capsules) once daily in combination with 5 mg of everolimus once daily. The daily doses of lenvatinib and, if necessary, everolimus are modified as needed according to the dose/toxicity management plan. Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Source: Kisplyx Summary of Product Characteristics (Appendix 8.1)
Abbreviations: EMA, European Medicines Agency; RCC, Renal cell carcinoma; VEGF, Vascular endothelial growth factor

1.3 Summary of the clinical effectiveness analysis

Lenvatinib in combination with everolimus (LEN+EVE) demonstrated improved PFS compared to everolimus monotherapy with a median PFS of 14.6 months vs. 5.5 months (HR°0.40; 95% CI 0.24 to 0.68; p=0.0005). An independent imaging review (IIR) corroborated the improvements seen in the original analyses with a median PFS of 12.8 months vs. 5.6 months compared to everolimus alone (HR, 0.45; 95% CI, 0.26 to 0.79; p=0.003) (Motzer, et al., 2015). Additional sensitivity analyses performed confirmed the robustness of observed PFS.

Furthermore, encouraging signs of a prolonged OS were seen in patients treated with lenvatinib in combination with everolimus in the primary analysis as well as in two updated analyses (Motzer, et al., 2016). A similar trend towards prolonged OS was also observed in favour of single agent lenvatinib but less obvious than with combination therapy.

Based on the ITC of the PFS reported in the trials, the lenvatinib plus everolimus combination was superior to nivolumab, axitinib and placebo, while there was no evidence of a difference to cabozantinib. In terms of OS and ORR, there was no statistical significant difference between lenvatinib plus everolimus versus nivolumab, cabozantinib or axitinib. Lenvatinib plus everolimus was superior to placebo in OS in the intention-to-treat analysis, but not after adjustment for cross-over of placebo patients to active treatment, which resulted in a lower point estimate (0.35 compared with 0.51) but wider confidence intervals.

There was no change to the known safety profile of lenvatinib when it was combined with everolimus. The safety profile observed with the combination of lenvatinib with everolimus was consistent with the known toxicities of each individual agent. The observed toxicities in the combination group that worsened compared with each of the agents as monotherapy are hypercholesterolemia, and diarrhoea. These can be managed with diligent monitoring, dose reduction and interruption as recommended in the lenvatinib's SmPC, and prompt medical treatment.

Overall the ITC suggests that the combination of lenvatinib plus everolimus is at least as efficacious as nivolumab, cabozantinib or axitinib, and possibly superior in terms of PFS to nivolumab and axitinib. In terms of safety, there is no evidence of a statistical difference between lenvatinib plus everolimus and cabozantinib or axitinib, however the data suggests that the safety profile of nivolumab is more benign.

1.4 Summary of the cost-effectiveness analysis

In the absence of relevant economic evaluations found in the literature, a de novo cost effectiveness analysis was conducted for lenvatinib in combination with everolimus (LEN+EVE). The economic evaluation was performed by developing a partition survival model similar to previous models and according to the NICE technical and clinical guidelines. Clinical data from the pivotal Phase II Study 205 (HOPE) trial were used to inform the clinical effectiveness estimates for lenvatinib and everolimus; an indirect treatment comparison was used to extend the analysis to compare to axitinib, cabozantinib and everolimus.

HRQL data as not collected during the Phase II study and so, in line with recent draft NICE committee recommendations during the review of cabozantinib (GID-TA10075), the utilities values used in the basecase were based on those from the axitinib NICE submission (TA333) from the AXIS study.

The assumptions of the economic model were validated by oncologists practicing in the NHS and with experience of lenvatinib and other treatments approved by NICE for this indication.

The lenvatinib and everolimus combination is predicted to be a cost-effective treatment option for advanced/metastatic RCC patients, versus cabozantinib and nivolumab, representing good value for money to the NHS.

The base case incremental cost-effectiveness ratios for LEN+EVE versus axitinib and everolimus are higher than the £30,000 per QALY cost effectiveness threshold. It is important to note that all the ICERs presented in Figure 3 are based on the list price of everolimus and as there is currently a PAS in place for everolimus, are not an accurate reflection of the true cost effectiveness of LEN+EVE.

Figure 3 Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)
LEN+EVE	[redacted]	[redacted]	[redacted]				
Axitinib	54,470	1.38	0.85	[redacted]	[redacted]	[redacted]	32,906
Cabozantinib	73,079	2.10	1.31	[redacted]	[redacted]	[redacted]	1,683
Nivolumab	69,896	1.98	1.23	[redacted]	[redacted]	[redacted]	17,146
Everolimus	39,988	1.73	1.08	[redacted]	[redacted]	[redacted]	96,403

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

2 The technology

2.1 Description of the technology

Kisplyx® (INN lenvatinib) is an antineoplastic agent belonging to the therapeutic class of protein kinase inhibitors (ATC Code, L01XE29).

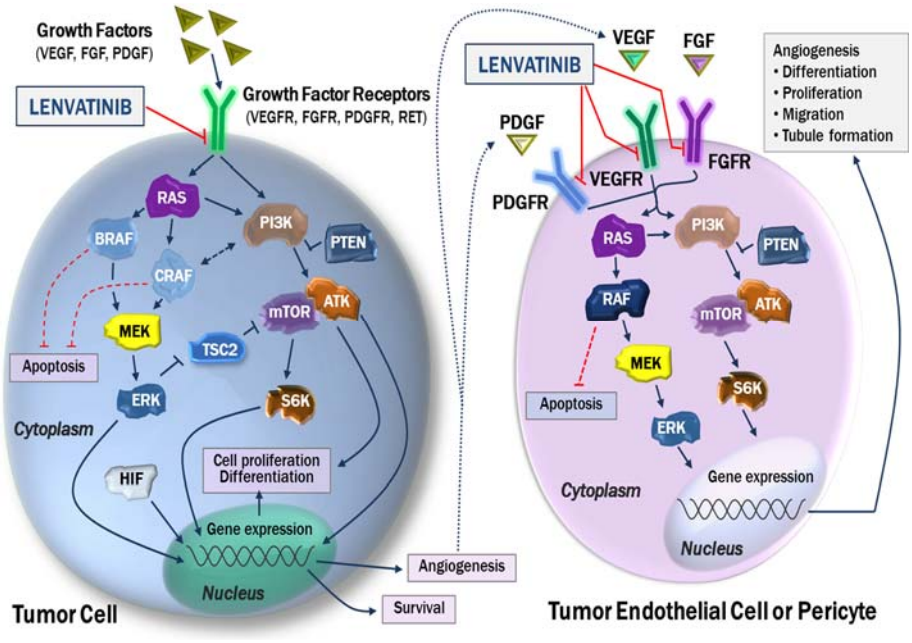
Mechanism of action of lenvatinib

Lenvatinib is an orally administered multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor [PDGF] receptor PDGFRα; KIT; and RET) involved in tumour proliferation (European Medicines Agency, 2016).

Kinase inhibitors are categorised into several types depending on the binding site and the conformation of the targeted kinase in complex with them (Okamoto, et al., 2015). Most of the currently approved tyrosine kinase inhibitors are either Type I or Type II, however, according to X-ray crystal structural analysis, lenvatinib was found to possess a new Type V binding mode of kinase inhibition to VEGFR2 that is distinct from existing compounds. In addition, lenvatinib was confirmed via kinetic analysis to exhibit rapid binding to the target molecule and potent inhibition of kinase activity and it is suggested that this may be attributed to its novel binding mode (Okamoto, et al., 2015).

The mechanism of action of lenvatinib involves effects on both endothelial cells, which are involved in tumour angiogenesis, and directly on tumour cells (Figure 4). In preclinical models, lenvatinib displayed potent antiangiogenic and antilymphogenic activity, inhibited tumour cell proliferation, induced tumour regression, and inhibited cell migration and invasion (Matsui, et al., 2008a; Matsui, et al., 2008b; Bruheim, et al., 2011; Glen, et al., 2011).

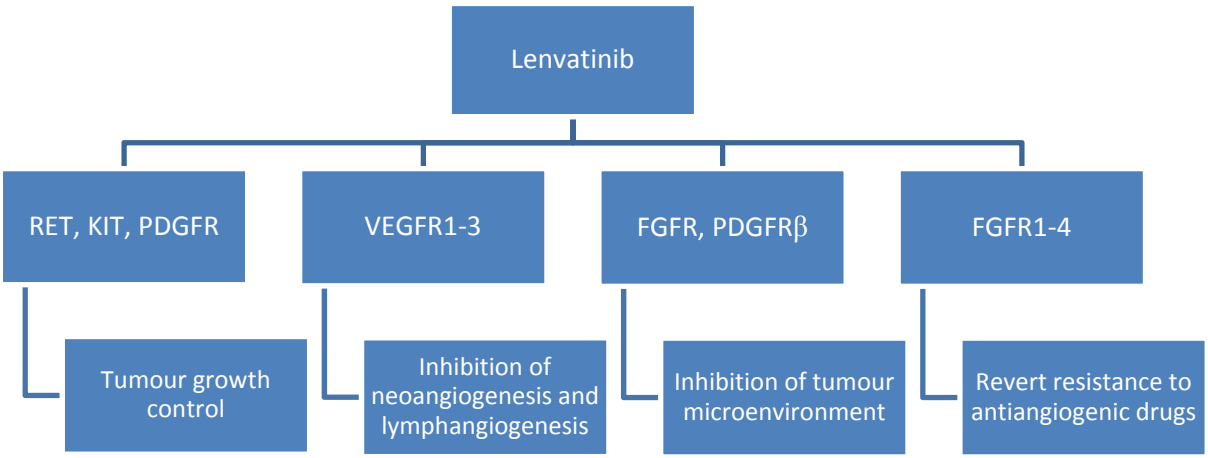
Figure 4 Mechanism of action of lenvatinib on tumour cells and endothelial cells



Adapted from (Andrae, et al., 2008); (Matsui, et al., 2008a); (Matsui, et al., 2008b); (Turner, 2010); (Folkman, 2002).

Figure 5 shows the proposed multiple modes of action of lenvatinib. The difference between lenvatinib and other TKIs is its potency with regard to inhibition of FGFR-1 offering a potential opportunity to block one of the well-known mechanisms of resistance to VEGF/VEGFR inhibitors (Stjepanovic & Capdevila, 2014).

Figure 5 Proposed mechanism of action of lenvatinib



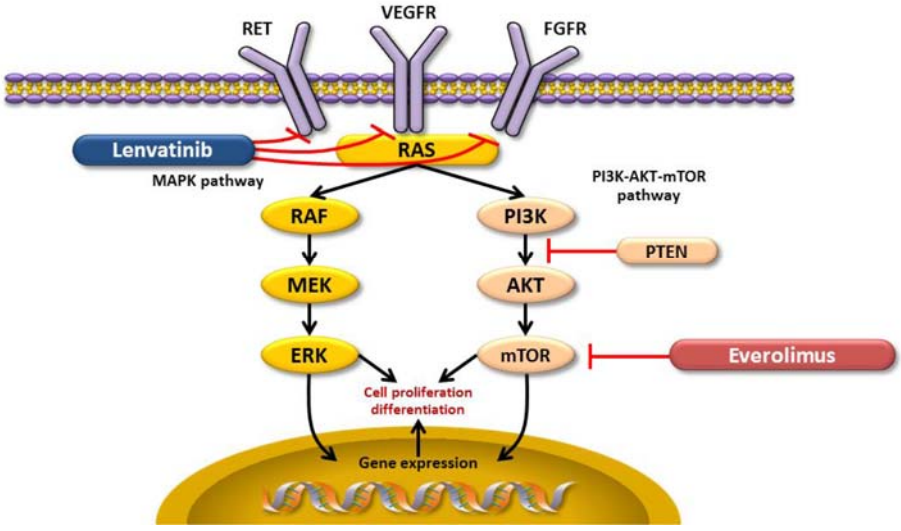
Adapted from Stjepanovic & Capdevila, 2014. (Stjepanovic & Capdevila, 2014)
RET, rearranged during transfection tyrosine kinase receptor; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor.

Rationale for development of lenvatinib in combination with everolimus for advanced RCC

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to an intracellular protein, forming a complex that inhibits mTOR activity. The inhibition of this signalling pathway interferes with the translation and synthesis of proteins involved in the cell cycle, angiogenesis and glycolysis. Everolimus also reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours in vitro and *in vivo* (European Medicines Agency, 2014).

The scientific rationale for combining lenvatinib and everolimus was to target angiogenesis and tumour cell survival, as well as to escape resistance mechanisms to antiangiogenic therapy. The dual targeting of the receptor tyrosine kinase and mTOR pathways by lenvatinib and everolimus respectively (Figure 6) may contribute towards the increased anti-tumour activity of the combination compared to each agent alone.

Figure 6 Inhibition of receptor tyrosine kinase and mTOR pathways by lenvatinib and everolimus: proposed mechanism of action



2.2 Marketing authorization and health technology assessment

Lenvatinib was granted a European marketing authorisation, valid in the UK, on Aug 28th, 2016.

The indication authorised by EMA, which is the object of the present appraisal, is the following:

> *Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.*

Kisplyx treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies.

The SmPC for Kisplyx is included in Appendix 8.1. Summary of product characteristics and the assessment report issued by the EMA is provided in Appendix 8.2 European Medicines Agency. Kisplyx Assessment Report. Procedure Nº EMEA/H/C/004224/0000.

The EMA requested a post-hoc blinded independent imaging review to confirm the benefit shown in the primary analysis, in which, as per the protocol stated, response was assessed by the investigators. In addition, two updated OS analyses with the span of more than 1 year were presented to the EMA.

Kisplyx was launched in the UK on the 12th October in 2016.

Kisplyx is not / has not been subject to any other technology assessment in the UK.

2.3 Administration and costs of the technology

Figure 7 Costs of the technology being appraised

Pharmaceutical formulation	Lenvima® is supplied as 4mg and 10mg hard capsules, available in packs of 30.
Acquisition cost (excluding VAT) *	The list price for the 4mg and 10mg packs is £1,437.00.
Method of administration	Oral
Doses	The recommended daily dose of lenvatinib is 18 mg (one 10 mg capsule and two 4 mg capsules) once daily in combination with 5 mg of everolimus once daily. The daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/toxicity management plan.
Dosing frequency	Once daily
Average length of a course of treatment	The median duration of treatment for patients taking the lenvatinib and everolimus combination was 8.0 months in the Phase II Study 205. (EisaiDoF, 2016)
Average cost of a course of treatment	For lenvatinib, at the list price, based on the median daily dose of 13.6mg in the Phase II Study 205 (Motzer, et al., 2015), this equates to 1x10mg tablet and 1x4mg tablet, which is £2,874 per month. For everolimus, at the list price, the median daily dose was 4.7mg in the Phase II Study 205 (Motzer, et al., 2015), which is £2,250 per month. Therefore, at a median duration of treatment of 8.0 months ((EisaiDoF, 2016), the lenvatinib and everolimus combination works out at an overall cost of £40,992.
Anticipated average interval between courses of treatments	Not applicable.
Anticipated number of repeat courses of treatments	Not applicable.

Pharmaceutical formulation	Lenvima® is supplied as 4mg and 10mg hard capsules, available in packs of 30.
Dose adjustments	Management of adverse reactions may require dose interruption, adjustment, or discontinuation of the combination therapy. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of the combination of medicines until improvement. For toxicities thought to be related to lenvatinib, upon resolution/improvement of an adverse reaction treatment should be resumed at a reduced dose of 14, 10 or 8 mg daily based on the previous dose level. For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate day dosing, or discontinued. For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced prior to reducing everolimus.
Anticipated care setting	Lenvatinib treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. Lenvatinib in combination everolimus will be prescribed in hospital oncology units and dispensed to outpatients.

Source: Kisplyx Summary of Product Characteristics (Appendix 8.1), unless otherwise stated

2.4 Changes in service provision and management

No additional tests or investigations are needed to identify the population to be treated with lenvatinib in combination with everolimus.

Kisplyx treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. Hospital oncology units already have the staffing needed for the administration of cancer treatments and no changes in the pattern of services provided are expected. Since both lenvatinib and everolimus are orally administered drugs, they can be administered at an outpatient clinic and/or taken at home. No additional infrastructure will therefore need to be put in place.

Compared to axitinib, lenvatinib in combination with everolimus adds the convenience of once daily administration, which potentially could improve treatment adherence. Compared to nivolumab, lenvatinib in combination with everolimus has the advantages of the oral route versus intravenous administration.

Patients treated with lenvatinib in combination with everolimus should be followed-up and monitored for detection of adverse events as recommended in the SmPC:

- BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter to start antihypertensive therapy as soon as elevated BP is confirmed.
- Urine protein should be monitored regularly with dipsticks.
- Patients should be monitored for clinical symptoms or signs of cardiac decompensation.
- Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment.
- Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment.
- Thyroid function should be monitored before initiation of, and periodically throughout treatment.

Although these precautions add extra time to be devoted to these patients, it is considered that they do not differ from those which are the standard monitoring measures for cancer patients treated with other TKIs.

In addition to everolimus, no other concomitant therapies are specified in the marketing authorisation for lenvatinib. Specific treatments for correct AE management are recommended as required.

2.5 Innovation

The current clinical practice for mRCC is treatment with single agents in a sequential manner that target VEGF or mTOR (Escudier, et al., 2016). Combinations of mTOR-targeted agents (everolimus and temsirolimus) and VEGF-targeted agents (bevacizumab and sorafenib) investigated in first line treatment of advanced RCC yielded disappointing results, showing only modest clinical activity and greater toxic effects than with single-agent targeted treatments (Motzer, et al., 2015). In addition, combination of the TKI sunitinib and mTOR inhibitors (everolimus or temsirolimus) appeared prohibitively toxic in separate phase I trials (Buonerba, et al., 2016).

Lenvatinib in combination with everolimus is considered to provide substantial innovation to current management of second-line mRCC patients who have

progressed after one previous VEGF-targeted therapy since this is the first and only TKR inhibitor plus mTOR inhibitor regimen authorised in this setting. A synergistic effect has been shown for the combination, with higher efficacy levels in terms of PFS and response rate than for each of the individual agents separately. This benefit has been proved clinically significant for the combination compared to everolimus, which has been very recently recommended by NICE for second line treatment of RCC after TKI failure. In addition, the combination allows the administration of lower doses than those used for each of the individual agents and offers an acceptable safety profile at a convenient once daily oral regimen for patients that could help fulfil the high unmet need in this population.

No other health-related benefits but those already captured in the QALY calculation were identified.

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

3.1 Disease overview

Kidney cancer is a generic term that includes both the cancers originating in the renal parenchyma itself and those originating in the urothelial epithelium of the renal pelvis, the renal vessels and the connective tissue. The most common type of kidney cancer is renal cell cancer (RCC), which originates in the epithelium of the renal tubules and accounts for about 85% of all diagnosis of kidney cancer. Within RCC, clear cell cancer is by far the most frequent histological subtype, accounting for up to 80% of all cases.

Smoking and obesity are well-known risk factors for developing renal cancer. Patients with end-stage renal disease, undergoing hemodialysis for a long time and those who have received a kidney transplant are also at a higher risk of kidney cancer. In addition to these, diabetes and high blood pressure have also been identified as possible risk factors. A small number of kidney cancers are hereditary.

Classically, RCC is diagnosed by the triad of pain in the flank, haematuria and abdominal palpable mass. Nevertheless, more than 50% of cases are now diagnosed incidentally when a renal mass is discovered in an abdominal US examination or MRI scan performed for any other reason (Escudier, et al., 2016).

The American Joint Committee on Cancer (AJCC) have designated a tumour–node–metastasis (TNM) staging classification system for RCC. The diagnosis of advanced or metastatic stage IV cancer is made when the tumour has invaded the connective sheath surrounding the kidney (T4NxM0) or when there are distant metastasis, irrespective of the size of the tumour (TxNxM1) (Edge, et al., 2010).

Even though some patients with advanced and metastatic RCC can still benefit from surgery, when the tumour relapses after surgical excision, the disease is spread at the time of diagnosis or the tumour is unresectable, systemic drug treatment is the only remaining option (National Comprehensive Cancer Network, NCCN, 2016). The choice of the systemic treatment is driven by histological type and risk stratification.

There are several prognostic classifications to stratify risk in metastatic RCC. The Memorial Sloane Kettering Cancer Centre (MSKCC) score is based on five criteria (interval from diagnosis to treatment, Karnofsky performance status [PS], and serum levels of LDH, calcium and haemoglobin) and allows risk stratification in three different levels: good, intermediate and poor. This score was further refined by the International Metastatic RCC Database Consortium (IMDC) who identified six prognostic factors for survival: all those in the MSKCC score but the LDH serum level criterion, plus the neutrophil and platelet counts. IMDC criteria are also known as Heng's model (National Comprehensive Cancer Network, NCCN, 2016; Escudier, et al., 2016).

Until late 2005, systemic treatment choices for metastatic RCC were restricted to cytokine therapy. This last decade has witnessed the arrival of targeted therapy with the approval of a number of tyrosine-kinase inhibitors (TKIs) and anti-VEGF antibodies, which have become widely used both in first and second line treatment of advanced RCC (National Comprehensive Cancer Network, NCCN, 2016). Anyway, there is still a large unmet need for these patients, since median overall survival in patients treated with 1-2 TKIs still ranges from 14 to 25 months (OS results from RCTs comparative vs active treatment) and less than 10% of patients survive for 5 years or longer (Cancer Research UK, 2017b).

3.2 Effects on patients, carers and society

Kidney cancer is the seventh most common cancer in the UK (2014), accounting for 3% of all new cases of cancer. There were around 12,500 new cases diagnosed in 2014 with a male to female incidence ratio of 5 to 3. Half (50%) of kidney cancer cases in the UK each year are diagnosed in people aged 70 and over (2012-2014) with the highest incidence in people aged 85-89 (2012-2014). Kidney cancer incidence rates have increased by 41% in the UK over the last decade and are projected to further increase by 26% between 2014 and 2035 (Cancer Research UK, 2017b).

Early stages of kidney cancer are usually asymptomatic and by the time symptoms appear and the patient seeks medical assistance the disease is very often extended locally or disseminated. More than 40% of patients are diagnosed at a late stage with

a huge impact in overall survival. When diagnosed at its earliest stage, more than 80% people with kidney cancer will survive their disease for five years or more, compared with less than 1 in 10 people when at the latest stage (Cancer Research UK, 2017b).

There were around 4,400 kidney cancer deaths in the UK in 2014, accounting for 3% of all cancer deaths. Kidney cancer mortality rates have increased by 6% over the last decade, they are projected to fall by 15% in the UK between 2014 and 2035 (Cancer Research UK, 2017b).

Health-related quality of life (HRQoL) issues related to tumor burden include anorexia-cachexia syndrome which, in addition to weight loss and lethargy, may involve fever, night sweats, and dysgeusia; anemia, which is often a presenting symptom; hypercalcemia, which may cause confusion and constipation; pain (somatic, visceral, and neuropathic); and venous thromboembolism (Cella, 2011). RCC usually spreads in the vicinity of the kidney or distantly to lungs, bone, brain and liver (Cancer Research UK, 2017a) and metastases are associated with symptoms specific to the site involved; for example, lung metastases may cause airway obstruction, bleeding, and dyspnea. The psychosocial impact of diagnosis with an incurable, poor-prognosis malignancy such as mRCC also is considerable. Among patients participating in a study to develop a kidney cancer–specific symptom index, patient-identified psychosocial concerns included emotional distress, losing hope, worry about the illness progressing, and HRQoL concerns (Cella, et al., 2006)

3.3 Clinical pathway of care

Most patients are currently being treated in first line with a TKI (Escudier, et al., 2016). Amongst the TKIs, sunitinib and pazopanib are the most commonly used first line treatments worldwide (Escudier, et al., 2016; Cancer Research UK, 2017a). In England and Wales no other targeted therapies but sunitinib and pazopanib are recommended in first line by NICE.

Sorafenib, everolimus, axitinib, nivolumab and cabozantinib are the VEGF-targeted therapies approved for second line treatment after failure of treatment with a first-line TKI. Axitinib was approved by NICE for second line treatment in February 2015. Until

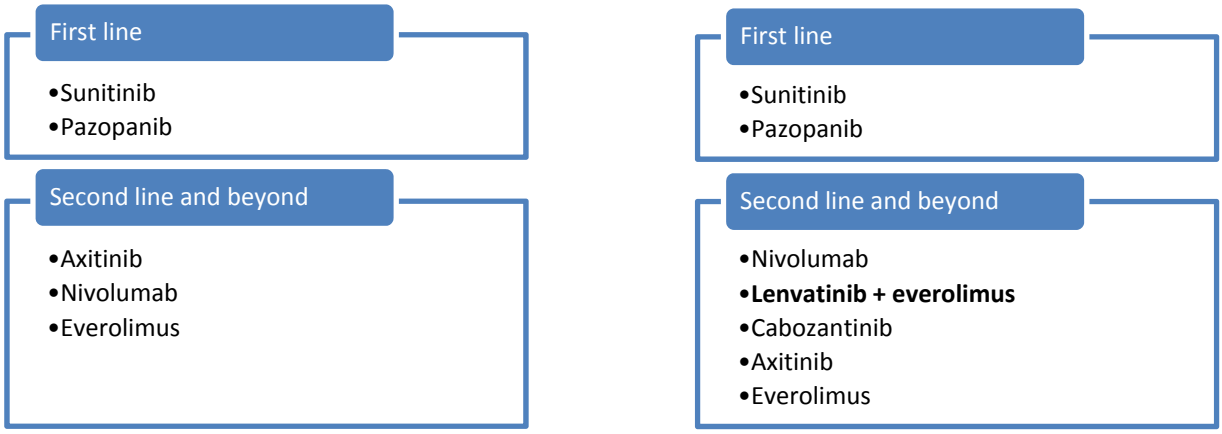
everolimus was recommended by NICE very recently, it was available through the CDF only for those patients who had already received sunitinib or pazopanib and for which second line axitinib was not an option. Sorafenib is not recommended by NICE.

Second line treatment after TKI failure is expected to be challenged by the arrival of nivolumab and cabozantinib (Escudier, et al., 2016), which are very likely destined to become standard treatments for patients already exposed to TKIs in first line. Nivolumab has already been recommended by NICE and cabozantinib is currently undergoing NICE assessment with final guidance expected in June 2017.

Lenvatinib in combination with everolimus emerges as an option to both currently approved nivolumab and axitinib for the most serious patients in whom big tumour mass or fast-progressing disease necessitate a rapid response. In this context, lenvatinib will benefit from the recently approved use of everolimus in second line.

Current and anticipated future clinical pathways for drug treatment for advanced and metastatic renal cancer in England are presented in the diagram in Figure 8.

Figure 8 Current and anticipated future clinical pathways for drug treatment for advanced and metastatic renal cancer in England



3.4 Life expectancy and estimation of the population to be treated

The number of adults in England and Wales who have advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy and are eligible to receive

the lenvatinib and everolimus combination are estimated below and detailed further in Section 6.

The number of cases of kidney cancer was estimated by applying an annual incidence rate (CancerResearchUK, 2017c) to the population of England and Wales estimating the incidence of kidney cancer to be 11,713.

Of these 11,713 patients with kidney cancer, it is estimated that 86% (10,074 patients) will have renal cell carcinoma (CancerResearchUK, 2017d)) and 25% (2,519 patients) of these patients will have metastatic or advanced disease (CancerResearcUK, 2017e).

Further estimations of number of metastatic RCC patients who would receive second-line treatment are taken from the the RCC treatment architecture report developed by Kantar Health (CancerMPact, 2015), giving a total number of 990 patients who are eligible to receive second-line treatment.

3.5 NICE guidance

A NICE pathway on Renal Cancer is available and has just been updated in February 2017 (National Institute for Health and Care Excelence, NICE, 2017). With regards to drug therapy for advanced and metastatic renal cancer, NICE recommendations are the following:

- First-line treatment
  - Pazopanib 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
  - Sunitinib 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
  - Bevacizumab, sorafenib and temsirolimus are **not recommended** as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma

- Second-line treatment

  - Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy
  - Nivolumab is recommended, within its marketing authorisation, as an option for previously treated advanced renal cell carcinoma in adults
  - Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine
  - Sorafenib and sunitinib are **not recommended** as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma

No third-line treatments are currently recommended by NICE

Figure 9 summarises technology appraisal guidance issued by NICE in advanced and metastatic renal cancer and their recommendations.

Figure 9 Related NICE technology appraisal guidance

NICE Guidance	Recommendation
Everolimus for advanced renal cell carcinoma after previous treatment Technology appraisal guidance [TA 432] (Replaces TA219) Published Feb 22nd, 2017	Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy, only if the company provides it with the discount agreed in the patient access scheme.
Nivolumab for previously treated advanced renal cell carcinoma. Technology appraisal guidance [TA 417] Published Nov 23rd, 2016	Nivolumab is recommended, within its marketing authorisation, as an option for previously treated advanced renal cell carcinoma in adults, when the company provides nivolumab with the discount agreed in the patient access scheme.
Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. Technology appraisal guidance [TA333] Published Feb 25th, 2015	Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.

NICE Guidance	Recommendation
Pazopanib for the first-line treatment of advanced renal cell carcinoma. Technology appraisal guidance [TA215] Published: Feb 23rd, 2011 Last updated: Aug 1st, 2013	Pazopanib 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 Eastern Cooperative Oncology Group (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.
Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma [TA178] Published Aug 29th, 2009	Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma. Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.
Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Technology appraisal guidance [TA169] Published: Mar 25th, 2009	Sunitinib is recommended as a possible first drug treatment for people with advanced and/or metastatic renal cell carcinoma if immunotherapy (for example, interferon alfa) would be suitable for them and they are mobile and can do light housework or office work.

3.6 Other clinical guidelines

Treatment guidelines have been developed by the European Society for Medical Oncology (ESMO) in Europe and by the National Comprehensive Cancer Network (NCCN) in the United States.

ESMO Clinical guidelines on RCC

The European Society of Medical Oncology (ESMO) updated their clinical practice guidelines for diagnosis, treatment and follow-up or renal cell carcinoma in 2016 (Escudier, et al., 2016).

Figure 10 summarises the ESMO algorithm for the management of metastatic clear cell RCC. Recommendations mainly relate to clear cell histology and differ according to risk stratification. Beyond the first line, recommendations are based on the treatments already administered in previous lines.

Sunitinib, bevacizumab in combination with interferon and pazopanib are the standard recommended options for first line treatment of patients with good or intermediate prognosis. Temsirolimus is the standard first line treatment for patients with poor prognosis whilst sunitinib qualifies as the best alternative in this population.

After first line cytokines, axitinib, sorafenib and pazopanib have been shown to be active. After first line with VEGF-targeted therapy, everolimus, axitinib and sorafenib could be used. Nevertheless, second line treatment after TKIs is being *dramatically modified* by the arrival of nivolumab and cabozantinib, which have shown very significant improvement in OS and response rate versus everolimus. Both are now recommended by ESMO as the standard post-TKI second line therapy on the basis of their availability. In addition, a positive reference is made towards the combination of lenvatinib and everolimus in this setting, citing the small size of the E7080-2017 study as the reason for the combination not to be added to current guidelines at this stage. It is worth noting that the guidelines were issued before the EMA granted the marketing authorisation for Kisplyx® in combination with everolimus for second line treatment of advanced RCC.

Figure 10 ESMO guidelines for the management of metastatic RCC of clear cell histology

First line treatment	**Good or intermediate risk**		**Poor risk**	
	Standard: Sunitinib [I, A] Bevacizumab + IFN [I, A] Pazopanib [I, A]		Standard: Temsirolimus [II, A]	
	Option: High dose IL2 [III, C] Sorafenib [II, B] Bevacizumab + low dose IFN [III, B]		Option: Sunitinib [II, B] Sorafenib [III, B] Pazopanib [III, B]	
Second line treatment	**Post cytokines**		**Post TKIs**	
	Standard: Axitinib [II, A] Sorafenib [I, A] Pazopanib [II, A]		Standard: Nivolumab [I, A] Cabozantinib [I, A]	
	Option: Sunitinib [III, A]		Option: Axitinib [II, B] Everolimus [II, B] Sorafenib [III, B]	
Third line treatment	**Post 2 TKIs**	**Post TKI and mTOR**	**Post TKI / nivolumab**	**Post TKI / Cabozantinib**
	Standard: Nivolumab [II, A] Cabozantinib [II, A]	Standard: Sorafenib [I, B] Nivolumab [V, A] Cabozantinib [V, A]	Standard: Cabozantinib [V, A]	Standard: Nivolumab [V, A]
	Option: Everolimus [II, B]	Option: Other TKI [IV, B] Rechallenge [IV, B]	Option: Axitinib [IV, C] Everolimus [IV, C]	Option: Everolimus [V, B] Axitinib [V, B]

Abbreviations: mTOR, Mammalian Target of Rapamycin; TKI, Tyrosine Kinase Inhibitor
Source: (Escudier, et al., 2016).

Levels of evidence: I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomised trials without heterogeneity; II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity; III Prospective cohort studies; IV Retrospective cohort studies or case–control studies; V Studies without control group, case reports, experts opinions
Grades of recommendation: A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended; B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended; C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional;D Moderate evidence against efficacy or for adverse outcome, generally not recommended; E Strong evidence against efficacy or for adverse outcome, never recommended

Figure 11 NCCN Guidelines for the management of relapse or stage IV and surgically unresectable RCC

Clear cell histology First-line therapy*	▪ Clinical trial ▪ Pazopanib (category 1, preferred) ▪ Sunitinib (category 1, preferred) ▪ Bevacizumab + interferon (category 1) ▪ Temsirolimus (category 1 for poor-prognosis patients, category 2B for selected patients of other risk groups) ▪ Axitinib ▪ High-dose IL-2 for selected patients ▪ Sorafenib for selected patients
Clear-cell histology Subsequent therapy*	▪ Clinical trial ▪ Cabozantinib (category 1, preferred) ▪ Nivolumab (category 1, preferred) ▪ Axitinib (category 1) ▪ Lenvatinib+everolimus (category 1) ▪ Everolimus ▪ Pazopanib ▪ Sorafenib ▪ Sunitinib ▪ Bevacizumab (category 2B) ▪ High-dose IL-2 for selected patients (category 2B) ▪ Temsirolimus (category 2B)
Non-clear cell histology Systemic therapy*	▪ Clinical trial (preferred) ▪ Sunitinib (preferred) ▪ Axitinib ▪ Bevacizumab ▪ Cabozantinib ▪ Erlotinib ▪ Everolimus ▪ Lenvatinib+everolimus ▪ Nivolumab ▪ Pazopanib ▪ Sorafenib ▪ Temsirolimus (category 1 for poor-prognosis patients, category 2A for other risk groups)

* Best supportive care must be included in all case
Adapted from (National Comprehensive Cancer Network, NCCN, 2016)

NCCN Categories of evidence and consensus
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
Unless otherwise noted, all recommendations are category 2A

NCCN Guidelines on Kidney Cancer

The National Comprehensive Cancer Network (NCCN) issued the version 2.2017 of their Guidelines on Kidney Cancer in October 2016 (National Comprehensive Cancer Network, NCCN, 2016). NCCN recommendations for the systemic treatment of relapse or stage IV and surgically unresectable RCC are summarised in Figure 11. The NCCN Kidney Cancer Panel has listed pazopanib and sunitinib as preferred category 1 options for first-line treatment. Also recommended as category 1 options are bevacizumab plus interferon and temsirolimus in patients with poor prognosis. For subsequent therapy for patients with predominantly clear cell carcinoma, cabozantinib and nivolumab are the category 1 preferred options. Also recommended as category 1 by the NCCN are lenvatinib in combination with everolimus and axitinib. For non-clear cell carcinoma, the preferred options are inclusion in clinical trials and sunitinib.

3.7 Issues relating to clinical practice

Despite recent availability within NHS England of several VEGF-targeted therapies for treatment of advanced RCC after failure of a first TKI, there is still a huge unmet need in this population. New treatments with demonstrated efficacy in terms of OS and response rate and with a different safety profile are very much needed to increment patient's and doctor's choice, especially for those patients with a big tumour burden or rapidly progressing disease, who could benefit from synergistic combinations that to date have not been explored in this clinical setting.

3.8 Assessment of equality issues

The use of lenvatinib in combination with everolimus for previously treated advanced RCC is not expected to raise any equality issues.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic literature review was carried out in order to identify relevant studies for lenvatinib in combination with everolimus and relevant comparators (specifically cabozantinib, nivolumab, temsirolimus, everolimus, pazopanib, sunitinib, sorafenib, bevacizumab or axitinib) for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy. The comparators listed in the systematic literature search exceeded that in the final decision problem, in which comparators were limited to axitinib, nivolumab, everolimus and cabozantinib. (Figure 1).

Search strategy

The following databases were screened in line with standard methodology:

- Embase + MEDLINE;
- the Cochrane Library; and
- MEDLINE In-process and Other Non-indexed Citations (PubMed).

Additional trial databases and relevant scientific conferences were also included for the clinical search and “grey” literature sources were searched manually for any additional information.

The search strategies are provided in the Appendix 8.3. Systematic literature Review.

Study selection

The searches were limited to records for English language articles, excluding non-human studies and publications that are reviews (except for systematic reviews and meta-analyses), case reports, editorials, letters and notes/comments, where the indexing allowed. Figure 12 summarises the inclusion and exclusion criteria, language restrictions and the study selection process.

Figure 12 Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	▪ Lenvatinib ▪ Cabozantinib ▪ Nivolumab ▪ Temsirolimus ▪ Everolimus ▪ Pazopanib ▪ Sunitinib ▪ Sorafenib ▪ Bevacizumab ▪ Axitinib	Not second line a/mRCC treatment after one prior anti-VEGF therapy Surgical /Radiotherapy /Diagnostic intervention
Outcomes	▪ Progression free Survival ▪ Overall survival ▪ Response Rate ▪ Adverse events ▪ Quality of life	
Study design	Randomised controlled trials Systematic reviews Meta-analysis	Experimental or non-human studies Not a randomised trial or meta-analysis/systematic review Subgroup analyses/ abstracts/ publications of already identified trial with no additional information provided
Language restrictions	English	Non-English language

Abbreviations: a/m RCC, Advanced /metastatic Renal cell carcinoma; RCC, Renal cell carcinoma; VEGF, Vascular endothelial growth factor

4.2 List of relevant randomised controlled trials

The clinical evidence literature searches for randomised controlled studies in second-line treatment of a/mRCC yielded 3671 unique citations, from which a total of 14 citations corresponding to 8 RCTs were identified for inclusion in this review. Overall, 13 articles were identified from Embase/MEDLINE/Cochrane library and one article identified from the grey literature. One further article was added manually. The PRISMA flow diagram of the number of studies included and excluded at each stage is shown in Figure 13. Figure 14 and Figure 15 list the articles included in the SLR. The complete reference list for excluded studies is provided in the Appendix 8.3. Systematic literature Review.

Figure 13 PRISMA Study Attrition Diagram for Systematic Literature Review of a/mRCC (clinical studies)

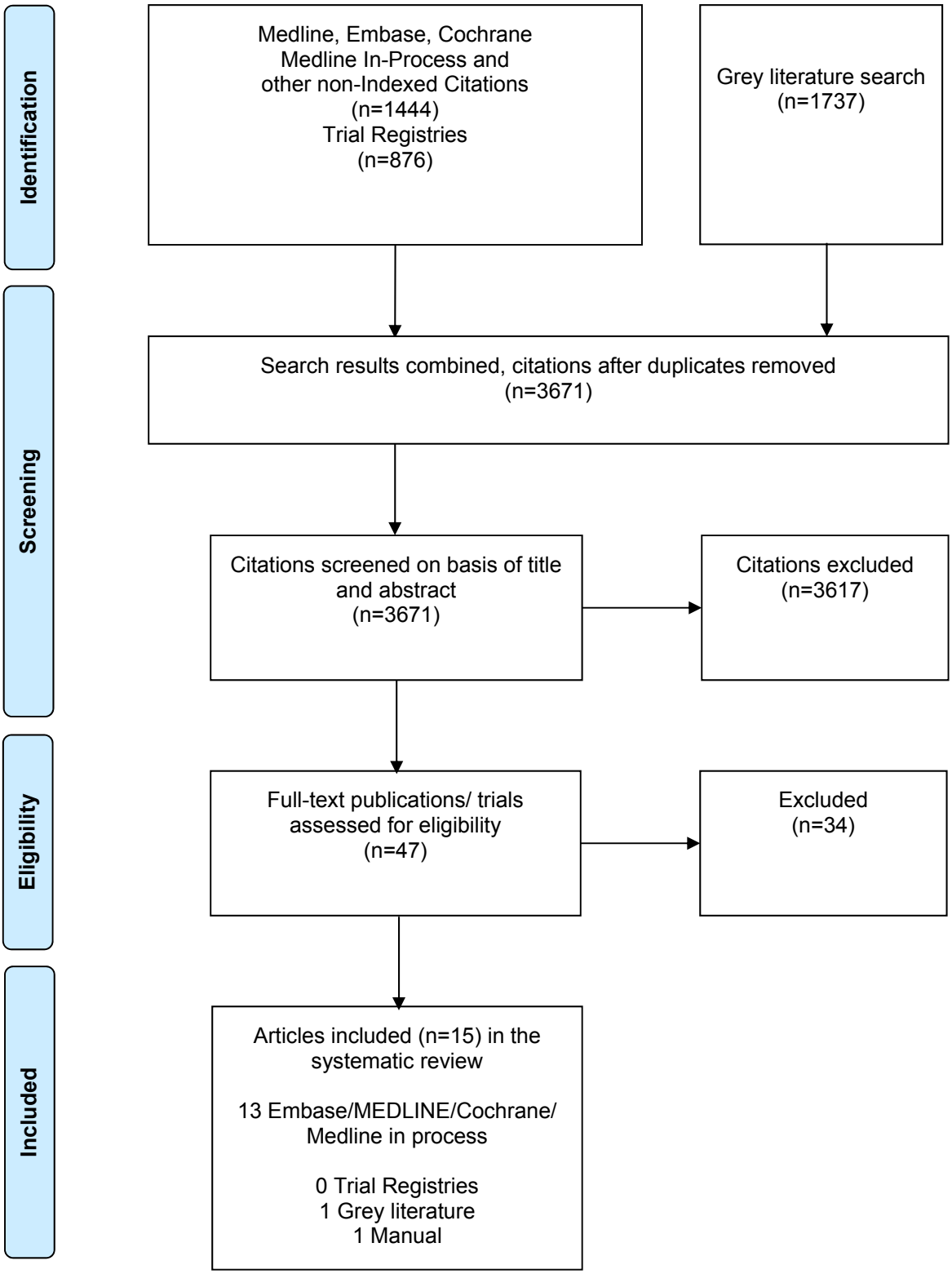


Figure 14 List of included studies from Embase/ MEDLINE/ Cochrane library

	Reference
1	Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al (2015). "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial." Lancet Oncol 16, 1473-1482.
2	Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al (2015). "Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma." The New England journal of medicine 373, 1803-1813.
3	Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. (2015). "Cabozantinib versus everolimus in advanced renal-cell carcinoma." The New England journal of medicine 373, 1814-1823.
4	Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. (2016). "Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial." Lancet Oncol 17(7): 917-927.
5	Motzer RJ, Escudier B, Oudard S, Hutson, TE, Porta C, Bracarda S, et al. (2008). "Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial". The Lancet 372: 449-456.
6	Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al (2010). "Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors." Cancer 116, 4256-4265.
7	Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, Porta C, et al. (2012). "Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study". European Journal of Cancer 48, 333-339.
8	Hutson TE, Bracarda S, Escudier B, Porta C, Figlin RA, Calvo E, et al. (2011). "Phase III, randomised, placebo-controlled study of everolimus in patients with metastatic renal cell carcinoma (mRCC): Subgroup analysis of patients intolerant of prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy." Genitourinary Cancers Symposium, http://meetinglibrary.asco.org/content/46292?media=vm
9	Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. (2011). "Comparative effectiveness of axitinib versus sorafenib in metastatic renal cell carcinoma (AXIS): a randomised phase 3 trial." Lancet 378, 1931-1939.
10	Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. (2013). "Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial." Lancet Oncol 14(6): 552-562.
11	Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, et al. (2014). "Randomised phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma." Journal of Clinical Oncology 32(8): 760-767.
12	Qin S, Bi F, Jin J, Cheng Y, Guo J, Ren X, et al. (2015). "Axitinib versus sorafenib as a second-line therapy in Asian patients with metastatic renal cell carcinoma: results from a randomised registrational study." Onco Targets Ther 8: 1363-1373.
13	Eichelberg C, Vervenne WL, De Santis M, Fischer Von Weikersthal L, Goebell PJ, Lerchenmüller C, et al. (2015). "SWITCH: A randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer." European Urology 68(5): 837-847.

Figure 15 List of included studies from grey literature

	Reference
1	Motzer RJ, Sharma P, McDermott DF, George S, Hammers HJ, Srinivas S, et al (2016). "CheckMate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC)." J Clin Oncol 34, (suppl 2S; abstr 498).
2	Motzer RJ, Hutson TE, Ren M, Dutcus C, Larkin J. (2016) Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. The Lancet. Oncology 17 e4-5

Only one RCT examining the intervention appraised was identified in the literature search. This study, E7080-G000-205, is an open-label, multicentre phase 1b/2 study of lenvatinib alone, and in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma following one prior VEGF-targeted treatment. The study E7080-G000-205 compared lenvatinib with everolimus, one of the appropriate comparators identified in the final scope as relevant to the decision problem and provided most of the evidence on the clinical benefit of lenvatinib in this indication. Figure 16 below summarises the population of the study and the treatments compared in study E7080-G000-205. The primary reference for this study was published by Motzer et al. in Lancet Oncology in 2015 (Motzer, et al., 2015). A letter to the editor also by Motzer et al. published in the same journal in 2016 reported the ad hoc retrospective analysis of efficacy with an independent review of response agreed with regulatory agencies (Motzer, et al., 2016).

Figure 16 List of relevant RCTs

Trial number	Population	Intervention	Comparator	Primary study reference
E7080-G000-205 (Study 205)	▪ Male or female aged ≥18 years ▪ Unresectable or advanced RCC, histological or cytological confirmation of predominant clear cell RCC ▪ Disease progression on or within 9 months of stopping prior therapy, 1 prior VEGF-targeted therapy ▪ ECOG PS ≤1	▪ Lenvatinib 18 mg/day plus everolimus 5 mg/day ▪ Lenvatinib 24 mg/day	Everolimus 10 mg/day	(Eisai Ltd., 2015) (Motzer, et al., 2015) (Motzer, et al., 2016)

To date, no RCTs comparing lenvatinib with any other TKI in RCC have been carried out.

Seven other RCTs identified in the SLR examining the active comparators included in the final scope are described in section 4.10. Indirect and mixed treatment comparisons.

4.3 Summary of methodology of the relevant randomised controlled trials

Unless otherwise stated all methodology key aspects in section 4.3 are referred to the Clinical Study Report of the trial E7080-G000-205 (Eisai Ltd., 2015)

Trial design

Randomised, phase 2, open-label, multicentre study, conducted at 37 centres in five countries. Patients were randomly allocated in a 1:1:1 ratio to one of the three treatment arms in the study (lenvatinib + everolimus, lenvatinib alone or everolimus alone) using and interactive voice response system.

Patients were stratified by two factors, both of them lab test results: haemoglobin and corrected serum calcium. Gender-specific cut-off levels were considered.

Eligibility criteria

Eligible participants were male and female adults aged ≥18 years old diagnosed with unresectable or advanced RCC and histological or cytological confirmation of predominant clear cell RCC and radiographic evidence of disease progression on or within 9 months of stopping prior therapy with 1 prior VEGF-targeted therapy. They had at least one measurable lesion according to RECIST criteria (version 1.1). Patients were ECOG performance status of 0 or 1 and had an adequate renal, bone marrow, blood coagulation, liver, and cardiac function confirmed by relevant lab and functional tests.

Patients with brain metastasis and those previously exposed to either lenvatinib or everolimus were excluded from the study.

Settings and locations where the data were collected

This study was conducted by qualified investigators under the sponsorship of Eisai at 37 secondary and tertiary hospitals and cancer centres in 5 countries: Czech Republic (5 sites), Poland (4 sites), Spain (4 sites), the United Kingdom (11 sites), and the United States (13 sites).

The sites in the UK were the following:

- Royal Marsden Hospital – Fulham, London
- Clatterbridge Centre for Oncology - Wirral, Bebington
- Christie Hospital NHS Foundation Trust - Manchester
- Addenbrooke's Hospital, University of Cambridge - Cambridge
- Royal Surrey County Hospital, NHS Foundation Trust - Guildford, Surrey
- Southampton General Hospital - Southampton
- Bristol Haematology and Oncology Centre - Bristol
- Beatson West of Scotland Cancer Centre - Glasgow
- Velindre Cancer Centre - Whitchurch, Cardiff
- The Leeds Teaching Hospitals NHS Trust St. James Institute of Oncology, St. James University Hospital - Leeds
- Tayside Cancer Centre Ninewells Hospital - Dundee

Recruitment took place between March 2012 and June 2014.

Overall, 50 patients were included in the UK, 39 of them in England and Wales.

Trial drugs and concomitant medications

Study treatment was administrated orally once daily in 28-days continuous cycles. Patients in the three study arms were treated as follows:

- Combination lenvatinib plus everolimus: lenvatinib 18 mg/day (one 10 mg and two 4 mg capsules) plus everolimus 5 mg/day (one 5 mg tablet).
- Single-agent lenvatinib: lenvatinib 24 mg/day (two 10 mg and one 4 mg capsules
- Single-agent everolimus: everolimus 10 mg/day (two 5 mg tablets)

Toxicity was managed by treatment interruption, dose reduction, and/or treatment discontinuation. For subjects who experienced single agent everolimus-related severe and/or intolerable suspected AEs, dose alterations were done in accordance

with prescribing information. Dose reduction and interruption for subjects who experienced lenvatinib-everolimus combination therapy-related toxicity and single-agent lenvatinib-related toxicity were done in accordance with protocol pre-specified dose adjustment instructions. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent.

Primary and secondary outcomes

The primary objective of the study was to compare the progression-free survival (PFS) of 1) lenvatinib in combination with everolimus and 2) single-agent lenvatinib vs single-agent everolimus. PFS was defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by the investigator using RECIST 1.1

Secondary objectives were the following:

- To determine the tolerability and safety profile of lenvatinib in combination with everolimus and of single agent lenvatinib.
- To compare PFS of lenvatinib-everolimus combination therapy to single-agent lenvatinib.
- To assess Overall Survival (OS), measured from the date of randomization until date of death from any cause.
- To assess

  - Objective response rate (ORR), defined as the proportion of subjects who had best overall response (BOR) of Complete response (CR) or Partial response (PR) as determined by the investigator using RECIST 1.1
  - Disease control rate (DCR), defined as the proportion of subjects who had BOR of CR or PR or Stable disease (SD) (minimum duration from randomization to SD ≥7 weeks)
  - Durable SD, defined as the proportion of subjects with duration of SD ≥23 weeks.
  - Clinical benefit rate (CBR) defined as the proportion of subjects who had BOR of CR or PR or durable SD.

Figure 17 Summary of E7080-G000-205 study methodology

Settings and locations	Multicentre trial conducted at 37 tertiary care hospitals and cancer centres in 5 countries: Czech Republic (5 sites), Poland (4 sites), Spain (4 sites), the United Kingdom (11 sites), and the United States (13 sites)
Trial design	Parallel-group, randomised, open-label, comparative vs active treatment
Eligibility criteria	▪ Adults aged ≥18 years old ▪ Unresectable or advanced RCC and histological or cytological confirmation of predominant clear cell RCC ▪ Radiographic evidence of disease progression on or within 9 months of stopping prior therapy with 1 prior VEGF-targeted therapy ▪ One measurable lesion according to RECIST criteria ▪ ECOG performance status of 0 or 1 ▪ Adequate renal, bone marrow, blood coagulation, liver, and cardiac function
Trial drugs	Study treatment was administrated orally once daily in 28-days continuous cycles. The study included three treatment arms: ▪ Combination lenvatinib-everolimus (n=51): lenvatinib 18 mg/day (one 10 mg and two 4 mg capsules) plus everolimus 5 mg/day (one 5 mg tablet). ▪ Single-agent lenvatinib (n=52): lenvatinib 24 mg/day (two 10 mg and one 4 mg capsules ▪ Single-agent everolimus (n=50): everolimus 10 mg/day (two 5 mg tablets)
Permitted and disallowed concomitant medications	Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs) could be given at the discretion of the investigator, unless it was expected to interfere with the evaluation of (or to interact with) lenvatinib and/or everolimus. Subjects were not permitted to receive additional antitumor therapies or investigational agents other than study medication (lenvatinib and everolimus) during the study.
Primary outcome	PFS, defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by the investigator using RECIST 1.1
Secondary outcomes	▪ Tolerability and safety ▪ OS, measured from the date of randomization until date of death from any cause. ▪ ORR: proportion of subjects with BOR of CR or PR as determined by the investigator using RECIST 1.1 ▪ DCR: proportion of subjects with BOR of CR or PR or SD (minimum duration from randomization to SD ≥7 weeks) ▪ Durable SD defined as the proportion of subjects with duration of SD ≥23 weeks ▪ CBR: proportion of subjects with BOR CR or PR or durable SD

Settings and locations	Multicentre trial conducted at 37 tertiary care hospitals and cancer centres in 5 countries: Czech Republic (5 sites), Poland (4 sites), Spain (4 sites), the United Kingdom (11 sites), and the United States (13 sites)
Pre-planned sub-groups	▪ Haemoglobin level (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females ▪ Corrected serum calcium (≥10 mg/dL vs <10 mg/dL)

Abbreviations: AEs, Adverse Events; BOR, Best Overall Response; CBR, Clinical Benefit Ratio; CR, Complete Response; DCR, Disease Control Rate; ECOG, Eastern Cooperative Oncology Group; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression Free Survival; PR, Partial Response; RCC, Renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours; SD, Stable Disease; VEGF, Vascular endothelial growth factor

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Sample size calculation

The planned sample size for the primary analysis required a total of at least 90 PFS events to be observed across all 3 treatment groups and at least 60 PFS events were observed for each of the comparisons of the combination versus the everolimus arm, and the lenvatinib versus the everolimus arm. The assumed median PFS for everolimus 10 mg was 5 months based on historical data. Given that there were no prior clinical data available for the combination of lenvatinib plus everolimus, and limited data for lenvatinib alone in the target population, it was appropriate to consider that a HR=0.67 represents a clinically meaningful improvement in PFS. Under the assumption of an exponential event distribution of the time to PFS random variable, this effect translated into median PFS of 7.5 months. The study was designed as a Phase 2 study where a total of 90 PFS events were required to detect a HR of 0.67 with 70% power using an (1-sided) alpha of 0.15 for the comparison of the combination arm (and lenvatinib arm) versus the everolimus arm. An independent statistical review was conducted to ensure that at least 60 PFS events were observed for each of the comparisons of the combination versus the everolimus arm, and the lenvatinib versus the monotherapy arm. The actual observed number of PFS events was to be used to calculate the hazard ratio when comparing treatment arms.

Interim analysis and stopping guidelines

No interim analyses were planned.

Statistical methods

Full Analysis Set included all randomized subjects. This was the primary analysis set for efficacy, as well as for demographics and baseline characteristics.

Kaplan-Meier (K-M) estimates were used to estimate the median PFS. Median PFS for each arm was presented with 2-sided 95% CIs, and the cumulative PFS probabilities were plotted over time. Hazard ratio (HR) between treatment groups and corresponding 95% CI were estimated using stratified Cox regression model (stratified by haemoglobin and corrected serum calcium) with treatment as a factor.

ORR, DCR, CBR, and durable SD rate were calculated with exact 95% CIs using the method of Clopper and Pearson. Ad-hoc analyses were performed to estimate the crude rate ratio of each treatment comparison and to compute P values using the Fisher's exact (2-sided) test.

For OS, median survival time and the cumulative probability of survival at 12 months, 18 months, and 24 months were calculated using K-M estimates for each treatment arm and presented with 2-sided 95% CIs. K-M survival probabilities for each arm were plotted over time. Subjects who were lost to follow-up and those who were alive at the date of data cut-off were censored. Planned analyses were performed to test null hypothesis of treatment difference in OS at a nominal significance level of 0.05 (2-sided) using the stratified log-rank test using stratification factors. The stratified Cox proportional hazard model was performed to estimate HR between treatment groups and their corresponding 95% CI.

Figure 18 summarises the statistical analysis for the primary endpoint in trial E7080-G000-205.

Figure 18 Summary of statistical analyses in the RCTs

Hypothesis objective	Statistical analysis	Sample size, power calculations	Data management, patient withdrawals
A HR=0.67 represents a clinically meaningful improvement in PFS. Under the assumption of an exponential event distribution of the time to PFS random variable, this effect translated into median PFS of 7.5 months.	Median PFS for each arm was presented with 2-sided 95% CIs. HR between treatment groups and corresponding 95% CI were estimated using stratified Cox regression model with treatment as a factor.	At least 90 PFS events to be observed across all 3 treatment groups and at least 60 PFS events for each of the comparisons versus the everolimus arm. 70% power using an (1-sided) alpha of 0.15 for the comparison of the combination arm versus the everolimus arm	All randomised subjects

Figure 19 CONSORT 2010 Flow diagram E7080-G000-205 study

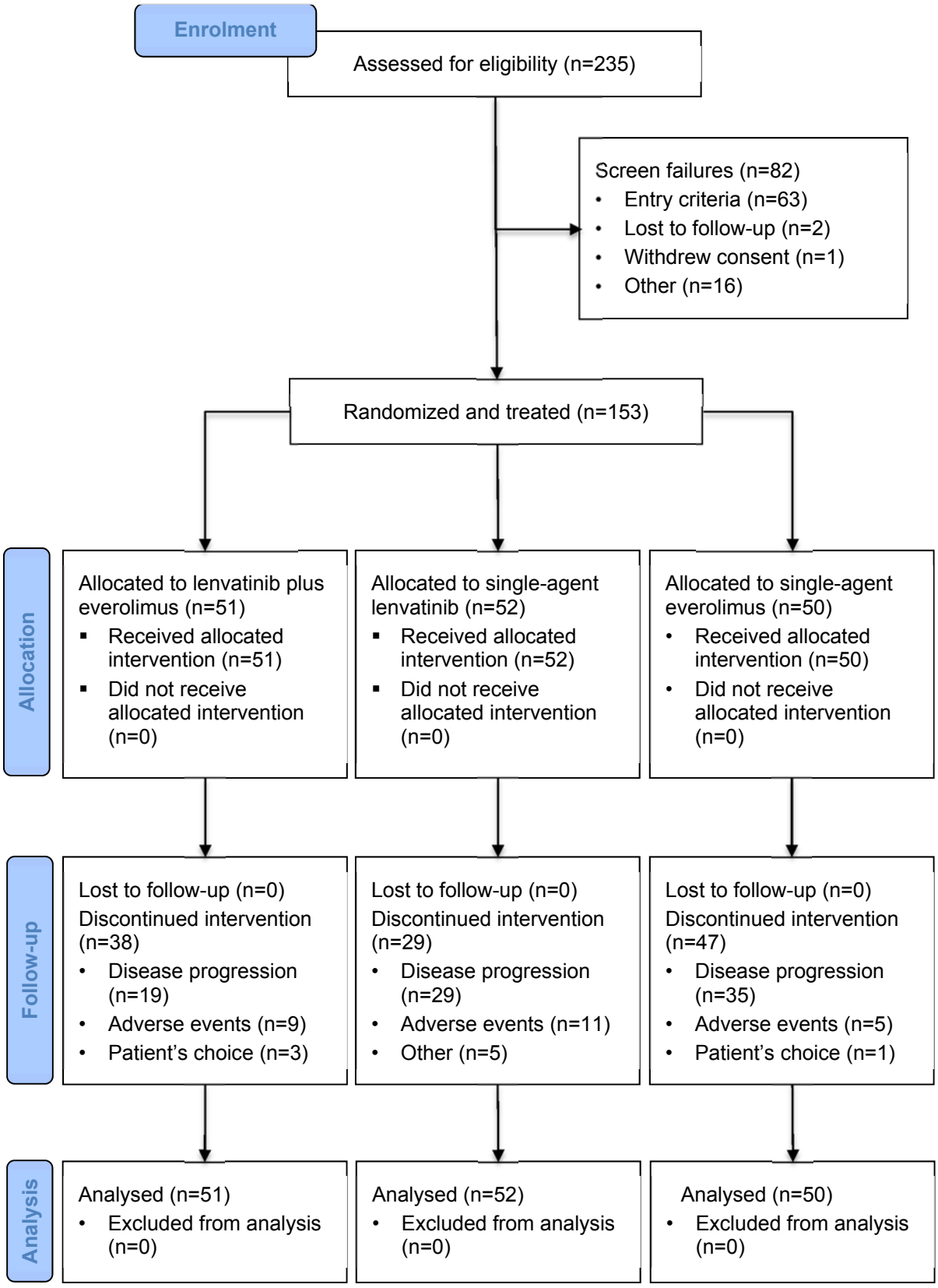


Figure 20 Baseline demographic and disease characteristics of participants in study E7080-G000-205

Baseline characteristic	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Age (years)	61 (44–79)	64 (41–79)	59 (37–77)
Sex			
Men	35 (69%)	39 (75%)	38 (76%)
Women	16 (31%)	13 (25%)	12 (24%)
ECOG Performance status			
0	27 (53%)	29 (56%)	28 (56%)
1	24 (47%)	23 (44%)	22 (44%)
MSKCC risk group			
Favourable	12 (24%)	11 (21%)	12 (24%)
Intermediate	19 (37%)	18 (35%)	19 (38%)
Poor	20 (39%)	23 (44%)	19 (38%)
Heng risk group*			
Favourable	8 (16%)	7 (14%)	9 (18%)
Intermediate	32 (64%)	33 (64%)	29 (58%)
Poor	10 (20%)	12 (23%)	12 (24%)
Haemoglobin, n (%)			
≤130 g/L (men) or ≤115 g/L (women)	33 (65%)	36 (69%)	31 (62%)
>130 g/L (men) or >115 g/L (women)	18 (35%)	16 (31%)	19 (38%)
Corrected serum calcium, n (%)			
≥2・5 mmol/L	6 (12%)	8 (15%)	8 (16%)
<2・5 mmol/L	45 (88%)	44 (85%)	42 (84%)
Number of metastases			
1	18 (35%)	9 (17%)	5 (10%)
2	15 (29%)	15 (29%)	15 (30%)
≥3	18 (35%)	28 (54%)	30 (60%)
Sites of metastasis			
Bone	12 (24%)	13 (25%)	16 (32%)
Liver	10 (20%)	14 (27%)	13 (26%)
Lung	27 (53%)	35 (67%)	35 (70%)
Lymph nodes	25 (49%)	31 (60%)	33 (66%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center

Data are number of patients (%), or median (range). * One patient in the lenvatinib plus everolimus group was excluded because of missing baseline laboratory values.

4.5 Participant flow in the relevant randomised controlled trials

Patients demographic and disease characteristics at baseline are summarised in Figure 20 whilst Figure 21 shows previous treatments received by the participants in the study. The CONSORT diagram showing the flow of participants through each stage of each of the trials is provided in Figure 19.

Figure 21 Previous treatments in study E7080-G000-205

Baseline characteristic	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Previous nephrectomy†	44 (86%)	43 (83%)	48 (96%)
Previous VEGF-targeted therapy‡			
Axitinib	1 (2%)	2 (4%)	0
Bevacizumab	0	1 (2%)	4 (8%)
Pazopanib	9 (18%)	13 (25%)	13 (26%)
Sorafenib	1 (2%)	0	2 (4%)
Sunitinib	36 (71%)	35 (67%)	28 (56%)
Tivozanib	3 (6%)	1 (2%)	2 (4%)
Other	1 (2%)	0	1 (2%)
Duration of previous VEGF-targeted therapy (months)	9.8 (2.0–66.2)	14.5 (0.7–81.8)	8.9 (1.6–57.8)
Best response for previous VEGF-targeted therapy			
Complete response	1 (2%)	0	0
Partial response	14 (28%)	10 (19%)	10 (20%)
Stable disease	20 (39%)	28 (54%)	21 (42%)
Progressive disease	7 (14%)	10 (19%)	15 (30%)
Not evaluated or unknown	9 (18%)	4 (8%)	4 (8%)
Previous checkpoint inhibitor therapy	1 (2%)	2 (4%)	2 (4%)
Previous interferon therapy	4 (8%)	3 (6%)	7 (14%)
Previous radiotherapy	6 (12%)	11 (21%)	11 (22%)

Abbreviations: VEGF, Vascular endothelial growth factor

† One patient in the lenvatinib group had two nephrectomy procedures (partial and left radical) but was only counted once. ‡ All patients had one previous VEGF-targeted therapy.

4.6 Quality assessment of the relevant randomised controlled trials

The methodological quality of the study E7080-G000-205 was examined using the Criteria for assessment of risk of bias in RCTs of the Centre for Reviews and Dissemination of the University of York. Responses to each of the assessment criteria are tabulated in Figure 22.

Study randomisation was done through an interactive voice & web response system (IxRS), the most robust method for concealing the sequence of treatment allocation. With the exception of age (which is not a prognostic factor for RCC), in general the treatment arms were well balanced across parameters, including the independent prognostic factors in RCC: ECOG PS, corrected serum calcium (stratification factor), and haemoglobin level (stratification factor), and the MSKCC and Heng's risk groups.

Since the study was open label, patients and investigators were not blinded for the treatment allocated to each patient. It is uncertain whether this could result in performance bias. Tumour response data were obtained from investigator's assessment of the imaging scans and no independent tumour assessments were performed. It is uncertain whether this could impact the assessment of the main analysis of PFS and ORR but it did not affect the assessment of OS. An ad hoc analysis of efficacy using independent radiological review for response assessment was undertaken as suggested by regulatory agencies.

Figure 22 Criteria for assessment of risk bias in RCT E7080

Trial acronym	E7080-G000-205
Was the method used to generate random allocations adequate?	Yes
Was the allocation adequately concealed?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. Open-label study. Uncertain impact for response assessment for PFS and ORR. No impact for OS.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No

Trial acronym	E7080-G000-205
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Censoring of patients lost to follow-up or alive.

Abbreviations: ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression Free Survival

All patients received the intervention to which they were randomised and there were no unexpected imbalances in drop-outs between the three treatment groups in the study. No other outcomes than those specified in the protocol were measured.

An ITT analysis was performed. Patients lost to follow-up or alive at data cut-off were censored at the date they were last known to be alive.

The study is considered to closely reflect routine clinical practice in England.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Progression free survival

Figure 23 summarises the PFS and PFS rates for all 3 arms. The combination arm showed a statistically significant and clinically meaningful improvement in PFS (HR=0.40, [95% CI: 0.24, 0.68], P=0.0005) compared with the everolimus arm, a 2.5-fold increase in PFS, indicating the superior efficacy of the combination of lenvatinib 18 mg with everolimus 5 mg compared with everolimus 10 mg (Figure 23 and Figure 24). Median PFS was 14.6 months for the combination arm, compared with 5.5 months for the everolimus arm. The superior efficacy of the combination arm was supported by the higher PFS rates at 6 and 12 months for the combination arm compared with the everolimus arm.

The lenvatinib arm also showed a statistically significant improvement in PFS compared with the everolimus arm, with a median PFS of 7.4 months and 5.5 months, respectively (P=0.0479). The HR, as estimated from the stratified Cox regression model, was 0.61 (95% CI: 0.38, 0.98), indicating the superior efficacy of lenvatinib compared with everolimus (Figure 23). This increase in PFS in the

lenvatinib arm was supported by the higher PFS rates at 6 and 12 months (Figure 23) in the lenvatinib arm than in the everolimus arm.

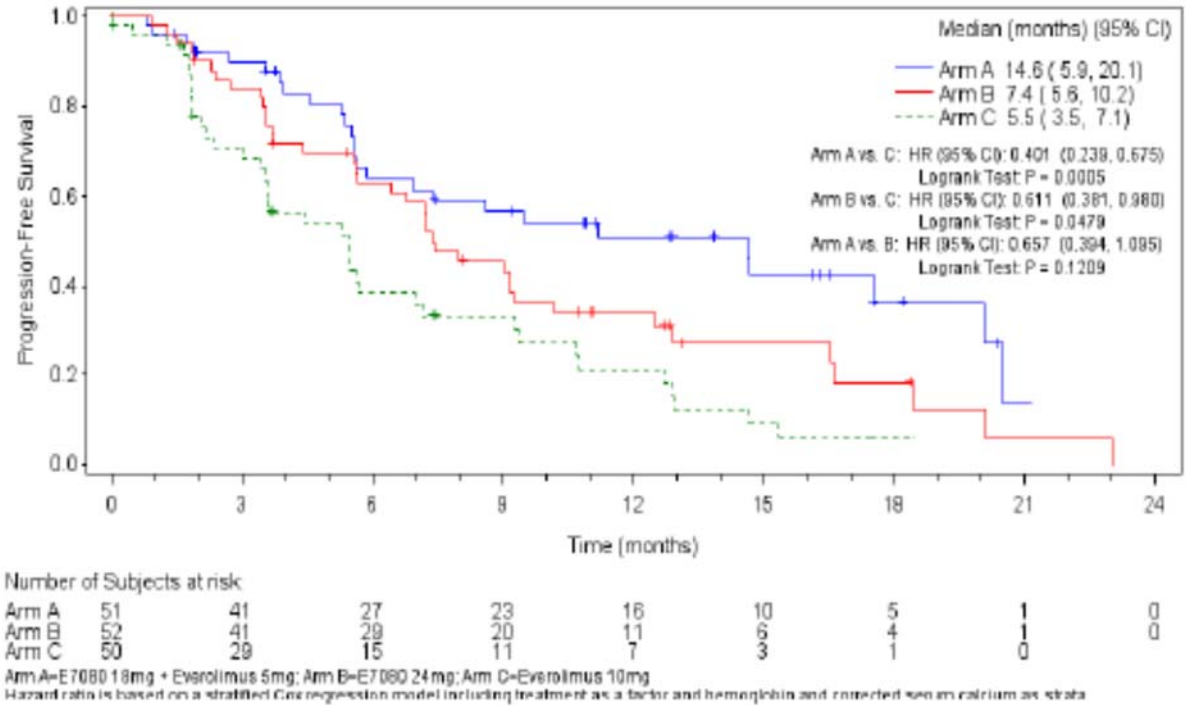
Comparison of the PFS results between the combination arm and the lenvatinib arm was a secondary objective of the study. The combination arm showed a numerical improvement in PFS compared with the lenvatinib arm, with a median PFS of 14.6 months compared with 7.4 months, respectively (Figure 23 and Figure 24). This difference in PFS between the combination arm and the lenvatinib arm was not statistically significant (HR: 0.66; 95% CI: 0.39, 1.10), P=0.1209).

Figure 23 Progression-Free Survival Based on Investigator Assessment – Full Analysis Set

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Events (n)	26 (51%)	38 (73%)	37 (74%9
PFS (months) Median (95% CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
Stratified Hazard Ratio (95% CI)			
Primary endpoints: vs single-arm everolimus	0.40 (0.24, 0.68)	0.61 (0.38, 0.98)	
Secondary endpoint: vs single-arm lenvatinib	0.66 (0.39, 1.10)		
P value based on stratified log-rank test			
Primary endpoints: vs single-arm everolimus	0.0005	0.0479	
Secondary endpoint: vs single-arm lenvatinib	0.1209		
Progression-free survival rate (%) (95% CI)			
At 9 months	56.7 (40.7, 69.9)	45.6 (31.1, 59.0)	33.4 (19.6, 47.8)
At 12 months	50.9 (34.8, 64.9)	34.2 (21.0, 47.8)	21.2 (9.9, 35.5)

Abbreviations: CI, Confidence interval; PFS, Progression-free survival

Figure 24 Kaplan-Meier plot of progression-free survival based on investigator assessment



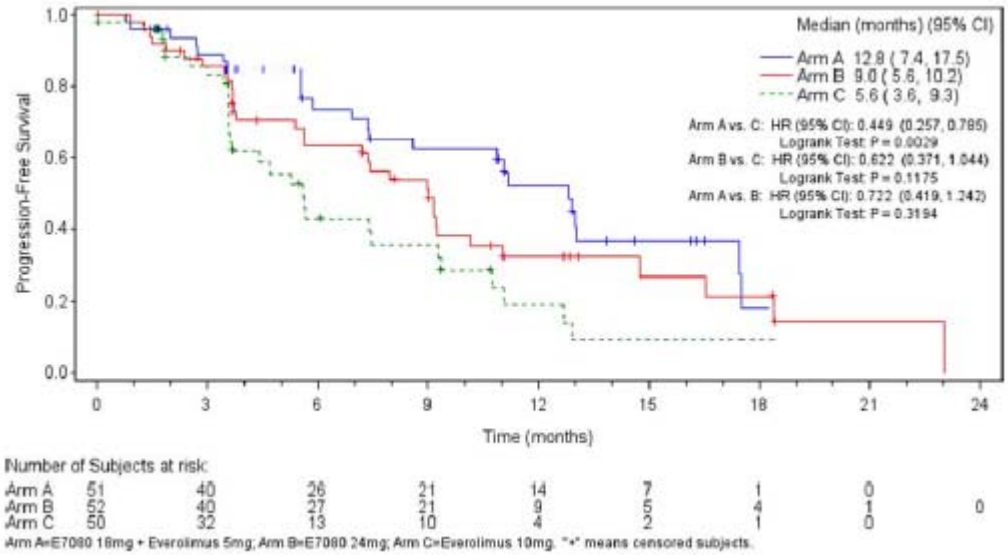
As stated previously, in response to a request from the regulatory agencies, an ad hoc analysis of efficacy using independent radiological review for response assessment was undertaken. Consistent efficacy results were seen regardless of whether the tumour assessment scans were assessed by the investigator or by blinded IIR. (Figure 25, Figure 26)

Figure 25 Progression-Free Survival Based on Independent Assessment

	Lenvatinib + everolimus (n=51)	Single-arm everolimus (n=50)
PFS (months) Median (95% CI)	12.8 (7.4, 17.5)	5.6 (3.6, 9.3)
Hazard Ratio (95% CI)	0.45 (0.26, 0.79) p=0.003	

Abbreviations: CI, Confidence interval; PFS, Progression-free survival

Figure 26 Kaplan-Meier plot of progression-free survival based on independent assessment



Overall survival

At the data cut-off date of 13 Jun 2014, fewer subjects had died in the combination arm (19; 37.3%) than in the everolimus arm (26; 52.0%). The combination arm showed a trend toward prolonged survival compared with the everolimus arm (HR = 0.55 [95% CI: 0.30, 1.01]), with a median OS of 25.5 months for the combination arm and 17.5 months for the everolimus arm (Figure 27).

At the data cut-off date of 13 Jun 2014, 26 subjects had died in each of the lenvatinib (50.0%) and everolimus (52.0%) arms. Overall survival was similar in the 2 treatment arms (HR: 0.74; 95% CI 0.42, 1.31, P=0.29), with a median survival of 18.4 months and 17.5 months in the lenvatinib and everolimus arms, respectively (Figure 27).

At the data cut-off date of 13 Jun 2014, fewer subjects in the combination arm than in the lenvatinib arm had died: 19 subjects (37.3%) versus 26 subjects (50.0%). Overall survival was longer in the combination arm than in the lenvatinib arm, with a median survival of 25.5 months versus 18.4 months, respectively. This numerical difference was not statistically significant (HR: 0.74; 95% CI 0.40, 1.36, P=0.29) (Figure 27).

Figure 27 Summary of Overall Survival - Full Analysis Set

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Deaths (n)	19 (37.3)	26 (50.0)	26 (52.0)
OS (months) Median (95% CI)	25.5 (20.8, 25.5)	18.4 (13.3, NE)	17.5 (11.8, NE)
Stratified Hazard Ratio (95% CI)			
Primary endpoints: vs single-arm everolimus	0.55 (0.30, 1.01)	0.74 (0.42, 1.31)	
Secondary endpoint: vs single-arm lenvatinib	0.74 (0.40, 1.36)		
P value based on stratified log-rank test			
Primary endpoints: vs single-arm everolimus	0.0623	0.2896	
Secondary endpoint: vs single-arm lenvatinib	0.3023		
Overall survival rate (%) (95% CI)			
At 12 months	74.2 (59.7, 84.1)	71.1 (56.7, 81.5)	61.6 (46.6, 73.5)
At 18 months	66.7 (51.2, 78.3)	54.3 (38.9, 67.4)	46.8 (30.5, 61.6)

Data cut-off date = June 13th, 2014. Abbreviations: CI, Confidence Interval; NE = Not estimable.

An ad-hoc analysis was performed to update the OS analysis based on a data cut-off date of 10 Dec 2014. As of this cut-off date, 24 subjects (47.1%) in the combination arm and 33 subjects (66.0%) in the everolimus arm had died. The trend toward a survival benefit seen at the data cut-off for the primary analysis (13 Jun 2014) reached statistical significance in the updated OS analysis (HR 0.51; 95% CI 0.30–0.88; P=0.02) with a median survival of 25.5 months for the combination arm and 15.4 months for the everolimus arm (Figure 28).

As of the updated cut-off date of 10 Dec 2014, 31 subjects (59.6%) in the lenvatinib arm and 33 (66.0%) subjects in the everolimus arm had died. Median OS was 19.1 months versus 15.4 months, respectively (HR: 0.68; 95% CI 0.41, 1.14, P=0.12) (Figure 28).

As of the updated cut-off date of 10 Dec 2014, 24 subjects (47.1%) in the combination arm and 31 (59.6%) subjects in the lenvatinib arm had died. Median survival was 25.5 months in the combination arm versus 19.1 months in the lenvatinib arm. This difference was not statistically significant (HR: 0.75; 95% CI 0.43, 1.30, P=0.32) (Figure 28).

Figure 28 Summary of first update of overall survival – Full Analysis Set

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Deaths (n)	24 (47.1%)	31 (59.6%)	33 (66.0%)
OS (months) Median (95% CI)	25.5 (16.4, NE)	19.1 (13.6, 26.2)	15.4 (11.8, 19.6)
Stratified Hazard Ratio (95% CI)			
Primary endpoints: vs single-arm everolimus	0.51 (0.30, 0.88)	0.68 (0.41, 1.14)	
Secondary endpoint: vs single-arm lenvatinib	0.75 (0.43, 1.30)		
P value based on stratified log-rank test			
Primary endpoints: vs single-arm everolimus	0.0242	0.1181	
Secondary endpoint: vs single-arm lenvatinib	0.3157		
Overall survival rate (%) (95% CI)			
At 12 months	74.5 (60.2, 84.3)	71.2 (56.8, 81.5)	61.6 (46.6, 73.5)
At 18 months	64.7 (50.0, 76.1)	55.8 (41.3, 68.0)	41.1 (27.3, 54.3)

Data cut-off date = December 10th, 2014. Abbreviations: CI, Confidence Interval; NE, Not estimable.

A second OS update was performed at the request of the EMA and FDA, based on the data cut-off date of 31 Jul 2015, when 32 subjects (62.7%) in the combination arm and 37 subjects (74.0%) in the everolimus arm had died. The EMA results of this datacut are presented below and included in the cost effectiveness model (Section 5.3). The difference between the EMA and FDA data lies in the use of different stratification variables: the third cut IVRS dataset was used for the FDA while the third cut CRF data was used for the EMA. Figure 29 below summarises the datacut updates.

Figure 29 Data cut summary

Data cut	Description	Reference
Updated analysis in Motzer, et al., 2015 Date: December 2014 Median follow-up: 24.2 months for LEN+EVE and 25 months for EVE OS completion: 47% PFS completion: 66%	This data cut was originally planned in the clinical trial protocol. The stratification variable used and the power for each analysis was pre-specified. The Motzer (2015) publication included an initial data cut and an updated data cut.	Motzer et al. (2015). Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. The Lancet Oncology , Volume 16 , Issue 15 , 1473 – 1482 Eisai Ltd Study 205 Clinical Study report
EMA request Date: July 2015 (OS); June 2014 (PFS) OS completion: 63% PFS completion: 51%	EMA requested a longer follow-up for overall survival to reduce uncertainty in the OS estimated of Motzer (2015).	Eisai Ltd Summary of Clinical Efficacy
FDA re-stratification Date: July 2015 (OS); June 2014 (PFS) OS completion: 63% PFS completion: 51%	FDA requested a changed in the OS and PFS cox model calculation i.e. a change in the calculation of the stratification variables. The same data as the EMA was used.	FULL PRESCRIBING INFORMATION (FDA label), LENVIMA® (lenvatinib) capsules, for oral use, Reference ID: 3931091, 2015

The trend toward a survival benefit seen at the data cutoff for the primary analysis (13 Jun 2014) and the first OS update (10 Dec 2014) continued to be evident in this updated 31 Jul 2015 OS analysis (HR: 0.59; 95% CI 0.36-0.97, P=0.065). Median survival remained at 25.5 months for the combination arm and 15.4 months for the everolimus arm (Figure 30 and Figure 31).

As of the updated cut-off date of 31 Jul 2015, 34 subjects (65.4%) in the lenvatinib arm and 37 (74.0%) subjects in the everolimus arm had died. Median OS was 19.1 months versus 15.4 months, respectively (HR: 0.75; 95% CI 0.46, 1.20, P=0.13) (Figure 30 and Figure 31).

As of the updated cut-off date of 31 Jul 2015, 32 subjects (62.7%) in the combination arm and 34 (65.4%) subjects in the lenvatinib arm had died. Median survival was

25.5 months in the combination arm versus 19.1 months in the lenvatinib arm. This difference was not statistically significant (HR: 0.79; 95% CI 0.48, 1.30, P=0.31) (Figure 30 and Figure 31).

Figure 30 Summary of second update of overall survival – Full Analysis Set

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Deaths (n)	32 (62.7%)	34 (65.4%)	37 (74.0%)
OS (months) Median (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
Stratified Hazard Ratio (95% CI)			
Primary endpoints: vs single-arm everolimus	0.59 (0.36, 0.96)	0.75 (0.46, 1.20)	
Secondary endpoint: vs single-arm lenvatinib	0.79 (0.48, 1.30)		
P value based on stratified log-rank test			
Primary endpoints: vs single-arm everolimus	0.065	0.130	
Secondary endpoint: vs single-arm lenvatinib	0.309		
Overall survival rate (%) (95% CI)			
At 12 months	72.5 (58.1, 82.7)	71.2 (56.8, 81.5)	61.6 (46.6, 73.5)
At 18 months	64.7 (50.0, 76.1)	55.8 (41.3, 68.0)	41.1 (27.3, 54.3)

Source: Eisai Ltd Summary of Clical Efficacy (Eisai, 2016)
Data cut-off date = July 31st, 2015. Abbreviations: CI, Confidence Interval; NE, Not estimable.

Figure 31 Kaplan-Meier estimate of updated overall survival, by treatment group

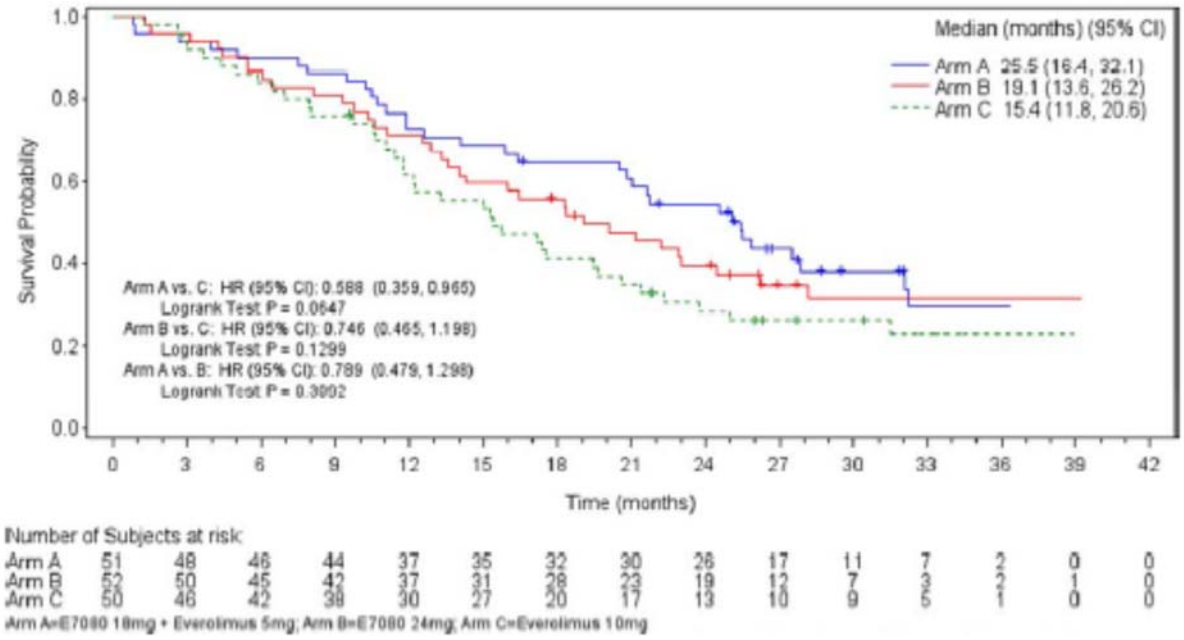


Figure 32 summarises the results of the three OS analyses performed. The consistency of the hazard ratios, <0.6 across all 3 OS analyses and the fact that the upper limit of the 95% CI excludes 1 with more mature OS data (10 Dec 2014 and 31 Jul 2015 cutoff) indicates the robustness of the OS results and demonstrates that there is an OS benefit with combination therapy over everolimus monotherapy.

Figure 32 Summary of the Results of the Overall Survival Analyses

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)
Primary Analysis			
Median (months) (95% CI)	25.5 (20.8, 25.5)	18.4 (13.3, NE)	17.5 (11.8, NE)
HR (95% CI) vs everolimus	0.55 (0.30, 1.01)	0.74 (0.42, 1.31)	0.74 (0.40, 1.36)
P-value vs everolimus	0.06	0.29	0.30
First Update (10 Dec 2014)			
Median (months) (95% CI)	25.5 (16.4, NE)	19.1 (13.6, 26.2)	15.4 (11.8, 19.6)
HR (95% CI) vs everolimus	0.51 (0.30, 0.88)	0.68 (0.41, 1.14)	0.75 (0.43, 1.30
P-value vs everolimus	0.02	0.12	0.32
Second Update (31 Jul 2015)			
Median (months) (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
HR (95% CI) vs everolimus	0.59 (0.36, 0.96)	0.75 (0.47, 1.20)	0.79 (0.48, 1.30)
P-value vs everolimus	0.06	0.13	0.31

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; NE, Not estimable.

Tumour Response

The ORR in the combination arm, 43.1%, with 1 CR and 21 PRs (median duration: 13 months), was significantly higher than the ORR in the everolimus arm of 6.0%, with 3 PRs (median duration: 8.5 months) (Figure 33). This represents a 7.2-fold increase in ORR for the combination arm over the everolimus arm, and this difference was statistically significant (RR=7.2 [95% CI: 2.3, 22.5], P<0.0001) in favour of the combination arm. This confirms the contribution of lenvatinib to the ORR. The marked increase in ORR is consistent with and supports the increased PFS (primary endpoint) and increased OS (secondary endpoint) seen in the combination arm compared with the everolimus arm. Median time to response was similar in the combination and everolimus arms and corresponded with the first protocol-specified tumour assessment timepoint: 8.2 weeks and 8.0 weeks, respectively

The combination arm showed improvement in the DCR (CR+PR+SD ≥7 weeks) and CBR (CR+PR+SD ≥23 weeks) compared with the everolimus arm. The DCR was 84.3% for the combination arm and 68.0% for the everolimus arm, and the CBR was 68.6% and 42.0% for the combination and everolimus arms, respectively. The durable SD rate was 25.5% for the combination arm and 36.0% for the everolimus arm (

Figure 33).

The ORR in the lenvatinib arm, 26.9% with 14 PRs also was higher than the ORR in the everolimus arm, 6.0% with 3 PRs (Figure 33). This represents a 4.5-fold increase in ORR for the lenvatinib arm over the everolimus arm and this difference was statistically significant (RR=4.5 [95% CI: 1.4, 14.7], P=0.0067). Median time to first response was 7.9 weeks in the lenvatinib arm and 8.0 weeks in the everolimus arm.

The lenvatinib arm showed improvement in the DCR (CR+PR+SD ≥7 weeks) and CBR (CR+PR+SD ≥23 weeks) compared with the everolimus arm. The DCR was 78.8% for the lenvatinib arm and 68.0% for the everolimus arm, and the CBR was 65.4% for the lenvatinib arm and 42.0% for the everolimus arm. The durable SD rate was 38.5% for the lenvatinib arm and 36.0% for the everolimus arm (

Figure 33).

Figure 33 Summary of Tumour Response based on investigators assessment – Full Analysis Set

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Complete response (CR), n (%)	1 (2.0)	0	0
Partial response (PR), n (%)	21 (41.2)	14 (26.9)	3 (6.0)
Stable disease (SD), n (%)	21 (41.2)	27 (51.9)	31 (62.0)
Progressive disease (PD), n (%)	2 (3.9)	3 (5.8)	12 (24.0)
Not assessed, n (%)	6 (11.8)	8 (15.3)	4 (8.0)
Objective Response Rate (CR+PR), n (%)	22 (43.1)	14 (26.9)	3 (6.0)
95% CI	(29.3, 57.8)	(15.6, 41.0)	(1.3, 16.5)
Disease Control Rate (CR+PR+SD ≥ 7weeks), n (%)	43 (84.3)	41 (78.8)	34 (68.0)
95% CI	(71.4, 93.0)	(65.3, 88.9)	(53.3, 80.5)
Durable Stable Disease Rate (SD ≥ 23 weeks), n (%)	13 (25.5)	20 (38.5)	18 (36.0)
95% CI	(14.3, 39.6)	(25.3, 53.0)	(22.9, 50.8)
Clinical Benefit Rate (CR+PR+SD ≥ 23 weeks)	35 (68.6)	34 (65.4)	21 (42.0)
95% CI	(54.1, 80.9)	(50.9, 78.0)	(28.2, 56.8)

The ORR in the combination arm also was higher than the ORR in the lenvatinib arm; 43.1% (1 CR and 21 PRs) and 26.9% (14 PRs), respectively. These results suggest the synergistic effect of combining everolimus with lenvatinib to increase the ORR seen in the monotherapy arms. This represents a 1.6-fold increase in ORR for the combination arm over the lenvatinib arm, however, this difference was not statistically significant (RR=1.6 [95% CI: 0.9, 2.8], P=0.1007).

The DCR (CR+PR+SD ≥7 weeks) and CBR (CR+PR+SD ≥23 weeks) were similar in the combination and lenvatinib arms. The DCR was 84.3% for the combination arm and 78.8% for the lenvatinib arm; the CBR was 68.6% and 65.4% for the combination and lenvatinib arms, respectively. The durable SD rate was 25.5% for the combination arm and 38.5% for the lenvatinib arm (

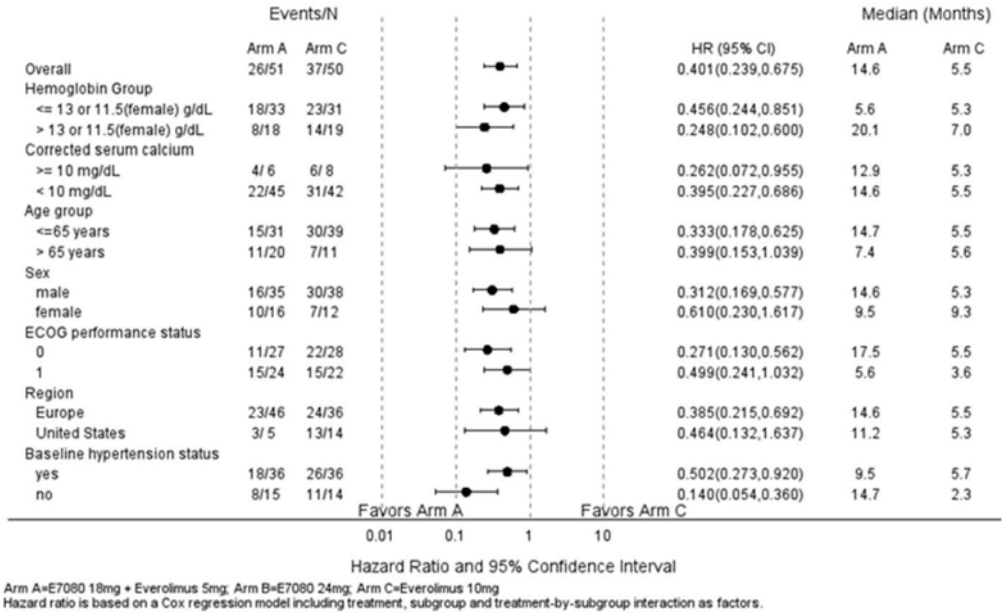
Figure 33).

4.8 Subgroup analysis

Results of the exploratory subgroup analyses of PFS support the results of the primary PFS analysis. Results of these analyses for the combination arm vs the single agent everolimus arm provided as a Forest plot are presented in Figure 34.

The combination arm showed improvement in PFS over the everolimus arm for all subgroups (HRs range from 0.14 to 0.61).

Figure 34 Forest Plot of HRs for PFS by Subgroup (Combination Arm vs Everolimus Arm) – Full Analysis Set



Arm A=E7080 18mg + Everolimus 5mg; Arm B=E7080 24mg; Arm C=Everolimus 10mg
Hazard ratio is based on a Cox regression model including treatment, subgroup and treatment-by-subgroup interaction as factors.

Although the magnitude of the improvement in PFS for the subgroups was greater in the combination arm, the lenvatinib arm also showed trends of greater improvement in PFS over the everolimus arm for all subgroups (HRs range from 0.33 to 0.83). The combination arm also showed a trend toward greater improvement in PFS over the lenvatinib arm for all subgroups (HRs range from 0.40 to 0.91), except the effect within the US (sample size was very limited). While these analyses are considered exploratory and are limited by the sample size within each subgroup, the consistent improvements (at least numerically) in PFS suggest that the combination regimen has superior efficacy compared to standard doses of either single agent in terms of

PFS across the subgroups. The results for the various subgroups and comparisons were comparable with those for the overall population.

4.9 Meta-analysis

No meta-analysis was carried out but an indirect and mixed treatment comparison of lenvatinib in combination with everolimus and selected comparators was conducted and this is covered in the next section.

4.10 Indirect and mixed treatment comparisons

Search strategy

The literature search performed covering Embase, MEDLINE and the Cochrane library is described in section 4.1. The inclusion and exclusion criteria, language restrictions and the study selection process are summarized in Figure 12 and the flow diagram providing details on the process for selecting studies is shown in Figure 13. A list of information sources and the full electronic search strategies for all the databases are provided in Appendix 8.3. Systematic literature Review,

The eight trials examining a total of ten treatment regimens for patients with a/mRCC who have failed at least one prior anti-VEGF therapy identified in the literature search are summarised in the network diagram provided in Figure 35. Three of the trials compared active treatment with everolimus: nivolumab in CHECKMATE-025 (Motzer, et al., 2015; Motzer, et al., 2016), cabozantinib in METEOR (Choueiri, et al., 2015; Choueiri, et al., 2016), and lenvatinib plus everolimus and alone in E7080-G000-205 (Motzer, et al., 2015; Motzer, et al., 2016); a fourth trial compared everolimus with placebo (RECORD-1) (Motzer, et al., 2008; Motzer, et al., 2010; Calvo, et al., 2011). Four trials compared active treatment with sorafenib: axitinib in AXIS (Rini, et al., 2011; Motzer, et al., 2013) and Qin et al. (2015), temsirolimus in INTORSECT, and sunitinib in SWITCH (Eichelberg, et al., 2015). SWITCH was a cross over trial comparing sequential treatment of sorafenib followed by sunitinib and vice-versa.

All trials included patients who had failed one prior anti-VEGF therapy; however, some had a broader mix of prior experience. Both CHECKMATE-025 and METEOR

allowed patients who had failed at least one anti-VEGF therapy, with close to 30% having failed more than one. Earlier trials such as RECORD-1 and AXIS, and Qin et al. (2015) included patients who had failed one prior treatment and included patients who had failed cytokines. In INTORSECT, patients had failed sunitinib only. The trials included results according to number and type of prior therapies. As expected, outcomes were superior with one prior therapy compared with two, and tended to be worse following treatment with sunitinib compared with cytokine.

Study selection

Four trials are included in the indirect treatment comparison (ITC) using everolimus as common comparator: E7080-205 (Motzer, et al., 2015; Motzer, et al., 2016), CHECKMATE-025 (Motzer, et al., 2015; Motzer, et al., 2016), RECORD-1 (Motzer, et al., 2008; Motzer, et al., 2010; Calvo, et al., 2011) and METEOR (Choueiri, et al., 2015; Choueiri, et al., 2016). These four trials permit the indirect comparison of the treatment combination lenvatinib plus everolimus with placebo, nivolumab and cabozantinib as well as the direct comparison with everolimus as shown in the network diagram in Figure 35. However, there has been no randomised trial of axitinib in patients with a/mRCC having prior VEGF therapy which would enable an

Figure 35 Trials in patients with a/mRCC who failed one prior anti- EGF therapy

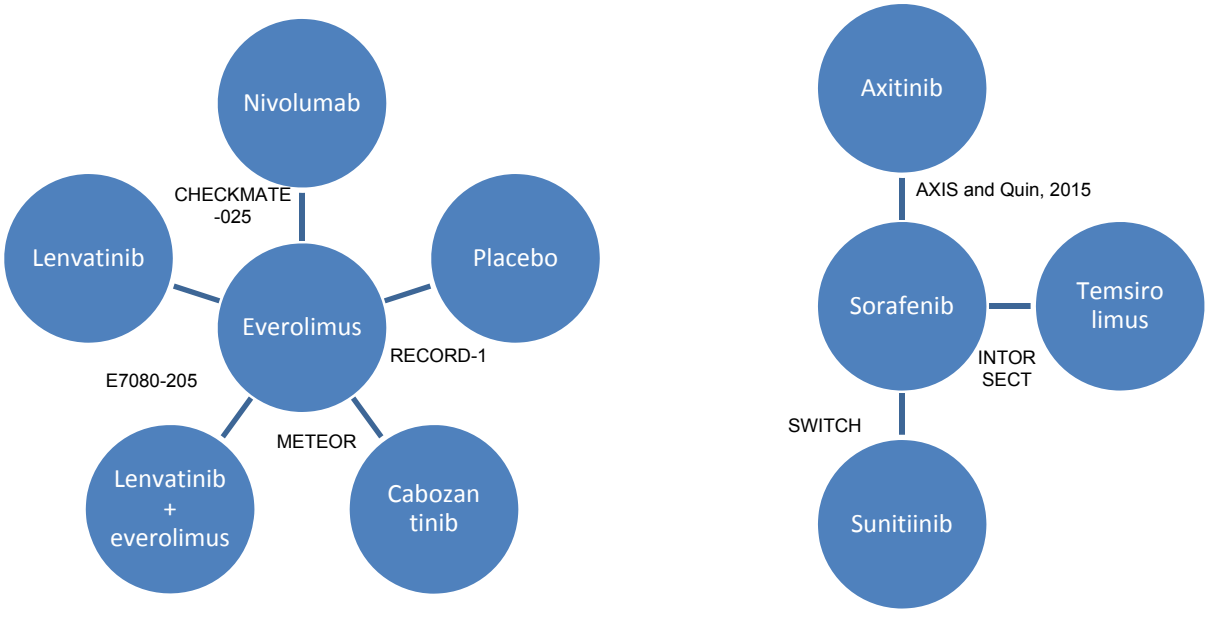
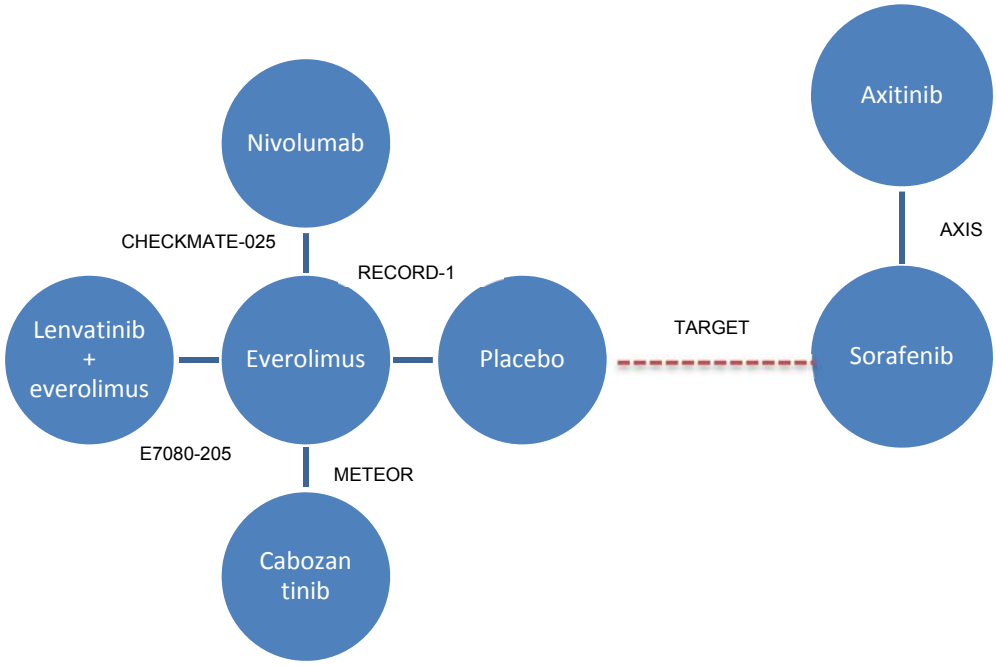


Figure 36 Network of trials included in the ITC for a/mRCC



indirect comparison to compare axitinib with lenvatinib plus everolimus; that is, there are no trials that connect the everolimus-controlled network to the sorafenib-controlled network (Figure 35). Therefore, a multi-step indirect comparison using the TARGET trial in a/mRCC patients with prior cytokine therapy will be used to connect the axitinib trial (AXIS) to the lenvatinib trial (E7080-205) via sorafenib and placebo using the TARGET and RECORD-1 trials as illustrated in Figure 36. A list of the trials finally included in the ITC is provided in Figure 37.

In addition to the trials INTORSECT with temsirolimus and SWITCH with sunitinib, which had not been identified as relevant comparators in the final scope, two other RCTs were excluded from the ITC network (Figure 38). A second axitinib versus sorafenib trial (Qin, et al., 2015)was excluded from the ITC as it was conducted in smaller population than the pivotal AXIS trial (less than one third of its size); and the patient characteristics of the Qin trial were less consistent with E7080-205 than AXIS: the Qin trial was predominantly Asian whereas other trials were conducted worldwide in a mixed population with up to 22% Asian (only 3 Asian patients were enrolled in E7080-205); and importantly the Qin trial had a higher proportion of

patients not eligible for the E7080-205 study (50% had prior cytokine treatment only in the Qin trial compared with 35% in AXIS and 0% in E7080-205).

Figure 37 Trials included in the indirect treatment comparison

Treatment and study population	References
Everolimus network	
E7080-205 Lenvatinib plus everolimus One prior VEGF	Motzer RJ, Hutson TE, Glen H, et al. (2015). "Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial." Lancet Oncol 16, 1473-1482. (Motzer, et al., 2015) Motzer RJ, Hutson TE, Ren M, et al. (2016) "Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma." Lancet Oncol 17, e4-5. (Motzer, et al., 2016) Eisai Ltd Summary of Clinical Efficacy (Eisai, 2016)
CHECKMATE-025 Nivolumab One or two prior antiangiogenic therapies	Motzer RJ, Escudier B, McDermott DF, et al. (2015). "Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma." N Engl J Med 373, 1803-1813. (Motzer, et al., 2015) Motzer RJ, Sharma P, McDermott DF, et al (2016). "CheckMate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC)." J Clin Oncol 34, (suppl 2S; abstr 498). (Motzer, et al., 2016)
METEOR Cabozantinib At least one prior VEGF	Choueiri TK, Escudier B, Powles T, et al. (2015). "Cabozantinib versus everolimus in advanced renal-cell carcinoma." N Engl J Med 373, 1814-1823. (Choueiri, et al., 2015) Choueiri TK, Escudier B, Powles T, et al. (2016). "Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial." Lancet Oncol 17(7): 917-927. (Choueiri, et al., 2016)
RECORD-1 Placebo Prior sorafenib and/or sunitinib	Motzer RJ, Escudier B, Oudard S, et al. (2008). "Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial". The Lancet 372: 449-456. (Motzer, et al., 2008) Motzer RJ, Escudier B, Oudard S, et al. (2010). "Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors." Cancer 116, 4256-4265. (Motzer, et al., 2010) Calvo E, Escudier B, Motzer RJ, et al. (2012). "Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study". Eur J Cancer 48, 333-339. (Calvo, et al., 2011) Korhonen P, Zuber E, Branson M et al (2012) "Correcting overall survival for the impact of crossover via a Rank-Preserving Structural Failure Time (RPSFT) model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma." J Biopharm Stat 22(6): 1258-1271.[a] (Korhonen, 2012)
Sorafenib network	
AXIS Axitinib One prior systemic treatment (cytokine or VEGF)	Rini BI, Escudier B, Tomczak P, et al. (2011). "Comparative effectiveness of axitinib versus sorafenib in metastatic renal cell carcinoma (AXIS): a randomised phase 3 trial." Lancet 378, 1931-1939. (Rini, et al., 2011) Motzer RJ, Escudier B, Tomczak P, et al. (2013). "Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial." Lancet Oncol 14(6): 552-562. (Motzer, et al., 2013)
TARGET	Escudier B, Eisen T, Stadler WM, et al (2007) "Sorafenib in advanced

Treatment and study population	References
Placebo Prior systemic treatment (cytokines)	clear-cell renal-cell carcinoma".N Engl J Med 2007;356:125-34. (Escudier, 2007) Escudier B, Eisen T, Stadler WM, et al (2009) "Sorafenib for Treatment of Renal Cell Carcinoma: Final Efficacy and Safety Results of the Phase III Treatment Approaches in Renal Cancer Global Evaluation Trial" J Clin Oncol 27:4068-75. (Escudier, 2009)

a Reference not identified originally in Systematic literature review

Figure 38 Trials excluded from the indirect treatment comparison

Treatment	References	Reason for exclusion
Sorafenib network		
Axitinib Qin 2015	Qin S, Bi F, Jin J, Cheng Y, et al. (2015) "Axitinib versus sorafenib as a second-line therapy in Asian patients with metastatic renal cell carcinoma: results from a randomised registrational study." Onco Targets Ther 8: 1363-1373. (Qin, et al., 2015)	Less comparable patient population than pivotal AXIS trial (Asian, less prior VEGF)
Placebo Ratain 2006	Ratain MJ, Eisen T, Stadler WM, et al. (2006) "Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients With Metastatic Renal Cell Carcinoma" J Clin Oncol 24(16):2505-2512. (Ratain, 2006)	Randomised discontinuation design. Limited reporting of outcomes.

Methods and outcomes of included studies

Following the final scope, the outcome measures chosen in the ITC were the following:

- Progression free survival (PFS)
- Overall Survival (OS)
- Overall response rate (ORR)
- Safety

Progression-free survival (PFS) and overall response rate (ORR)

Two everolimus-controlled studies used investigator assessment based on RECIST 1.1 as the primary method of assessing response (lenvatinib study E7080-205 and nivolumab study CHECKMATE-025), and two used an independent radiology review (IRR) committee (cabozantinib study METEOR [RECIST 1.1] and placebo study RECORD-1 [RECIST 1.0]).

E7080-205 reported PFS and ORR based on both assessment methods; however, the IRR results were retrospectively performed at the request of the FDA. As such,

the IRR results for E7080-205 may be biased due to informative censoring – the independent reviewer was not able to review further scans after the investigator deemed the patient's tumour to have progressed.

The two sorafenib controlled studies reported both independent and investigator assessed response (the blinded IRR based PFS was the primary objective for AXIS).

The primary ITC analyses for PFS and ORR are based on the main results from each study; that is, using investigator review for E7080-205 and CHECKMATE-025 and independent review for METEOR, RECORD-1, TARGET and AXIS. Results are also provided based on each assessment methodology as a sensitivity analysis. Where more than one data cut was provided for ORR, the most recent was used in the ITC.

Overall survival (OS)

The latest data cut reported for each study is used in the ITC.

Estimates of OS are confounded in two trials due to permissible cross-over to the investigational treatment:

- RECORD-1: at the final data-cut (Nov 2008), 111 (80%) of the 139 patients randomised to placebo had crossed over to receive open-label everolimus
- TARGET: after the interim analysis, in May 2005, 48% of patients randomised to placebo crossed over to receive sorafenib.

Both trials made some attempt to adjust for crossover, using different methodologies: RECORD-1 used RPSFT model and TARGET censored placebo patients who were still alive at the time of cross-over.

Overall survival estimates may also be confounded by the use of subsequent therapies and the continuation of study drug after progression. In the active-controlled trials more patients randomised to everolimus/sorafenib used subsequent systemic therapies. The trial authors made no adjustment for this.

Safety

Indirect comparisons are reported for the proportion of patients experiencing at least one:

- Severe (grade 3 or 4) adverse event (AE)
- AE leading to discontinuation of study treatment.

The results for each of the outcomes of the studies included in the ITC are provided in Appendix 8.5. Indirect treatment comparison report.

Study populations

Patient characteristics were similar across trials in terms of median age, gender and prior nephrectomy. However, on average, patients in the lenvatinib and axitinib trials (E7080-205 and AXIS) had more severe disease as measured by performance status and MSKCC risk. No patients in the TARGET trial had a poor MSKCC risk. Patients in E7080-205 also had a lower proportion of patients with prior radiotherapy.

As noted above, patients in the lenvatinib trial were required to have had only one prior anti-VEGF therapy whereas the other everolimus controlled trials permitted more than one prior anti-VEGF. Approximately 30% of patients in the other everolimus controlled trials received two or more prior anti-VEGF therapies. In contrast, the sorafenib controlled trials did not require failure of prior anti-VEGF therapy; around one-third of patients in AXIS and all patients in TARGET had not received prior anti-VEGF therapy.

Baseline demographic and disease characteristics for the studies included in the ITC are provided in Appendix 8.5. Indirect treatment comparison report.

Risk of bias

A quality assessment of all the studies included in the ITC is provided in Appendix 8.3.Systematic literature Review.

Methods of analysis

The published hazard ratios (HR) were used in the ITC for progression-free survival (PFS) and overall survival (OS) on the natural log scale with the standard error (SE) calculated from the difference from the HR to the upper 95% confidence limit.

For binary outcomes, overall response rate (ORR) and safety, the odds ratio (OR), relative risk (RR) and risk difference (RD) were calculated from the frequency and percentage experiencing each outcome. As is customary, when no events were observed in a treatment group, 0.5 was added to each cell of the 2-by-2 table.

Indirect estimates of treatment difference of Drug A (lenvatinib plus everolimus) minus Drug B (nivolumab, cabozantinib or placebo) was conducted using the Bucher method (Bucher & Guyatt, 1997) with Drug C (everolimus) as the common comparator. That is,

the estimate of treatment difference:

$$\mu_{A-C} = \mu_{A-C} - \mu_{B-C}$$

the estimate of the standard error of the treatment difference:

$$SE_{A-B} = \sqrt{{SE_{A-C}}^2 + {SE_{B-C}}^2}$$

and the 95% confidence limits

$$\mu_{A-B} \pm 1.96 SE_{A-B}$$

Results

Progression-free survival

Indirect estimates of lenvatinib plus everolimus versus other treatments are presented in Figure 39. Consistency across trials was assessed by examining median PFS in patients treated with everolimus across trials. Median PFS was higher in the primary analysis of E7080-205 (5.5 months) than in the other three studies (3.8 to 4.4 months) which appears contrary to the larger proportion of

patients with poorer risk and worse performance status in E7080-205. This may be explained, at least in part, by the extent of prior therapy, with median PFS of 5.5 months in E7080-205 being similar to that of the subgroup with one prior VEGF in RECORD-1 (5.4 months). Estimates of median PFS did not vary substantially by method of response assessment (E7080-205: investigator 5.5 vs IRR 5.6 months; RECORD-1: investigator 4.6 vs IRR 4.0 months). Extent of prior therapy and method of response assessment did not substantially modify the hazard ratio estimates within the everolimus trials; and therefore indirect comparisons were conducted despite these potential differences in baseline risk.

Figure 39 Indirect treatment comparisons of progression-free survival: hazard ratio (95% CI) for lenvatinib plus everolimus versus other treatments

Treatment	Main analysis as reported by trial[a,b]	Independent assessment[b]	One prior VEGF[a]	Prior sunitinib[a]
Everolimus [c]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	NA	NA	NA
Cabozantinib	[redacted]	[redacted]	NA	[redacted] (NA)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; NA, not available; VEGF, vascular endothelial growth factor.
[a] Investigator assessment for E7080-205 and CHECKMATE-025 and independent assessment for METEOR, RECORD-1, TARGET and AXIS.
[b] 1 prior VEGF for E7080-205, 1-2 prior VEGF for CHECKMATE-025, ≥1 prior VEGF for METEOR, prior sunitinib and/or sorafenib (1-2 prior VEGF) for RECORD-1, 0 prior VEGF (cytokines only) for TARGET and 0-1 prior VEGF (sunitinib or cytokines) for AXIS.
[c] Direct comparison based on E7080-205.
[d] Using investigator assessment for both E7080-205 and RECORD-1 estimate is similar 0.12 (0.07-0.22).
[e] Except for TARGET which was conducted in patients with no prior VEGF treatment.

However, caution should be taken when interpreting the multi-step indirect comparison of lenvatinib plus everolimus and axitinib, due to major departure from the exchangeability (consistency) assumption. The least bias estimates are likely to be those which were able to restrict trial estimates to the "one prior VEGF" and "prior sunitinib" subgroups. However, these patients weren't eligible for the TARGET trial (sorafenib versus placebo) and therefore some bias remains. Extent of prior treatment (prior cytokines or prior VEGF) appears to be an effect modifier for PFS. The AXIS trial estimates the HR (axitinib versus sorafenib) for the prior cytokine subgroup as [redacted] compared with the HR for the prior sunitinib subgroup of [redacted] Motzer et al (2013, p560) write "Patients previously treated with sunitinib, however,

had already shown clinical resistance to VEGF-targeted therapy and might have had shorter overall survival after treatment with either agent." Thus it appears the assumption of constancy of the relative effect is violated which raises doubt on the accuracy of the multi-step indirect comparison estimates.

The lenvatinib plus everolimus combination was superior to everolimus alone (HR [redacted] and indirectly to nivolumab (HR [redacted]) and placebo ([redacted]) using the main analysis results from the respective trials and any sensitivity analyses able to be conducted. There was no evidence of a difference in PFS between lenvatinib plus everolimus and cabozantinib ([redacted]).

Lenvatinib plus everolimus may also be superior to axitinib. The extent of the bias due to the effect modification of none versus one prior VEGF therapy is not able to be estimated as the only trial with both subgroups (AXIS) does not report an estimate of the interaction term.

Overall survival

Indirect estimates of lenvatinib plus everolimus versus other treatments are presented in

Figure 40. Median OS in the common comparator group (everolimus) was similar in E7080-205 and CHECKMATE-025 (19.1 and 19.6 months respectively) and in METEOR (16.5 months). The slightly lower median OS with everolimus in RECORD-1 (14.8 months) may be due to smaller variety of subsequent treatments available in this trial which was conducted several years earlier; however, this was not reported by the trial authors.

Figure 40 Indirect treatment comparisons of overall survival: hazard ratio (95% CI) for lenvatinib plus everolimus versus other treatments

Treatment	Latest data cut[a]	One prior VEGF	Prior sunitinib
Everolimus [b]	[redacted]	[redacted]	NA
Nivolumab	[redacted]	[redacted]	NA
Cabozantinib	[redacted]	NA	NA
Placebo [c]	[redacted]	NA	NA
Axitinib [d]	[redacted]	NA	NA

CI, confidence interval; NA, not available; RPSFT, rank preserving structural failure time; VEGF, vascular endothelial growth factor.
[a] 1 prior VEGF for E7080-205, 1-2 prior VEGF for CHECKMATE-025, ≥1 prior VEGF for METEOR, prior sunitinib and/or sorafenib (1-2 prior VEGF) for RECORD-1, 0 prior VEGF (cytokines only) for TARGET and 0-1 prior VEGF (sunitinib or cytokines) for AXIS.
[b] Direct comparison based on E7080-205.
[c] Based on the intention to treat analysis of RECORD-1 which permitted patients on placebo to cross over to everolimus. Using the RPSFT estimates from RECORD-1 the indirect estimate of lenvatinib plus everolimus versus placebo is 0.35 (0.12-1.08).
[d] Based on the intention to treat analysis of RECORD-1 and TARGET which permitted patients on placebo to cross over to everolimus and sorafenib respectively. Using the RPSFT estimates from RECORD-1 and censoring at time of cross-over for TARGET the indirect estimate of lenvatinib plus everolimus versus axitinib is 0.47 (0.15-1.50).

No statistically significant difference was observed in the indirect comparisons of lenvatinib plus everolimus versus nivolumab ([redacted] versus cabozantinib ([redacted]) or versus axitinib ([redacted]) based on the primary analyses using full trial populations (variety of prior therapies) and intention to treat analysis (ignoring cross-over). Lenvatinib plus everolimus was superior to everolimus (based on the E7080-205 trial) and to placebo based on the intention to treat analysis (ignoring cross-over) of RECORD-1 ([redacted]) As with the analysis of PFS, results for the multi-step indirect comparison of lenvatinib plus everolimus to axitinib on OS should be interpreted with caution.

Overall response rate

Indirect estimates of lenvatinib plus everolimus versus other treatments based on the latest data cut are presented in

Figure 41 . Sensitivity analyses based on prior therapy subgroups are presented in Figure 42, where possible.

The ORR varied in the main analyses of the everolimus groups across trials from 2% in RECORD-1 and 3% in METEOR to 5% in CHECKMATE-025 and 6% in E7080-205. The lower ORR in RECORD-1 and METEOR may have been due to use of an IRR, or a higher proportion of patients with more than one prior VEGF therapies. However, the retrospective use of an IRR in E7080-205 resulted in no patients in the everolimus group being assessed with complete or partial response, and sensitivity analyses based on the IRR results are highly uncertain and have not been presented. There was also a large variation in ORR in the sorafenib groups across trials from 2% (TARGET) to 9% (AXIS) based on IRR. As noted above, due to lack of consistency in prior therapies across the multi-step ITC, the results should be interpreted with caution.

The lenvatinib plus everolimus combination was superior to everolimus alone (RR [redacted]) and therefore is shown to be superior to placebo. There was no statistical evidence of a difference between the lenvatinib plus everolimus combination and nivolumab, cabozantinib or axitinib.

Figure 41 Indirect treatment comparisons of overall response rate: lenvatinib plus everolimus versus other treatments

Single step ITC	Treatment n/N (%)	Everolimus n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
Lenvatinib plus everolimus vs Everolimus	22/51 (43.1%)	3/50 (6.0%)	[redacted]	[redacted]	[redacted]
Nivolumab vs Everolimus	103/410 (25.1%)	22/411 (5.4%)	[redacted]	[redacted]	[redacted]
Cabozantinib vs Everolimus	57/330 (17.3%)	11/328 (3.4%)	[redacted]	[redacted]	[redacted]
Placebo vs Everolimus	0/138 (0.0%)	5/272 (1.8%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Nivolumab			[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Cabozantinib			[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Placebo			[redacted]	[redacted]	[redacted]

Multi-step ITC	Drug A n/N (%)	Drug B n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
Lenvatinib plus everolimus (A) vs Everolimus (B)	22/51 (43.1%)	3/50 (6.0%)	[redacted]	[redacted]	[redacted]
Everolimus (A) vs Placebo (B)	5/272 (1.8%)	0/138 (0.0%)	[redacted]	[redacted]	[redacted]
Placebo (A) vs Sorafenib (B)	0/337 (0.0%)	7/335 (2.1%)	[redacted]	[redacted]	[redacted]
Sorafenib (A) vs Axitinib (B)	34/362 (9.4%)	70/361 (19.4%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Axitinib			[redacted]	[redacted]	[redacted]

CI, confidence interval; n/N, number with event/number in efficacy population; vs, versus.
Indirect estimates are presented in italics.

Subgroup analyses restricting the comparator trials to one prior VEGF were not possible as this information was not published. Furthermore, analysis of the subgroup with prior sunitinib was not possible as this subgroup was not analysed in E7080-205.

Figure 42 Sensitivity analyses of indirect treatment comparisons of overall response rate: relative risk (95% CI) for lenvatinib plus everolimus versus other treatments

Treatment	Main analysis as reported by trial [a,b]	One prior VEGF [a]	Prior sunitinib [a]
Everolimus [c]	[redacted]	[redacted]	NA
Nivolumab	[redacted]	[redacted]	NA
Cabozantinib	[redacted]	NA	NA
Placebo	[redacted]	NA	NA
Axitinib	[redacted]	NA	NA

CI, confidence interval; NA, not available; VEGF, vascular endothelial growth factor.
[a] Investigator assessment for E7080-205 and CHECKMATE-025 and independent assessment for METEOR and RECORD-1
[b] 1 prior VEGF for E7080-205, 1-2 prior VEGF for CHECKMATE-025, ≥1 prior VEGF for METEOR, prior sunitinib and/or sorafenib (1-2 prior VEGF) for RECORD-1, 0 prior VEGF (cytokines only) for TARGET and 0-1 prior VEGF (sunitinib or cytokines) for AXIS.
[c] Direct comparison based on E7080-205.

Safety

Indirect estimates of lenvatinib plus everolimus versus other treatments are presented in Figure 43 where possible. Indirect comparisons of safety to axitinib was not feasible due to the lack of overall safety reporting in RECORD-1, TARGET and AXIS.

Importantly, the median duration of everolimus treatment was similar across studies, as was the incidence of adverse events (AEs) in the everolimus groups. However, the duration of treatment in the comparator groups varied from 2.0 months (placebo) to 8.3 months (cabozantinib).

There was no statistically significant difference in the proportion of patients experiencing at least one severe (grade 3 or 4) AEs between lenvatinib plus everolimus or cabozantinib versus everolimus and no difference for the indirect comparison of lenvatinib plus everolimus versus cabozantinib.

There was a higher proportion of patients experiencing at least one treatment-related severe AE with lenvatinib plus everolimus versus everolimus and a lower proportion with nivolumab versus everolimus, resulting in more patients experiencing at least one treatment-related severe AE with lenvatinib plus everolimus versus nivolumab ([redacted]).

Figure 43 Indirect comparisons of safety: lenvatinib plus everolimus versus other treatments

Comparison	Treatment n/N (%)	Everolimus n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
At least one grade 3 or 4 AE					
Lenvatinib plus everolimus vs Everolimus	36/51 (70.6%)	25/50 (50.0%)	[redacted]	[redacted]	[redacted]
Cabozantinib vs Everolimus	235/331 (71.0%)	193/322 (59.9%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Cabozantinib			[redacted]	[redacted]	[redacted]
At least one treatment related grade 3 or 4 AE					
Lenvatinib plus everolimus vs Everolimus	32/51 (62.7%)	21/50 (42.0%)	[redacted]	[redacted]	[redacted]
Nivolumab vs Everolimus	76/406 (18.7%)	145/397 (36.5%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Nivolumab			[redacted]	[redacted]	[redacted]
Discontinuation due to AE					
Lenvatinib plus everolimus vs Everolimus	12/51 (23.5%)	6/50 (12.0%)	[redacted]	[redacted]	[redacted]
Nivolumab vs Everolimus[a]	31/406 (7.6%)	52/397 (13.1%)	[redacted]	[redacted]	[redacted]
Cabozantinib vs Everolimus	40/331 (12.1%)	34/322 (10.6%)	[redacted]	[redacted]	[redacted]
Placebo vs Everolimus	5/135 (3.7%)	28/269 (10.4%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Nivolumab			[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Cabozantinib			[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Placebo			[redacted]	[redacted]	[redacted]

AE, adverse event; CI, confidence interval; n/N, number with event/number in safety population; vs, versus.
Notes: Indirect estimates are presented in italics.
[a] CHECKMATE-025 reported discontinuation due to treatment-related AE.

Less patients discontinued treatment due to AE with nivolumab and placebo compared to everolimus, resulting in substantially more patients discontinuing treatment due to AE with lenvatinib plus everolimus versus nivolumab ([redacted]) and versus placebo ([redacted]). There was no statistically significant difference

in discontinuation due to AE with lenvatinib plus everolimus versus everolimus alone or cabozantinib.

4.11 Non-randomised and non-controlled evidence

No other non-randomised evidence was considered.

4.12 Adverse reactions

Extent of exposure

As of the 31 Jul 2015 data cutoff date for Study 205, median duration of treatment was 8.0 months in the lenvatinib and everolimus combination group, 7.4 months in the lenvatinib group, and 4.1 months in the everolimus group; duration of treatment with combination therapy was nearly 2-fold greater than that with everolimus monotherapy.

As of the 13 Jun 2014 data cut-off, median duration of exposure was 7.6 months in the combination arm, 7.4 months in the lenvatinib arm, and 4.1 months in the everolimus arm; exposure to combination therapy was 1.87-fold longer than exposure to everolimus monotherapy. In the combination arm, the median daily dose of lenvatinib per subject was 13.6 mg/day (approximately 75% of the intended dose of 18 mg/day). In the lenvatinib arm, the median daily dose of lenvatinib per subject was 20.3 mg/day (approximately 85% of the intended dose of 24 mg/day). The median daily dose of everolimus per subject in the combination arm was 4.7 mg/day (approximately 94% of the intended dose of 5 mg) and in the everolimus arm it was 9.7 mg (97% of the intended dose of 10 mg). Figure 44 summarises the duration of treatment, the mean dose per subject and its percent of the intended dose for the three treatment arms of the study E7080-G000-205.

The number of subjects with lenvatinib dose reductions and/or dose interruptions was similar in the combination and lenvatinib arms: 36 (70.6%) and 32 (61.5%) subjects, respectively, with dose reductions, and 41 (80.4%) and 39 (75.0%) subjects, respectively, with dose interruptions. There was only 1 (2%) subject with everolimus dose reduction in the combination arm, compared with 13 (26.0%) subjects in the everolimus arm. The number of subjects with everolimus dose

interruptions was higher in the combination arm than in the everolimus arm: 39 (76.5%) versus 27 (54.0%) subjects, respectively. The number of subjects with study treatment discontinuation due to AEs was similar in the combination and lenvatinib arms (12; 23.5% and 13; 25.0% subjects, respectively) and lower in the everolimus arm (6; 12.0% subjects).

Figure 44 Extent of exposure to study treatment – Safety analysis set

	Lenvatinib + everolimus (n=51)		Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Duration of treatment (days), n (%)				
Mean (SD)	9.4 (6.6)		8.0 (5.6)	6.2 (5.2)
Median	7.6		7.4	4.1
Range	0.7-22.6		0.1-23.0	0.3-20.1
Mean daily dose per subject (mg/day)	Lenvatinib	Everolimus		
Mean (SD)	13.3 (4.0)	4.4 (0.82)	19.0 (4.9)	9.0 (1.5)
Median	13.6	4.7	20.3	9.7
Range	6, 24	2, 6	7, 24	4, 10
Percent intended dose (%)				
Mean (SD)	73.8 (22.3)	88.0 (16.42)	79.3 (20.4)	89.6 (14.6)
Median	75.4	93.7	84.8	97.0
Range	31, 133	34, 125	28, 100	44, 100

Figure 45 summarises the number and percentage of subjects with dose reduction, interruption or discontinuation.

Figure 45 Study drug dose reduction, interruption or discontinuation

	Lenvatinib + everolimus (n=51)		Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Number of subjects with, n (%)	Lenvatinib	Everolimus		
Dose reduction	36 (70.6)	1 (2.0)	32 (61.5)	13 (26.0)
Dose interruption	41 (80.4)	39 (76.5)	39 (75.0)	27 (54.0)
Drug discontinuation due to AEs	12 (23.5)		13 (25.0)	6 (12.0)

Median time to first lenvatinib dose reduction was 1.6 months (95% CI: 1.2, 2.3) in the combination arm, and 2.3 months (95% CI: 1.9, 3.5) in the lenvatinib arm. Median time to dose reduction in the everolimus arm was 2.5 months (95% CI: 1.4, 5.6).

Figure 46 summarises the time to first dose reduction in those subjects with at least one dose reduction in the study.

Figure 46 Time to first dose reduction among subjects with dose reduction

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Time to dose reduction (months), median (95% CI)			
Lenvatinib dose reduction	1.6 (1.2, 2.3)	2.3 (1.9, 3.5)	
Everolimus dose reduction	4.8 (0.9, 6.0)		2.5 (1.4, 5.6)

In summary, subjects in the combination arm stayed on treatment for a longer period of time compared with each of the single-agent arms. In addition, subjects in the combination arm received 75% of the intended dose of lenvatinib in spite of the dose reductions and interruptions for toxicity compared with 85% in the lenvatinib arm. Subjects in the combination arm received 94% of the intended dose of everolimus compared with 97% in the everolimus arm.

Summary of adverse events

An overview of TEAEs presented by subject incidence and AE episodes adjusted by treatment duration is presented in Figure 47. All subjects in the 3 treatment arms had at least 1 TEAE. Grade 3 or higher TEAEs occurred most frequently in the lenvatinib arm (84.6%, n=44) followed by the combination arm (72.5%, n=37), and then the everolimus arm (54.0%. n=27).

Serious AEs occurred at a slightly higher incidence in the combination (54.9%, n=28) and lenvatinib arms (51.9%, n=27) than in the everolimus arm (42%, n=21). Fatal AEs occurred in 1 (2.0%) subject in the combination arm, 3 (5.8%) subjects in the lenvatinib arm, and 2 (4.0%) subjects in the everolimus arm. Therefore, there was no increase in the combination arm compared with the lenvatinib and everolimus arms in the occurrence of fatal AEs.

The frequency of TEAEs leading to study treatment adjustments (treatment discontinuation, dose reduction, and/or interruption) was similar between the

combination and lenvatinib arms: 88.2% (n=45) and 90.4% (n=47), respectively, and was lower in the everolimus arm (60.0%, n=30).

Figure 47 Overview of Treatment Emergent Adverse Events (TEAEs)

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
	n (%)	n (%)	n (%)
Any TEAEs	51 (100.0)	52 (100.0)	50 (100.0)
TEAEs with CTCAE Grade ≥3	37 (72.5)	44 (84.6)	27 (54.0)
SAEs	28 (54.9)	27 (51.9)	21 (42.0)
Deaths	1 (2.0)	3 (5.8)	2 (4.0)
Other SAEs	27 (52.9)	26 (50.0)	21 (42.0)
TEAEs leading to study treatment adjustment	45 (88.2)	47 (90.4)	30 (60.0)
TEAEs leading to study treatment withdrawal	12 (23.5)	13 (25.0)	6 (12.0)
TEAEs leading to dose reduction	34 (66.7)	31 (59.6)	8 (16.0)
TEAEs leading to dose interruption	35 (68.6)	36 (69.2)	25 (50.0)

Display of adverse events

A summary of TEAEs occurring in ≥10% of subjects in any treatment arm in decreasing order of frequency in the combination arm is presented in Figure 48. Diarrhoea was the most frequently reported TEAE across the 3 treatment arms. The incidence of diarrhoea was higher in the combination and lenvatinib arms than in the everolimus arm: 84.3% (n=43), 71.2% (n=37), and 34.0% (n=17), respectively.

The other most frequently reported TEAEs (>30% of subjects) in the combination arm were decreased appetite (51.0%, n=26), fatigue (47.1%, n=24), vomiting (45.1%, n=23), nausea (41.2%, n=21), hypertension (41.2%, n=21), cough (37.3%, n=19), hypertriglyceridemia (35.3%, n=18), hypercholesterolemia (33.3%, n=17), and weight decreased (31.4%, n=16). These events are consistent with the safety profile of lenvatinib.

Figure 48 Treatment-emergent adverse events occurring in at least 10% of subjects in any treatment arm – safety analysis set

	Lenvatinib + everolimus (n=51) n (%)	Single-arm lenvatinib (n=52) n (%)	Single-arm everolimus (n=50) n (%)
Diarrhoea	43(84.3)	37(71.2)	17(34.0)
Decreased appetite	26(51.0)	30(57.7)	9(18.0)
Fatigue	24(47.1)	20(38.5)	16(32.0)
Vomiting	23(45.1)	20(38.5)	5(10.0)
Nausea	21(41.2)	32(61.5)	8(16.0)
Hypertension	21(41.2)	25(48.1)	5(10.0)
Cough	19(37.3)	9(17.3)	15(30.0)
Hypertriglyceridaemia	18(35.3)	7(13.5)	12(24.0)
Hypercholesterolaemia	17(33.3)	6(11.5)	8(16.0)
Weight decreased	16(31.4)	25(48.1)	4(8.0)
Stomatitis	15(29.4)	13(25.0)	21(42.0)
Epistaxis	9(17.6)	4 (7.7)	11 (22.0)
Abdominal pain	9 (17.6)	12 (23.1)	1 (2.0)
Abdominal pain upper	9 (17.6)	7 (13.5)	4 (8.0)
Insomnia	9(17.6)	7 (13.5)	1 (2.0)
Anaemia	8(15.7)	4 (7.7)	13 (26.0)
Hyperglycaemia	8(15.7)	3 (5.8)	11 (22.0)
Musculoskeletal chest pain	8 (15.7)	6 (11.5)	2 (4.0)
Blood thyroid stimulating hormone increased	7 (13.7)	2 (3.8)	1 (2.0)
Constipation	6(11.8)	19 (36.5)	9 (18.0)
Dyspepsia	6(11.8)	6 (11.5)	5 (10.0)
Pruritus	6(11.8)	3 (5.8)	7 (14.0)
Nasopharyngitis	6(11.8)	3 (5.8)	6 (12.0)
Oral pain	6 (11.8)	5 (9.6)	1 (2.0)
Hypokalaemia	6(11.8)	1 (1.9)	1 (2.0)
Musculoskeletal pain	5 (9.8)	7 (13.5)	1 (2.0)
Pain in extremity	5 (9.8)	6 (11.5)	3 (6.0)
Mouth ulceration	5 (9.8)	0	5 (10.0)
Palmar-plantar erythrodysaesthesia syndrome	4 (7.8)	8 (15.4)	2 (4.0)
Lipase increased	4 (7.8)	6 (11.5)	3 (6.0)
Upper respiratory tract infection	3 (5.9)	7 (13.5)	5 (10.0)
Lethargy	3(5.9)	7 (13.5)	2 (4.0)
Myalgia	3(5.9)	7 (13.5)	1 (2.0)
Pneumonitis	3(5.9)	0	6 (12.0)
Dry mouth	2 (3.9)	6 (11.5)	3 (6.0)
Dyspnoea exertional	2 (3.9)	1 (1.9)	5 (10.0)
Lower respiratory tract infection	1 (2.0)	4 (7.7)	6 (12.0)
Rash macular	1 (2.0)	2 (3.8)	5 (10.0)

In the lenvatinib arm, the other most frequent (>30% of subjects) TEAEs were nausea (61.5%, n=32), decreased appetite (57.7%, n=30), hypertension (48.1%, n=25), weight decreased (48.1%, n=25), vomiting (38.5%. n=20), fatigue (38.5%, n=20), hypothyroidism (36.5%, n=19), dysphonia (36.5%. n=19), constipation (36.5%, n=19), and proteinuria (30.8%, n=16). These events are consistent with the safety profile of lenvatinib.

Adverse events severity

A summary of CTCAE Grade 3 or 4 TEAEs occurring in ≥5% of subjects in any treatment arm in decreasing order of frequency in the combination arm is provided in Figure 49. The majority of the Grade 3 or higher events were of Grade 3 in severity. Grade 3 AEs were reported in 70.6% (n=36), 82.7% (n=43), and 52.0% (n=26) of subjects in the combination, lenvatinib, and everolimus arms, respectively. Substantially fewer Grade 4 events were reported in all 3 treatment arms with similar incidence across the arms: 7 subjects (13.7%), 5 subjects (9.6%), and 6 subjects (12.0%) in the combination, lenvatinib, and everolimus arms, respectively). With the exception of Grade 4 lipase increased that was reported in 2 subjects (3.8%) in the lenvatinib arm, all other Grade 4 TEAEs were reported in no more than 1 subject in any treatment arm.

There were 6 fatal (Grade 5) TEAEs, 1 in the combination arm (cerebral haemorrhage), 3 in the lenvatinib arm (myocardial infarction, intracranial haemorrhage and sepsis) and 2 in the everolimus arm (respiratory failure and sepsis).

Grade 3 diarrhoea occurred in 19.6% (n=10) of subjects in the combination arm compared with 11.5% (n=6) in the lenvatinib and 2.0% (n=1) in the everolimus arm. Other frequently reported Grade 3 TEAEs in the combination arm were hypertension in 7 subjects (13.7%) and fatigue in 5 subjects (9.8%). The other Grade 3 TEAEs reported for ≥5% of subjects included: anaemia (7.8%), hypertriglyceridemia (7.8%), vomiting (7.8%), decreased appetite (5.9%), dehydration (5.9%), nausea (5.9%), and thrombocytopenia (5.9%).

Grade 3 TEAEs reported in ≥5% of subjects in the lenvatinib arm were proteinuria (19.2%), hypertension (17.3%), diarrhoea (11.5%), nausea (7.7%), fatigue (5.8%), acute renal failure (5.8%), lipase increased (5.8%), and weight decreased (5.8%).

In the everolimus arm, Grade 3 anaemia (12.0%), dyspnoea (8.0%), hyperglycaemia (8.0%), hypertriglyceridaemia (8.0%), and pneumonitis (6.0%) were reported in ≥5% of subjects. The incidence of Grade 3 pneumonitis in the everolimus monotherapy arm (6.0%) was consistent with the 4.0% incidence reported in the approved label, and was not increased when everolimus was used in combination with lenvatinib. No subject in the combination arm had Grade 3 pneumonitis.

Figure 49 Grade 3 and 4 Treatment-emergent adverse events occurring in at least 5% of subjects in any treatment arm

	Lenvatinib + everolimus (n=51)		Single-arm lenvatinib (n=52)		Single-arm everolimus (n=50)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any TEAE	36 (70.6)	7 (13.7)	43 (82.7)	5 (9.6)	26 (52.0)	6 (12.0)
Diarrhoea	10 (19.6)	0	6 (11.5)	0	1 (2.0)	0
Hypertension	7 (13.7)	0	9 (17.3)	0	1 (2.0)	0
Fatigue	5 (9.8)	0	3 (5.8)	0	0	0
Anaemia	4 (7.8)	0	1 (1.9)	0	6 (12.0)	0
Hypertriglyceridaemia	4 (7.8)	0	2 (3.8)	0	4 (8.0)	0
Vomiting	4 (7.8)	0	2 (3.8)	0	0	0
Decreased Appetite	3 (5.9)	0	2 (3.8)	0	0	0
Nausea	3 (5.9)	0	4 (7.7)	0	0	0
Dehydration	3 (5.9)	0	0	0	0	0
Thrombocytopenia	3 (5.9)	1 (2.0)	0	0	0	0
Lipase Increased	2 (3.9)	0	3 (5.8)	2 (3.8)	2 (4.0)	0
Renal Failure Acute	2 (3.9)	0	3 (5.8)	0	0	
Proteinuria	2 (3.9)	0	10 (19.2)	0	1 (2.0)	0
Weight Decreased	1 (2.0)	0	3 (5.8)	0	0	0
Dyspnoea	0	1 (2.0)	1 (1.9)	0	4 (8.0)	0
Hyperglycaemia	0	0	0	0	4 (8.0)	1 (2.0)
Pneumonitis	0	0	0	0	3 (6.0)	0

Relationship to study drug

Figure 50 summarises treatment-related TEAEs. The incidence of Grade 3 or higher treatment-related TEAEs was similar in the combination arm (64.7%) and the lenvatinib arm (65.4%) and was lower in the everolimus arm (42.0%). The frequencies of treatment-related TEAEs leading to study treatment adjustments (treatment discontinuation, dose reduction, and/or interruption) were similar between the combination arm and lenvatinib arm (82.4% and 76.9%, respectively) and lower in the everolimus arm (44.0%). The majority of these treatment adjustments in the 3 treatment arms were dose reductions and/or interruptions. Treatment-related TEAEs leading to treatment discontinuation were reported in 15.7% (n=8), 13.5% (n=7), and 6.0% (n=3) of subjects in the combination, lenvatinib, and everolimus arms, respectively.

Figure 50 Overview of Treatment-related Treatment Emergent Adverse Events (TEAEs)

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
	n (%)	n (%)	n (%)
Any TEAEs	51 (100.0)	51 (98.1)	49 (98.0)
TEAEs with CTCAE Grade ≥3	33 (64.7)	34 (65.4)	21 (42.0)
SAEs	16 (31.4)	11 (21.2)	11 (22.0)
Deaths	1 (2.0)	1 (1.9)	0
Other SAEs	15 (29.4)	10 (19.2)	11 (22.0)
TEAEs leading to study treatment adjustment	42 (82.4)	40 (76.9)	22 (44.0)
TEAEs leading to study treatment withdrawal	8 (15.7)	7 (13.5)	3 (6.0)
TEAEs leading to dose reduction	33 (64.7)	30 (57.7)	7 (14.0)
TEAEs leading to dose interruption	33 (64.7)	32 (61.5)	19 (38.0)

Almost all subjects in the 3 treatment arms had treatment-related TEAEs except for 1 subject each in the lenvatinib and everolimus arms. The most frequently reported (≥30% of subjects in any treatment arm) treatment-related TEAEs, all of which occurred more frequently with the combination or lenvatinib than with everolimus were diarrhoea, decreased appetite, hypertension, fatigue, nausea, vomiting, weight decreased, hypothyroidism and dysphonia. Treatment-related hypertriglyceridemia

was reported more often in the combination and everolimus arms than in the lenvatinib arm: 35.3% for the combination, 11.5% for lenvatinib, and 22.0% for everolimus. The most frequent treatment-related TEAE on the everolimus arm was stomatitis in 21 (42%) subjects, which is consistent with the known toxicity profile of everolimus.

The incidence of Grade 3 treatment-related TEAEs was similar in the combination arm (62.7%) and the lenvatinib arm (63.5%) and was lower in the everolimus arm (40.0%). Overall, the incidence of Grade 4 treatment-related TEAEs was similar across the 3 arms (n=2 for each arm) with each individual AE reported in not more than 1 subject in any treatment arm.

Two Grade 5 (fatal) treatment-related TEAEs were reported: one event (cerebral haemorrhage) in the combination arm and 1 event (myocardial infarction) in the lenvatinib arm.

4.13 Interpretation of clinical effectiveness and safety evidence

As described above, in a Phase II study, lenvatinib in combination with everolimus demonstrated improved PFS compared to everolimus monotherapy with a median PFS of 14.6 months vs. 5.5 months (HR˚0.40; 95% CI 0.24 to 0.68; p=0.0005). An independent imaging review (IIR) corroborated the improvements seen in the original analyses with a median PFS of 12.8 months vs. 5.6 months compared to everolimus alone (HR, 0.45; 95% CI, 0.26 to 0.79; p=0.003) (Motzer, et al., 2015). Additional sensitivity analyses performed confirmed the robustness of observed PFS.

Furthermore, encouraging signs of a prolonged OS were seen in patients treated with lenvatinib in combination with everolimus in the primary analysis as well as in two updated analyses.

There was no change to the known safety profile of lenvatinib when it was combined with everolimus. The safety profile observed with the combination of lenvatinib with everolimus was consistent with the known toxicities of each individual agent.

In the absence of direct head-head comparative evidence between the lenvatinib and everolimus combination and the relevant comparators as described in the

decision problem (Figure 1), an indirect treatment comparison was necessary to estimate relevant treatment effects.

Based on the ITC of the PFS reported in the trials, the lenvatinib plus everolimus combination was superior to nivolumab, axitinib and placebo, while there was no evidence of a difference to cabozantinib. In terms of OS and ORR, there was no statistical significant difference between lenvatinib plus everolimus versus nivolumab, cabozantinib or axitinib. Lenvatinib plus everolimus was superior to placebo in OS in the intention-to-treat analysis, but not after adjustment for cross-over of placebo patients to active treatment, which resulted in a lower point estimate (0.35 compared with 0.51) but wider confidence interval.

There was no statistically significant difference in the proportion of patients experiencing at least one severe (grade 3 or 4) AEs, or discontinuing due to AE between lenvatinib plus everolimus and cabozantinib. However, there was a higher proportion of patients experiencing at least one treatment-related severe AE with lenvatinib plus everolimus versus nivolumab. Nivolumab was also superior to lenvatinib plus everolimus in terms of discontinuations with less patients discontinuing treatment due to AE.

Overall the ITC suggests that the combination of lenvatinib plus everolimus is at least as efficacious as nivolumab, cabozantinib or axitinib, and possibly superior in terms of PFS to nivolumab and axitinib. In terms of safety, there is no evidence of a statistical difference between lenvatinib plus everolimus and cabozantinib or axitinib, however the data suggests that the safety profile of nivolumab is more benign.

It is important to note that there are limitations to the interpretation of the ITC analysis. The validity of an ITC is dependent on the exchangeability of the trials. The trials of lenvatinib plus everolimus (HOPE 205), nivolumab (CHECKMATE-025), and cabozantinib (METEOR) were reasonably similar, however the everolimus versus placebo trial (RECORD1), axitinib versus sorafenib trial (AXIS) and sorafenib versus placebo trial (TARGET) were conducted in an earlier time period and had different patient populations and/or design features.

TARGET was conducted in patients who had failed cytokine therapy while AXIS allowed patients who had failed therapy containing sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines. The extent of prior treatment (prior cytokines or prior VEGF) appears to be an effect modifier for PFS in the AXIS trial where the HR (axitinib versus sorafenib) for the prior cytokine subgroup was 0.46 compared with 0.76 for the prior sunitinib subgroup. Therefore, the assumption of constancy of the relative effect is violated which limits the validity of the ITC estimate.

In addition, RECORD1 and TARGET were both placebo controlled trials and allowed crossover from the placebo arm to the investigational drug post progression, thereby confounding the OS results. While the confounding has been adjusted for using a post hoc RPSFT analysis of RECORD1 and censoring the alive patients who crossed over in TARGET, these techniques add an additional element of uncertainty around the underlying estimate. Therefore, results for the multi-step indirect comparison of lenvatinib plus everolimus to axitinib on OS should be interpreted with caution.

Eisai does not believe that the lenvatinib in combination with everolimus is suitable for consideration as a 'life-extending treatment at the end of life'.

4.14 Ongoing studies

The following studies are currently ongoing with lenvatinib in advanced RCC but no new evidence is expected to become available before 2020.

- Study 218: Randomised, Double-blind, Phase II Trial of Lenvatinib at Two Different Starting Doses (14 mg/day or 18 mg/day) + Everolimus 5 mg/day in Advanced RCC following 1 prior VEGF-Targeted Therapy
- Study 221: A Phase 2 Trial to Evaluate Efficacy and Safety of Lenvatinib in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC) Who Have Not Received Any Chemotherapy for Advanced Disease (NCT02915783)
- CLEAR study: Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab vs. Sunitinib Alone as First Line Treatment of Advanced RCC (NCT02811861)

5 Cost effectiveness

Summary of Cost Effectiveness

- A systematic literature review was conducted to retrieve relevant information from the published literature regarding the cost-effectiveness of lenvatinib in combination with everolimus and the comparators listed in in the decision problem ie axitinib, everolimus, nivolumab and cabozantinib) for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.
- In the absence of a relevant economic evaluation found in the literature, a de novo cost effectiveness analysis was conducted.
- The economic evaluation was performed by developing a partition survival model according to the NICE technical and clinical guidelines.
- Health outcomes were measured in in terms of quality adjusted life years (QALYs). HRQoL was not collected during the Phase II trial of the lenvatinib and everolimus combination. Therefore, in line with recent feedback during NICE's assessment of cabozantinib and nivolumab, utility values for the estimation of the QALYs were based on those used in TA333.
- Cost assessment included the cost of treatments and their administration, as well as the cost of treating AEs. The cost of healthcare resources utilised over stable and progressive disease as well as resources related to palliative care were also considered.
- The assumptions of the economic model were validated by oncologists practicing in the NHS and with experience of lenvatinib and other treatments approved by NICE for this indication.
- As the survival data from the Phase II Study 205 was not mature, a piecewise approach was used for both OS and PFS extrapolation, where the Kaplan-Meier curve is used prior to the trial cut-off, followed by a parametric tail after the cut-off.
- Apart from probabilistic and deterministic sensitivity analyses, additional sensitivity analysis scenarios were performed assessing the impact of the variation in some key assumptions on the ICER.
- The lenvatinib and everolimus combination is predicted to be a cost-effective treatment option for advanced/metastatic RCC patients, versus cabozantinib and nivolumab, representing good value for money to the NHS.
- The base case incremental cost-effectiveness ratios for LEN+EVE versus axitinib and everolimus are higher than the £30,000 per QALY cost effectiveness threshold.
- It is important to note that all the ICERs presented in base case are based on

the list price of everolimus and as there is currently a PAS in place for everolimus, are not an accurate reflection of the true cost effectiveness of LEN+EVE.

5.1 Published cost-effectiveness studies

A systematic literature review was carried out in order to identify relevant cost-effectiveness studies for lenvatinib in combination with everolimus and relevant comparators (which include those listed in the scope and in the decision problem (Figure 1) ie axitinib, everolimus, nivolumab and cabozantinib) for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endotelial growth factor (VEGF)-targeted therapy.

Search strategy

The following databases were screened in line with standard methodology:

- Embase + MEDLINE;
- the Cochrane Library; and
- MEDLINE In-process and Other Non-indexed Citations (PubMed).
- EconLit

The search strategies are provided in the Appendix 8.3. Systematic literature Review.

Study selection

The searches were limited to records for English language articles published from 2005 and publications that are reviews (except systematic reviews, meta-analyses and pooled analyses), case reports, editorials, letters, notes/comments and errata were excluded, where the indexing allowed. The comparators listed in the systematic literature search exceeded that in the final decision problem, in which comparators were limited to axitinib, nivolumab, everolimus and cabozantinib. (Figure 1).

Figure 51 summarises the inclusion and exclusion criteria, language restrictions and the study selection process.

The PRISMA flow diagram of the number of studies included and excluded at each stage is shown in Figure 52.

The complete reference list for excluded studies is provided in the Appendix 8.3. Systematic literature Review.

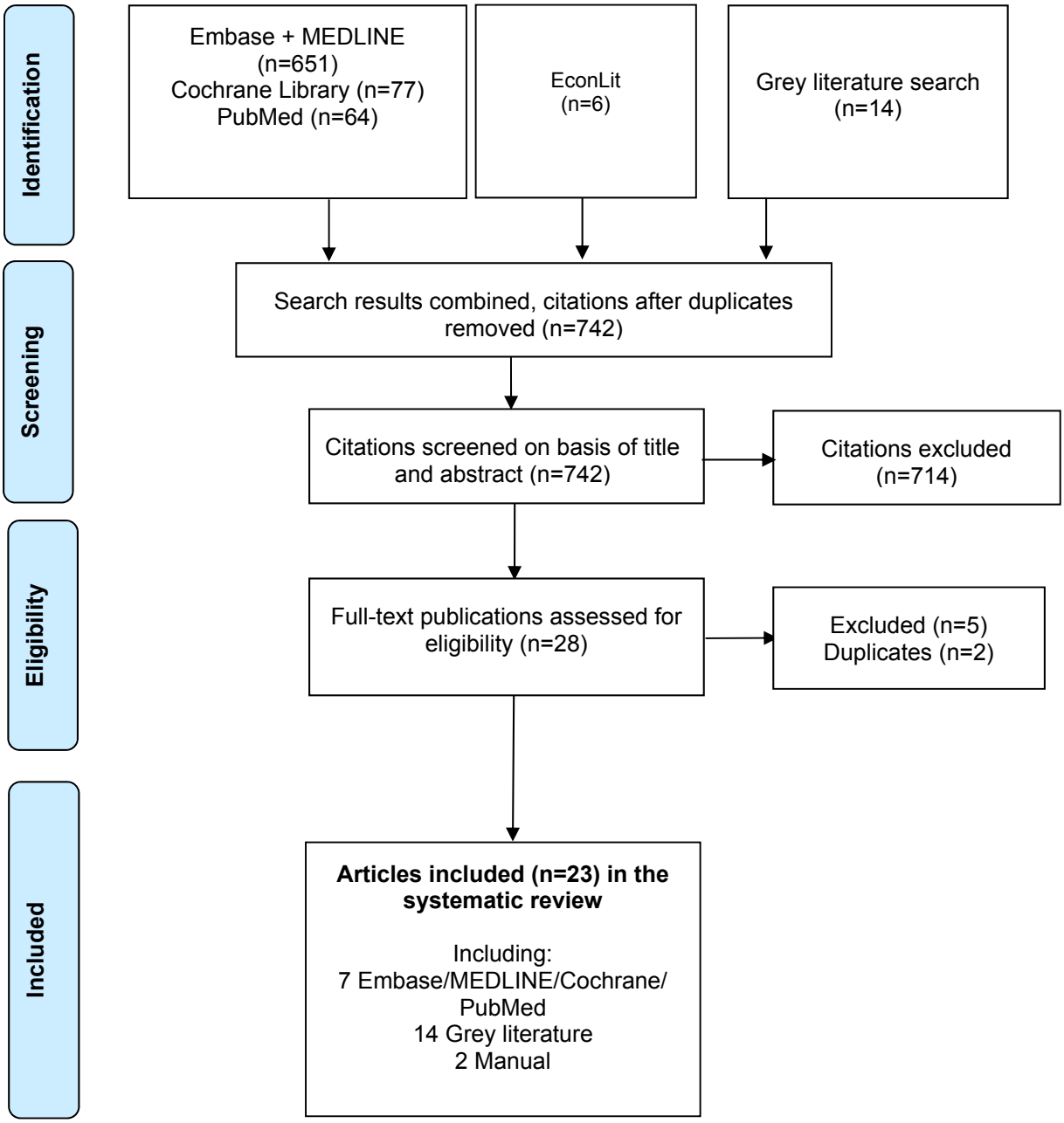
The comparators listed in the systematic literature search exceeded that in the final decision problem, in which comparators were limited to axitinib, nivolumab, everolimus and cabozantinib. (Figure 1).

Figure 51 Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	▪ Lenvatinib ▪ Cabozantinib ▪ Nivolumab ▪ Temsirolimus ▪ Everolimus ▪ Pazopnanib ▪ Sunitinib ▪ Sorafenib ▪ Bevacizumab ▪ Axitinib	Not second line a/mRCC treatment after one prior anti-VEGF therapy Surgical /Radiotherapy /Diagnostic intervention
Outcomes	Economic aspects, such as: ▪ costs and resource utilisation, ▪ economic evaluations, including cost-effectiveness, cost-utility and cost-benefit, ▪ economic models such as decision analytic model and Markov model, ▪ burden of illness.	
Study design	Systematic reviews Meta-analysis Pooled analyses	Reviews, case reports, editorials, letters, notes/comments, errata
Language restrictions	English	Non-English language

Abbreviations: a/mRCC, Advanced or metastatic renal cell carcinoma; VEGFR, Vascular endothelial growth factor receptor

Figure 52 PRISMA Study Attrition Diagram for Systematic Literature Review of a/mRCC: Economic Studies



Description of identified studies

As highlighted in Figure 52, the systematic review on the cost effectiveness of lenvatinib and the relevant comparators identified 23 separate citations, which are listed in Section 5.3 in the Appendix 8.3. Systematic literature Review.

Twenty economic studies were identified from these 23 citations and these included 14 HTA submissions and six economic studies. The applicability of these studies to this STA is assessed in Table 5.4.1 of the Systematic Literature Review Report (Appendix 8.3) and the 9 studies listed below (7 HTA submissions and 2 economic studies) were considered directly applicable to the UK:

Figure 53 List of included studies from Embase/ MEDLINE/ Cochrane library

	Reference
1	NICE (2011). "Everolimus for the second-line treatment of advanced RCC (TA219)". HTA submission. https://www.nice.org.uk/guidance/ta219. Review of NICE TA219: Pitt, M, Crathorne, L, Moxham, T, Bond, M and Hyde, C (2010) "Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis (Structured abstract)." Health Technology Assessment Database(3): 41. (Pitt, et al., 2010)
2	NICE (2009). "Bevacizumab (first-line), sorafenib (first and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic RCC (TA178)". HTA submission. https://www.nice.org.uk/guidance/ta178. Thompson Coon, J, Hoyle, M, Green, C, Liu, Z, Welch, K, Moxham, T, et al. (2010). "Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: A systematic review and economic evaluation." Health Technology Assessment 14(2): 1-184. (Thompson Coon, et al., 2010)
3	NICE (2015). "Axitinib for treating advanced RCC after failure of prior systemic treatment (TA333)". HTA submission. https://www.nice.org.uk/guidance/ta333. Riemsma R, Al M, Corro Ramos I, Deshpande S et al. (2012). "Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment: a Single Technology Appraisal." York:Kleijnen Systematic Reviews Ltd (October 2012) (Riemsma, et al., 2012)
4	NICE (2016). "Nivolumab for treated or metastatic renal cell carcinoma [ID853]". HTA submission. https://www.nice.org.uk/guidance/gid-ta10037/consultation/html-content.
5	SMC (2016). "Nivolumab, 10mg/mL, concentrate for solution for infusion (Opdivo®) SMC". HTA submission. http://www.scottishmedicines.org.uk/files/advice/nivolumab_Opdivo_RCC_FINAL_Oct_2016_for_website.pdf
6	SMC (2013). "Axitinib (Inlyta) resubmission 855/13 SMC Advice. http://www.scottishmedicines.org.uk/SMC_Advice/Advice/855_13_axitinib_Inlyta/axitinib_Inlyta_Resubmission
7	SMC (2007). "Sunitinib 50mg capsule (Sutent) 343/07 SMC advice" https://www.scottishmedicines.org.uk/files/sunitinib_Sutent_MRCC_343_07.pdf
8	Hoyle, M, Green, C, Thompson-Coon, J, Liu, Z, Welch, K, Moxham, T, et al. (2010). "Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma." Value in Health 13(1): 55-60. (Hoyle, et al., 2010)
9	Chandiwana, D, Perrin, A and Sherman, S (2014). "A cost effectiveness analysis of everolimus compared with axitinib in the treatment of metastatic renal cell carcinoma in the United Kingdom." Value in Health 17(7): A640. (Chandiwana, et al., 2014)

A quality assessment of the above 9 studies is provided in Table 5.4.2 of the Systematic Literature Review Report (Appendix 8.3) and each study is summarised in Figure 54.

Figure 54 Summary list of published cost effectiveness studies

Study and Year	Summary of model				QALYs (intervention, comparator)	Costs (£) (intervention, comparator)	Resource Utilisation Information	ICER (per QALY gained)
Authors (Year)	Country	Model Time Horizon	Intervention and Comparator(s)	Methods				
NICE everolimus appraisal committee (2011) (additional detail from Pitt et al, 2009)	UK	144 weeks Updated model: 312 weeks	Everolimus plus BSC vs BSC	Markov model The model included 4 health states: 1. Stable disease with no Aes 2. Stable disease with Aes 3. Progressed disease 4. Death - Cycle length = 8 weeks, no half-cycle correction	Mean of 0.607 QALYs for BSC plus everolimus, compared to 0.302 QALYs for BSC plus placebo	Not reported	Not available	ICER: (everolimus plus BSC vs BSC) Manufacturer submission (updated values): Cost per QALY = £49,272 with PAS ERG re-analysis = agreed with manufacturers updated values
NICE sorafenib and sunitinib appraisal committee (2009) (additional detail from Thompson et al, 2010)	UK	10 years	Sorafenib vs BSC Sunitinib vs BSC	Markov model Sorafenib: The model included 3 health states: 1. Progression-free survival 2. Progressed disease 3. Death - 6 week cycle Sunitinib: The model included 3 health states: 1. Progression-free survival 2. Progressed disease 3. Death - 6 week cycle	Sunitinib vs BSC sunitinib increased OS by 0.77 years and PFS by 0.54 years and resulted in an additional 0.60 QALYs compared with BSC.		Healthcare resource use was estimated in the absence of specific published literature.	ICER (sorafenib vs BSC) Manufacturer submission: Cost per QALY = £62,256 with PAS ERG re-analysis: Cost per QALY = £102,498 with original price DSU re-analysis: Cost per QALY = £65,929 with PAS and new price ICER (sunitinib vs BSC) Manufacturer submission: Cost per QALY = £37,519 with PAS ERG re-analysis:

Study and Year	Summary of model				QALYs (intervention,	Costs (£) (intervention,	Resource Utilisation	ICER (per QALY gained)
								Not evaluated as data considered inadequate
NICE axitinib appraisal committee (2015) (additional detail from Riemsma et al, 2012)	UK	10 years	Axitinib vs BSC	Markov model The model included 3 health states: 1. Progression-free survival 2. Progressive disease 3. Death - Cycle length = 4 weeks	Not reported	Not reported	Company submission included detailed information on healthcare resource utilisation which was based on previous NICE submissions and validated with expert clinical opinion. A scenario analysis examined the impact of assuming management by oncologist rather than GP.	ICER (axitinib vs BSC) Manufacturer submission: Prior cytokine group; Cost per QALY = £55,284 with PAS Prior sunitinib group; Cost per QALY = £33,538 with PAS Committee re-analysis: Prior cytokine group; Cost per QALY = ~£36,500 to ~55,300 with PAS Prior sunitinib group; Cost per QALY = ~£33,500 to ~£52,900 with PAS
NICE nivolumab appraisal committee Papers (2016)	UK	30 years	Nivolumab with everolimus, axitinib and best supportive care (BSC)	Partitioned-survival (AUC) model The model included 6 health states: 1. PFS on treatment 2. PFS off treatment 3. Post-progression survival (PPS) on treatment	QALY gain for nivolumab against everolimus was 0.63 QALY gain for nivolumab against axitinib was 1.07 QALY gain for	Not reported	Company submission included detailed information on healthcare resource utilisation which was based on	Company's base case: ICER Nivolumab vs axitinib: £43,109 ICER Nivolumab vs everolimus: £86,136 ICER Nivolumab vs BSC: £57,096 ERG's preferred

Study and Year	Summary of model				QALYs (intervention,	Costs (£) (intervention,	Resource Utilisation	ICER (per QALY gained)
				4. Post-progression survival (PPS) off treatment 5. Terminal care 6. Death - Cycle length = 1 week	nivolumab against BSC was 1.43		previous NICE submissions and estimated by clinicians currently practicing in the UK.	analysis: ICER Nivolumab vs axitinib: £74,132 ICER Nivolumab vs everolimus: £91,989 ICER Nivolumab vs BSC: £61,317 Updated ICER's: When the confidential discounts for nivolumab and axitinib were included, the company's revised base case and the majority of the ERGs revised base case were below £50,000/QALY gained for nivolumab compared with any comparator.
SMC Nivolumab 1188/16 (2016)	Scotland	30 years	Nivolumab vs axitinib or everolimus	Markov model The model included 6 health states: 1. PFS on treatment 2. PFS off treatment 3. Post-progression survival (PPS) on treatment 4. Post-progression survival (PPS) off treatment 5. Terminal care 6. Death - Cycle length = 1 week	QALY gain for nivolumab against everolimus was 0.61 • QALY gain for nivolumab against axitinib was 1.05 • LY gain for nivolumab against everolimus was 0.84 • LY gain for nivolumab against axitinib was 1.30	Incremental cost of nivolumab compared to everolimus is £59,949. Incremental cost of nivolumab compared to axitinib is £57,419	No details reported	ICER (nivolumab vs everolimus) £98,558 ICER (nivolumab vs axitinib) £54,747

Study and Year	Summary of model				QALYs (intervention,	Costs (£) (intervention,	Resource Utilisation	ICER (per QALY gained)
SMC Axitinib 855/13 (2013)	Scotland	10 years	Axitinib vs BSC using indirect comparison (AXIS).	Not explicitly stated – assumed Markov model The model included 3 health states: 1. Progression free survival 2. Progressive disease 3. Death - Cycle length = 4 weeks	Not reported	Not reported	Clinical management costs were estimated from a previous HTA review. No further details were provided.	ICER (axitinib vs BSC) Sunitinib refractory population; Cost per QALY = £33,837 with PAS Cytokine refractory population; Cost per QALY = £56,343 with PAS For this population, using the lognormal parametric function the ICER was: Cost per QALY = £61,100 with PAS Reducing the dose intensity to 80% the ICER was: Cost per QALY = £44,400 with PAS
SMC Sunitinib 343/07 (2007)	Scotland	6 years	Sunitinib vs BSC.	Not reported	Not reported	Not reported	Resource use and unit cost data were sourced from published literature and supplemented with opinion from clinical experts. No further details were provided.	ICER (sunitinib vs BSC) Cost per LYG = £30,066 Cost per QALY = £39,000
Hoyle et al. (2010)	UK	10 years	Sorafenib vs BSC	Markov-type decision analytic model The model included 3	• Lys: BSC = 1.30, sorafenib = 1.66 • QALYs: BSC = 0.91, sorafenib	Total cost: BSC = £3,797 sorafenib = £23,860	Assumptions were based on guidelines outlining current	ICER: (sorafenib vs BSC) Cost per LYG = £54,565 Cost per QALY =

Study and Year	Summary of model				QALYs (intervention,	Costs (£) (intervention,	Resource Utilisation	ICER (per QALY gained)
				health states: 1. Progression-free survival 2. Progressive disease 3. Death - Cycle length = 6 weeks	= 1.18 Discounted (sorafenib vs BSC): 0.37 LY 0.27 QALY	Discounted: (sorafenib vs BSC) = £20,063	practice and information provided by clinical experts. Detailed information is provided.	£75,398
Chandiwana, D., et al. (2014)	UK	12 years	Everolimus vs axitinib	Markov model The model included 3 health states: 1. Stable disease 2. Progressive disease 3. Death - Cycle length = monthly	QALY (everolimus vs axitinib) is 0.65 vs 0.63. Difference: (everolimus vs axitinib) 0.02	Total cost: Everolimus = £24,387 Axitinib = £42,533 Difference: (everolimus vs axitinib) - £18,146	Detailed healthcare resource information is reported. Frequency of GP and nurse visits and blood tests were based on published literature.	Everolimus is dominant.

Source: Systematic Literature review (Appendix 8.3
Abbreviations: AEs, adverse events; BSC, best supportive care; LY, Life year; QALYs, quality-adjusted life years; PAS, Patient access scheme; UK, United Kingdom;

None of the 9 studies evaluated the cost effectiveness of the lenvatinib and everolimus combination patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy and therefore a de novo analysis has been carried out (see Section 5.2).

5.2 De novo analysis

The cost-effectiveness model was developed according to methods guidance published by NICE and international good research practices for modelling, to ensure that the analysis was as methodologically rigorous as possible.

Patient population

This de novo economic evaluation was designed to assess the cost-effectiveness of lenvatinib plus everolimus (referred to as “LEN+EVE” throughout section 5), compared to axitinib, nivolumab, cabozantinib and everolimus alone (“EVE”) in a population identical to that of the HOPE 205 phase II clinical trial: unresectable advanced or metastatic renal cell carcinoma following one prior VEGF targeted treatment, as per the decision problem summary table (Figure 1). In line with NICE committee recommendations based on clinical expert input during the cabozantinib review (National Institute for Health and Care Excellence, NICE, 2017), best supportive care was not included as a comparator in the model.

For this analysis, the intention-to-treat population of the Phase II Study HOPE 205 (Eisai Ltd., 2015) was used, as these patients were considered to be representative of those who would receive LEN+EVE in the UK, based on its intended use. Detailed information on this study is provided in Sections 4.2 to 4.8.

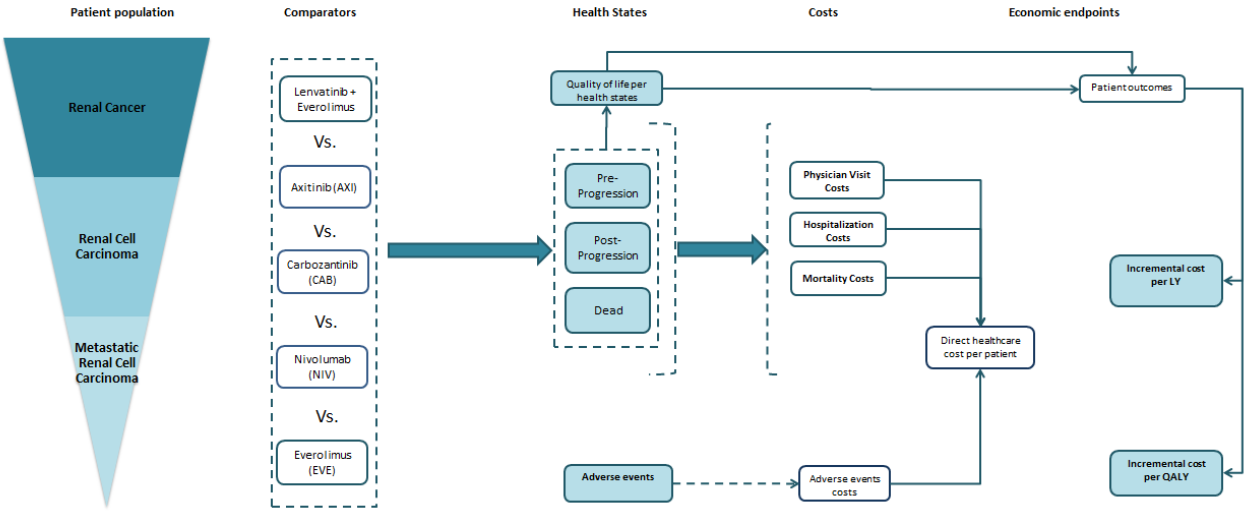
Comparisons to the interventions listed above were informed by results from an indirect treatment comparison as described in Section 4.10. (Appendix 8.5)

Model structure

A de novo partitioned survival cost utility model was developed to model the lifetime clinical and economic outcomes of LEN+EVE and the relevant comparators as described in the decision problem (Figure 1).

A partitioned survival model was used due to its intuitive implementation with the patient level data available, as the model is not deviating from the trial data, and because the patient data was relatively mature (i.e. most short- and medium-term events occurred within the trial period) and was considered reflective of clinical practice. Partition survival models eliminate the need to generate assumptions for the transition of patients between health states and allows for the direct use of the trial Kaplan-Meier curves in the model. As such, the estimated proportion of patients occupying each health state was derived directly from the cumulative survival probabilities. The conceptual model framework is presented in Figure 55.

Figure 55 Model Framework



Using the partitioned survival model approach, the proportion of patients in each health state was determined by the area under the curves fitted to the trial outcomes.

The Kaplan-Meier data was extracted on a monthly (30.4375-day) cycle basis for this analysis (i.e., at the end of each month). A half-cycle correction was used in this model. Every month (counted as one Markov cycle), patients face a probability of transition among health states based on disease status or death. Their health state at any point in time is derived from the clinical outcomes of their respective clinical trials – i.e. the time to event data (survival curve) for Progression Free Survival (PFS) and overall survival (OS). A one-month cycle length was used for the purpose of convenience of calculations and to align with the treatment dosing schedules.

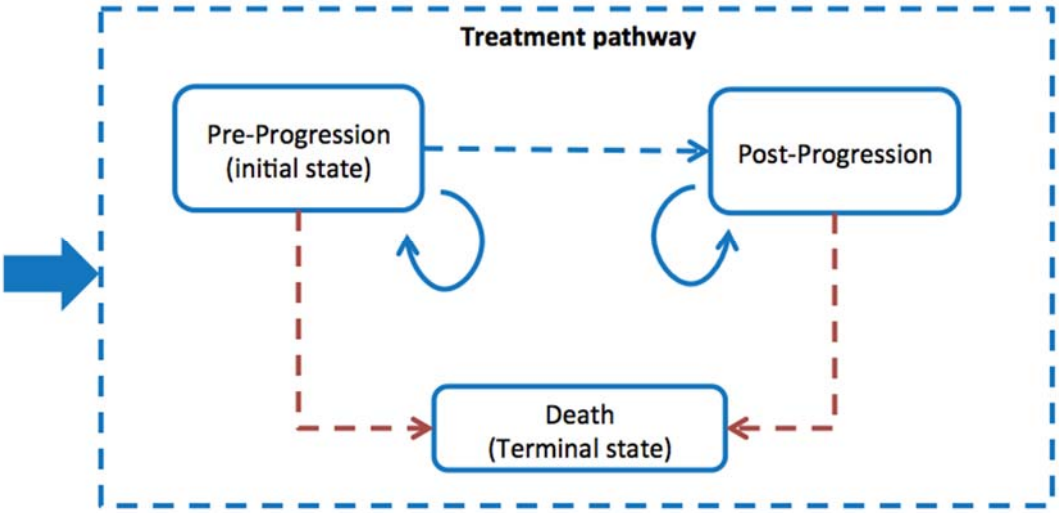
The model was created using Microsoft Excel and the survival analyses were performed in Stata 14.

Health States

As shown in Figure 56, the model included three health states:

- Pre-Progression or Stable disease health state,
- Post-Progression or Progressive disease health state, and
- Death or Terminal/Mortality health State

Figure 56 Transition of Health States



These health states were selected based on the clinical pathway and current guidelines for treatment of unresectable advanced or metastatic renal cell carcinoma following one prior VEGF targeted treatment. Health states were defined in consistency with clinical outcomes reported in oncology clinical trials, including the HOPE 205 clinical trial (Eisai Ltd., 2015).

Patients are assumed to transition between the four health states of “Pre-Progression”, “Post-Progression” and “Death”, based on time-dependent transition probabilities. Patients enter the model in the “Pre-progression” (or Stable disease) health state when they initiate treatment with LEN+EVE or the comparator arm. These patients stay at this health state until disease progression, when they enter into the “Post-Progression” (or Progressive disease) health state. Patients in the

“Post-progression” state are assumed to remain in this state until death. Patients in the “Pre-progression” health state can transition directly to the “Death” state without passing through the “Post-progression”. Patients continue transitioning across health states until all patients are in the “Death” state.

Each health state was mutually exclusive and was defined as follows:

Pre-Progression: Pre-progression is the initiating state (i.e., where patients enter the model) and where primary therapy begins. Primary therapy is given with the specific aim of inducing and continuing remission in the patient. Patients were assumed to continue their primary therapy until disease progression and then switch to secondary therapy which is defined as best supportive care (no treatment) in the model in the “Post-Progression” health state. Therefore, the proportion of patients in the pre-progression health state were based on the PFS partitions from the HOPE 205 clinical trial (explained in further detail below). In short, patient-level data from the HOPE 205 trial were used to directly derive the proportion of patients in pre-progression for LEN+EVE and EVE alone, as these were the therapies being assessed in this trial. For the remaining comparators used in this model, ITC-derived PFS hazard ratios were applied to the partition of LEN+EVE to determine the proportion of patients in pre-progression.

Post-Progression: As described in Section 0, in England and Wales, there are currently no treatments approved on the NHS for the third-line treatment of advanced or metastatic RCC. Therefore, in line with recommendations from recent NICE submissions for nivolumab and cabozantinib (National Institute for Health and Care Excellence, NICE, 2016; National Institute for Health and Care Excellence, NICE, 2017), patients were assumed to switch to secondary therapy, defined as best supportive care (no treatment) in the model, after progression on primary therapy. Post-progression survival was assumed to equal the difference between OS and PFS. Patients in the “Post-Progression” state are assumed to remain in this state until death. The proportion of patients in OS and PFS were based on partitions from the HOPE 205 clinical trial (as explained for the pre-progression health state above and in further detail later in this report).

Death: Mortality was the final, absorbing state in the model and was also based on the OS clinical trial data partitions.

The proportion of patients in each health state, over the course of time, was estimated based on the Kaplan-Meier survivor functions, parametric survival functions (or both) for response, PFS and OS from the comparators' respective clinical trials. Post-progression survival was assumed to equal the difference between OS and PFS. Expected response, PFS and expected OS were calculated as the area under their respective survival curves. This approach is similar to a traditional Markov model, except that clinical trial data is directly used instead of estimating transition probabilities between states.

Model Time Horizon

For the base case, a lifetime time horizon was used and consisted of 240 months (based on the expected lifespan of all patients), beginning at the time of primary therapy initiation. A lifetime horizon was used in order to capture all the relevant costs and benefits associated with the introduction of LEN+EVE in England and Wales. As per the decision problem summary table (Figure 1), additional time horizon scenarios (trial horizon, 5-year and 10-year horizon) were evaluated in sensitivity analyses for transparency and are presented in Section 5.8.

Cost & Utility Estimation

Costs and health related quality of life (HRQoL) were assumed to be conditioned on treatment and expected time in the given disease states. Patients were assumed to continue primary therapy until disease progression and then switch to secondary therapy, defined as best supportive care (no treatment) in the model, in the "Post-Progression" health state.

Model Perspective

This analysis was conducted from the perspective of the NHS and personal and social services in England & Wales, in line with current NICE guidelines. The analysis excluded patients' out-of-pocket expenses, carers' costs, and lost productivity costs.

Other structural characteristics

Discounting: Costs and utilities were discounted at the rate of 3.5% annually, per NICE guidelines.

Weight: Patient weight is an important factor for calculating the dose of IV chemotherapy regimens administered. Based on the HOPE 205 trial (Eisai Ltd., 2015), the mean weight was assumed to be 80.8 kg.

Dose Intensity: Treatment may have required dose reductions or delays in order to manage AEs. Therefore, patients in the clinical trials did not always receive the full intended doses of primary therapy. The dose intensities of the primary therapies (lenvatinib+everolimus, axitinib, cabozantinib, nivolumab, and everolimus alone) were based on the respective clinical trial data. Detailed information on how the dose intensity was calculated in the model can be found in Section 5.5.

Wastage: The available pack sizes of drugs may not allow for the exact dose of drug required. To account for wastage, rounding was applied for dose calculations based on the received doses (i.e. doses were rounded up to the nearest pack/vial size when necessary). For this economic evaluation, the cost of wasted drug was included in the model to be conservative. Further information can be found in Section 5.5.

Figure 57 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Basecase: Lifetime Sensitivity scenarios: trial-horizon, 5 and 10 years	Lifetime scenario was considered sufficient to capture all meaningful differences in technologies compared
Half-cycle correction	Included	Provide a more accurate estimate for each cycle
Were health effects measured in QALYs; if not, what was used?	Yes. Additionally, life years saved (LYs) were assessed.	According to NICE guidelines QALYs were the primary preference-based outcome evaluated.
Discount of 3.5% for utilities and costs	Yes	According to NICE guidelines

Factor	Chosen values	Justification
Perspective (NHS/PSS)	NHS England	No social services or indirect costs were included in the model as considered non relevant.

Abbreviations: PSS, personal social services; LYs, Life years; QALYs, quality-adjusted life years

Intervention technology and comparators

Primary therapies

The model considers lenvatinib in combination with everolimus (LEN+EVE) as the intervention technology. The following comparators were included in the model: axitinib, nivolumab, cabozantinib, and everolimus alone. As described in the decision problem summary table (Figure 1) these comparators were selected as they are either currently approved by NICE for the same indication as LEN+EVE (axitinib (National Institute for Health and Care Excellence, NICE, 2015), nivolumab (National Institute for Health and Care Excellence, NICE, 2016) and everolimus (National Institute for Health and Care Excellence, NICE, 2017) or are currently undergoing NICE review (cabozantinib (National Institute for Health and Care Excellence, NICE, 2017).

As described previously, in line with NICE committee recommendations based on clinical expert input during the cabozantinib review, (National Institute for Health and Care Excellence, NICE, 2017) best supportive care was not included as a comparator in the model.

All therapies are implemented in the model as per their marketing authorisations. Further information on the dosing applied in the model can be found in Section 5.5.

Secondary therapy

Secondary therapy is defined as best supportive care (no treatment) in the model. As stated previously, in England and Wales, there are currently no treatments approved on the NHS for the third-line treatment of advanced or metastatic RCC. Therefore, in line with recommendations from recent NICE submissions for nivolumab and cabozantinib (National Institute for Health and Care Excellence, NICE, 2016; National Institute for Health and Care Excellence, NICE, 2017), patients were

assumed to switch to best supportive care (no treatment) in the model, after progression on primary therapy.

Treatment Duration

The treatment duration partition for LEN+EVE was derived from the patient level data from the HOPE 205 study. The treatment start and treatment end data was used to determine when patients leave the Pre-Progression health state. The resulting curve is quite similar to PFS in nature, but with a thinner extrapolation tail. For LEN+EVE, all treatments were stopped at month 29. Everolimus treatment duration is also based on the HOPE 205 study, with a maximum treatment duration of 28 months. Other comparator treatment durations were also based on the LEN+EVE trial, where the relative ratio between the median treatment duration of the comparator and LEN+EVE were applied. In other words, the respective relative ratios extracted were applied using a hazard mapping technique, similar to that used in the OS and PFS mapping.

Figure 58 Median treatment duration

	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Treatment duration in the clinical trials	8.0	4.1	8.2	8.3	5.5
Relative ratio applied			1.025	1.0375	0.724

Sources: LEN+EVE (EisaiDoF, 2016); Everolimus (EisaiDoF, 2016) Axitinib (Motzer, et al., 2013), Cabozantinib (Choueiri, et al., 2016); Nivolumab (Motzer, et al., 2015)

5.3 Clinical parameters and variables

The following sections outline how the clinical data from the trials were incorporated into the model. Efficacy data for each comparator were obtained from the respective clinical trials and are presented in

Figure 59.

Figure 59 Sources of efficacy data

	Reference	Utilisation in the model
Efficacy & Safety data:		Progression Free Survival Overall Survival AE rates, duration of treatment
Lenvatinib + Everolimus	HOPE 205 Clinical Trial # NCT01136733 (Motzer, et al., 2015; Motzer, et al., 2016; Eisai Ltd., 2015; Eisai, 2016)	Hazard mapping of the comparators using ITC results (Hazard ratios)
Everolimus	HOPE 205 Clinical Trial # NCT01136733 (Motzer, et al., 2015; Motzer, et al., 2016; Eisai Ltd., 2015; Eisai, 2016) RECORD-1 ((Motzer, et al., 2010)	
Axitinib	AXIS (Rini, et al., 2011; Motzer, et al., 2013) ITC report (Appendix 8.5)	
Cabozantinib	METEOR (Choueiri, et al., 2015; Choueiri, et al., 2016) ITC report (Appendix 8.5)	
Nivolumab	CheckMate 025 (Motzer, et al., 2015) ITC report (Appendix 8.5)	

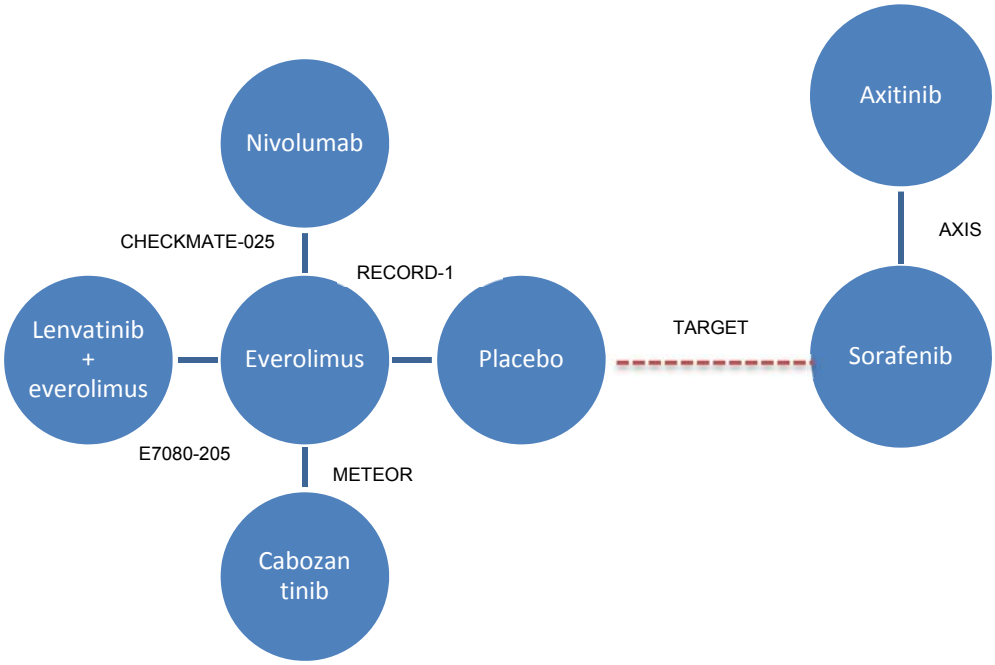
Abbreviations: AE, Adverse event; ITC, Indirect treatment comparison

Incorporation of Clinical Data in the Model

The clinical outcomes considered for the estimation of the patient transition among health states were PFS (investigator review) and OS. Expected PFS and OS were calculated as the area under their respective survival curves.

According to partitioned survival analysis, this patient transition among health states is time-dependent and based on time-to-event non-parametric Kaplan-Meier estimator. They reflect the curves derived by the Kaplan-Meier survival functions estimated based on patient-level data from the HOPE 205 clinical trial (Eisai, 2016). The results of the HOPE 205 clinical trial are described in detail in Section 4.

Figure 60 Network of trials included in the ITC for a/mRCC



The Kaplan-Meier Survivor functions for each treatment were extracted with Stata 14 for both OS and PFS.

In the absence of head-to-head clinical data, an Indirect Treatment Comparison (ITC) analysis was conducted to compare LEN+EVE to the comparators described in the decision problem (Figure 1). Details on the ITC were presented in Section 4.10 and are contained with the ITC report (Appendix 8.5). Results of the ITC were incorporated in the model by mapping LEN+EVE survival using a hazard mapping technique. Based on the patient population characteristics as well as the comparators of the identified studies, the following network of clinical trials was designed summarising all the potential comparisons (Figure 60). This illustration also includes the OS and PFS results of the selected treatments.

The clinical studies included were multicentre, randomised trials of patients being treated in the second line for mRCC (see Figure 61 for study descriptions). The primary and secondary endpoints of all trials were Progression Free Survival (PFS) or Overall Survival (OS).

Figure 61 Clinical Trials in RCC used in the ITC

Comparators	Study Phase	Study Details	Reference
Lenvatinib + everolimus (LEN+EVE) Everolimus (EVE)	Phase II	HOPE 205 This randomised study compared LEN+EVE and lenvatinib to everolimus in RCC patients following progression after 1 prior VEGF-targeted therapy	Motzer R.J., et al. (2015). Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. The Lancet Oncology, 16(15), 1473 – 1482 Motzer R.J.,et al. (2016). Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncology 17, e4-5 HOPE 205 Study CSR Eisai Ltd Summary of Clinical Efficacy 2016
Axitinib (AXI)	Phase III	AXIS This trial compares efficacy and safety of axitinib and sorafenib as a treatment for metastatic renal cell carcinoma.	Rini B.I., et al. Comparative effectiveness of axitinib versus sorafenib in metastatic renal cell carcinoma (AXIS) : a randomised phase 3 trial. Lancet 378, 1931-1939 Updated data: Motzer R.J. et al. (2013). Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncology, vol. 14, 552-562
Cabozantinib (CAB)	Phase III	METEOR This randomised, open-label, trial evaluated the efficacy of cabozantinib, as compared with everolimus, in patients with renal-cell carcinoma that had progressed after VEGFR-targeted therapy.	Choueiri T.K., et al. (2015). Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. The New England Journal of Medicine, 373(19), 1814-1823 Updated data: Choueiri T.K., et al (2016). Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncology 17(7), 917-927

Comparators	Study Phase	Study Details	Reference
Nivolumab (NIV)	Phase III	CHECKMATE-025 This randomised, open-label, study compared nivolumab with everolimus in patients with renal-cell carcinoma who had received previous treatment.	Motzer R.J., et al. (2015). Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. The New England Journal of Medicine, 373(19), 1803-1813 Motzer R.J., et al (2016). Checkmate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC). Journal of Clinical Oncology 34, (suppl 2S; abstr 498)

At the cut-off date for the primary efficacy analysis for HOPE 205 (December, 2014), the median follow-up for LEN+EVE was 24.2 month and for EVE median follow-up was 25 months. The EMA and FDA determined that a longer follow-up time for OS would be useful to avoid uncertainty. Updated OS and PFS analyses were performed at a later cut-off date (July, 2015 and June, 2014, respectively). The updated “third data cut” values for LEN+EVE and for everolimus were used for the ITC and for the base case economic analysis. See Section 4.7 for the full results and further information on the datacut.

The EMA data cut is used in the cost effectiveness model as it includes the updated data and satisfies the preference of the EMA for CRF data. The FDA datacut is presented, but not used in the basecase.

Figure 62 presents the efficacy results of the ITC that were used in the model for each comparator, apart from everolimus. The HR values for everolimus were taken directly from the HOPE 205 study. As described in Section 4.10, the primary ITC analyses for PFS are based on the main results from each study; that is, using investigator review for HOPE 205 study and CHECKMATE-025 and independent review for METEOR, RECORD-1, TARGET and AXIS. The respective HR values for each comparator were applied to the partition OS and PFS data for LEN+EVE to determine the proportion of patients in each health state.

Figure 62 Hazard ratios used in the model (based on ITC)

Comparator	Efficacy values after ITC	
	OS	PFS
AXI	[redacted]	[redacted]
CAB	[redacted]	[redacted]
NIV	[redacted]	[redacted]

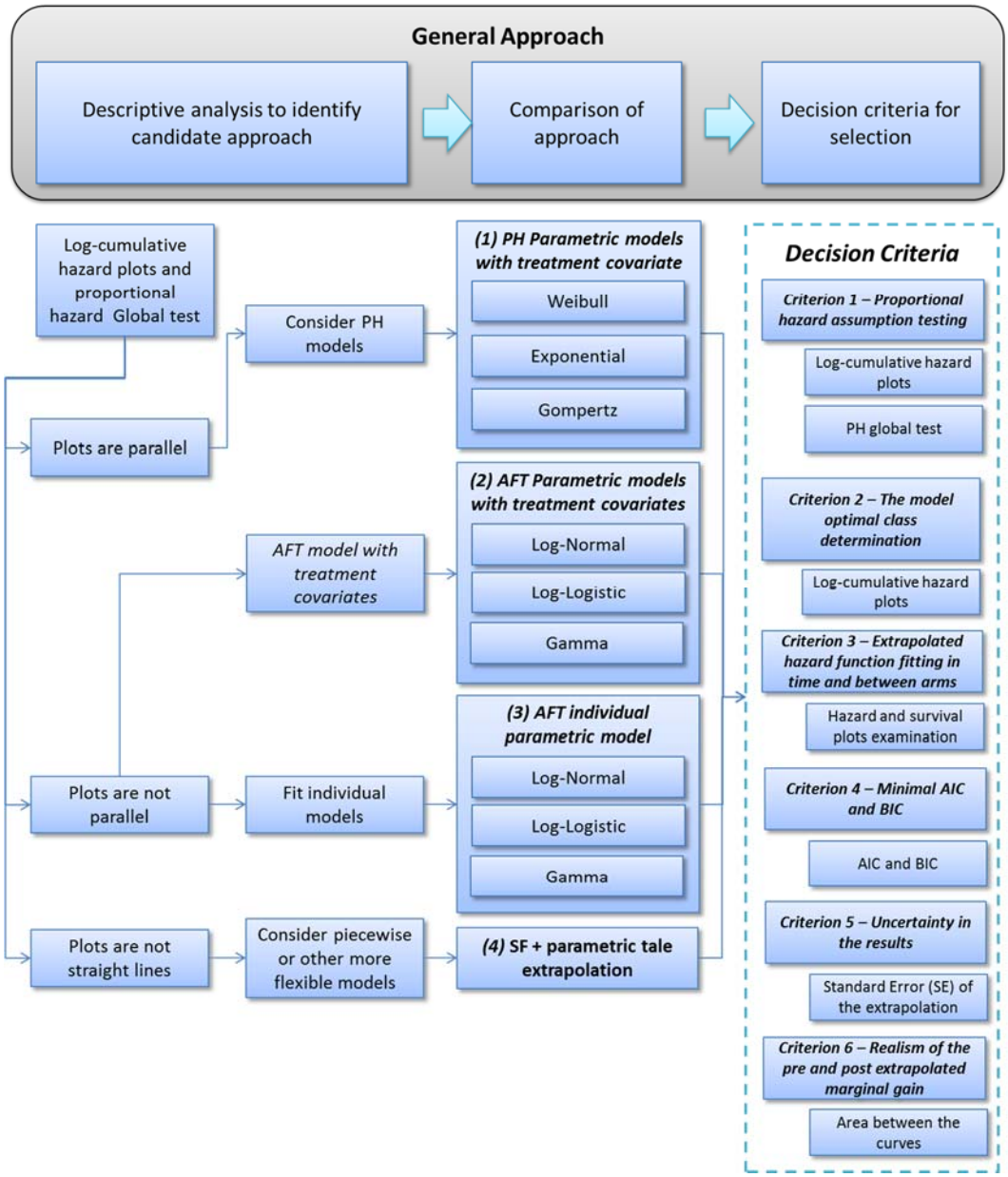
Source: Indirect Treatment Comparison report (Appendix 8.5)

Extrapolation

Extrapolation of survival data is required when the trial data prior to cut-off does not provide enough information on overall survival and progression free survival in oncology. (Tremblay, 2015; Latimer, 2011) Survival data were extrapolated up to a lifetime (240-month) horizon) in order to represent the complete treatment pathway of patients. Because approximately 30% and 23% of the patients were still alive in the LEN+EVE arm and everolimus arm (respectively) and approximately 15% and 2.3% of the patients had not progressed in the LEN+EVE arm and everolimus arm (respectively) at the end of the trial, piecewise extrapolation was used for both OS and PFS. In brief, a piecewise approach was used for both OS and PFS extrapolation, where the Kaplan-Meier curve is used prior to the trial cut-off, followed by a parametric tail after the cut-off.

The framework that was used to determine the best fitting extrapolation technique is below in Figure 63 and is the one presented in Tremblay, Haines, Briggs (2015) (Tremblay, 2015) which is based on the NICE DSU 14 (Latimer, 2011).

Figure 63 Extrapolation framework



As this trial is a long term extrapolation with potential for long tail, the Tremblay et al. (2016) recommendations (Tremblay, 2016) were followed (i.e. Royston & Parmar estimates flexible models will not be included in the comparison).

Model classes

In this analysis, we will compare four model classes (Tremblay, 2015)

- Parametric model with treatment covariate
- Class 1: Proportional hazard model

- Class 2: Accelerated Failure Time (AFT)
- Class 3: Individual parametric models
- Class 4: Piecewise – survivor function with parametric tail extrapolation.

Decision criteria

This section establishes decision criteria for selecting the optimal model for use in extrapolating outcomes (Tremblay, 2015)

Criterion 1 – proportional treatment (PT) assumption testing

The PT assumption must be supported by the log-cumulative hazard plot (which would be parallel in the case of a PT effect) and the PT global test.

Criterion 2 – extrapolated hazard function fitting in time and between trial arms

The hazard rates should have a similar time relation pattern between the extrapolation function and the KM survivor function. The characteristic of the relationship between the hazard rates of both arms should be replicated by the modelling technique selected (for example, crossing lines would advocate a separate parametric model for each arm).

Criterion 3 – minimal Akaike information criterion (AIC) and Bayesian information criterion (BIC)

For parametric models, the selected model must have a low AIC/BIC to demonstrate goodness-of-fit to the clinical data.

Criterion 4 – uncertainty in the results

Uncertainty in model parameters should be considered when selecting the best model, as a high uncertainty would be a sign of low robustness.

Criterion 5 – similitude of pre-extrapolation marginal gain and realism of the extrapolated marginal gain

The realism of the marginal gain should be accounted for when selecting the best model as an unrealistic marginal gain would create bias in the economic analysis.

The following section summarises the decision making process for the best fitting extrapolation technique. A lifetime horizon was used for the extrapolations of the treatment outcomes, but, as described previously other time horizons (trial horizon, 5-year and 10-year horizon) were presented in the scenario analysis.

The objectives of the extrapolation analysis were to: (1) evaluate the need for extrapolation for each endpoint of interest, (2) select the proper extrapolation technique, and (3) perform extrapolation and use the results in the partitioned survival cost-effectiveness model.

Extrapolation methods

Trial end was used as the starting point for extrapolation. Patients who were lost to follow-up and withdrawn were removed from the dataset. Patients that discontinued or withdrawn were not removed from the sample in order to replicate the CSR analysis.

The most appropriate distribution was selected using the following process: (a) assessment of the visual fit to the observed KM, (b) assessment of the statistical goodness of fit (measured using the Akaike Information Criteria [AIC] and Bayesian Information Criteria [BIC] and (c) assessment of the plausibility of the long-term extrapolation.

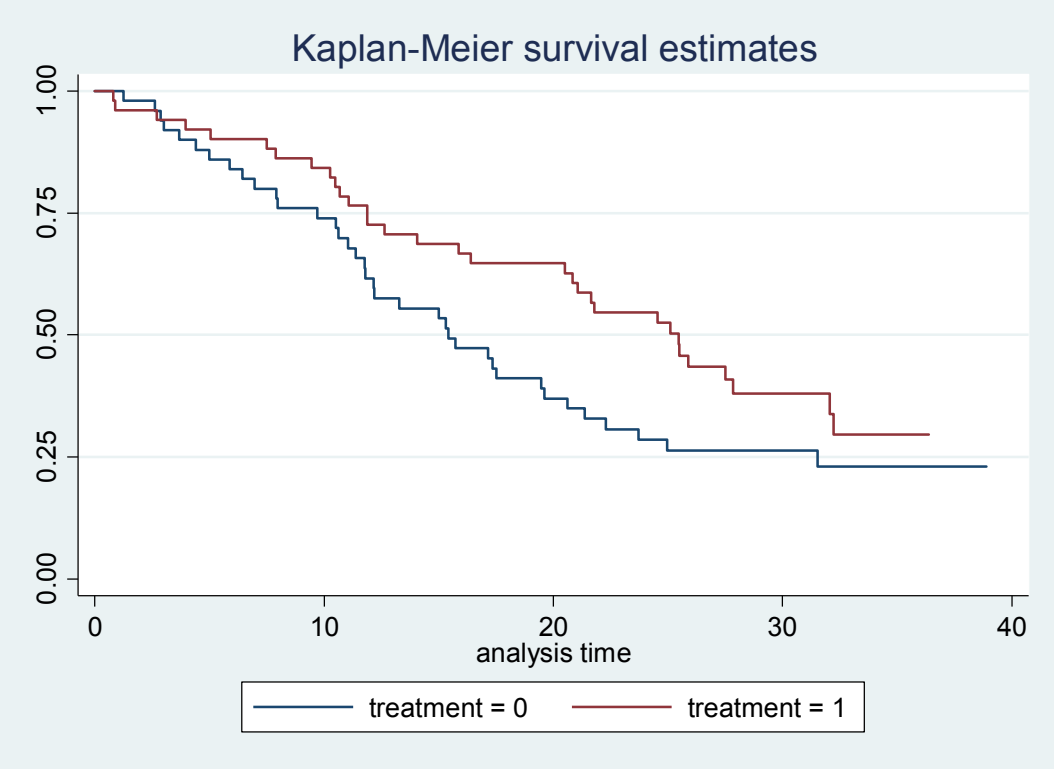
Overall survival

Figure 64 presents the Overall Survival Kaplan-Meier analysis for the EMA “third data cut” which is used for the base case economic analysis. The data is quite complete in general as most of the events were recorded. The curve is ending with little statistical plateau especially after month 30, but the importance or severity of this bias seems limited in this analysis.

Need for extrapolation: About 30% of the patients are still alive in the LEN+EVE arm versus 23% in the EVE arm at the end of the trial. The extrapolation is likely to have a significant impact on the cost-effectiveness.

Cut-off for extrapolation: For piecewise estimates, a cut-off must be selected where the data will be extrapolated. Based on the Kaplan-Meier analysis, it is recommended to use the last event (trial cut-off) as the extrapolation starting point because of the convergence of the curves between month 10 and 20. The smaller the distance between the curves, the smaller the uncertainty will be in the extrapolations.

Figure 64 Kaplan-Meier: Overall Survival

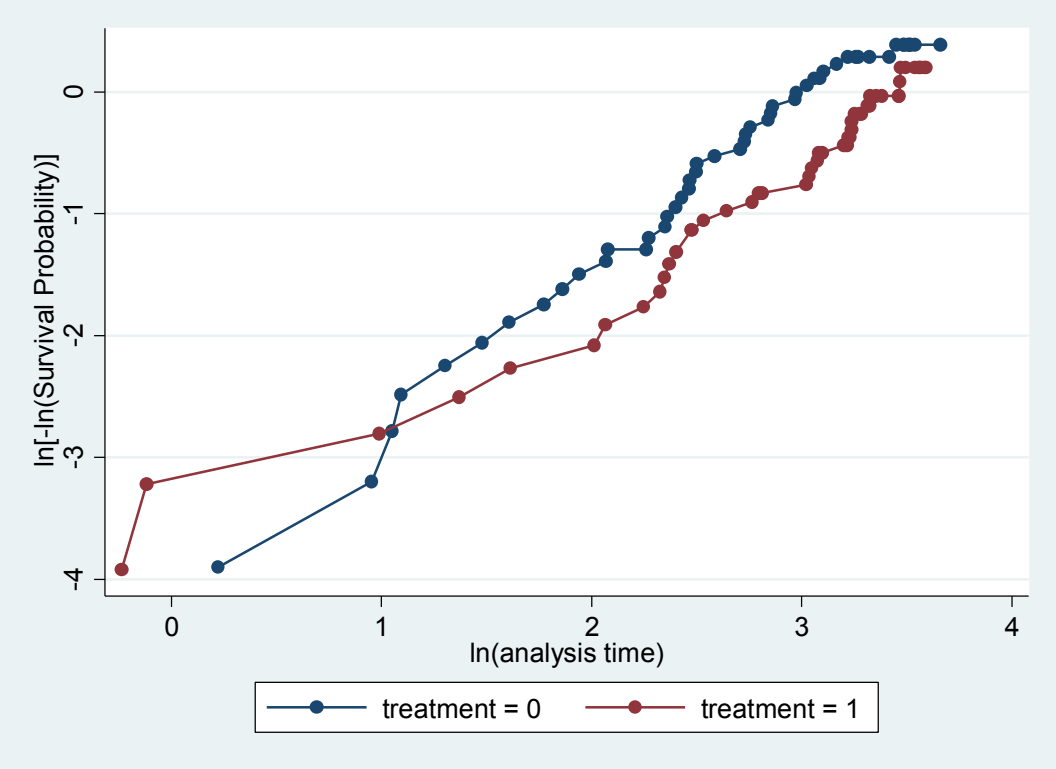


The curves seem to diverge for the first 20 months and then converge thereafter. Visual inspection suggests that a proportional hazard with treatment covariate technique is unlikely to be the best technique to replicate curve patterns.

Criterion 1 – Proportional treatment/Proportional Hazard (PT) assumption testing: The log-cumulative hazard plots were analysed to detect the hazard patterns and identify the optimal model class (Figure 65). For OS, the lines are relatively straight, and relatively parallel. However, the hazard plots for both treatment arms cross near X=1. They also converge between X=2 and X=3. Therefore, the validity of all models should be checked using the other decision making criteria. The global proportional hazard test based on residuals does not

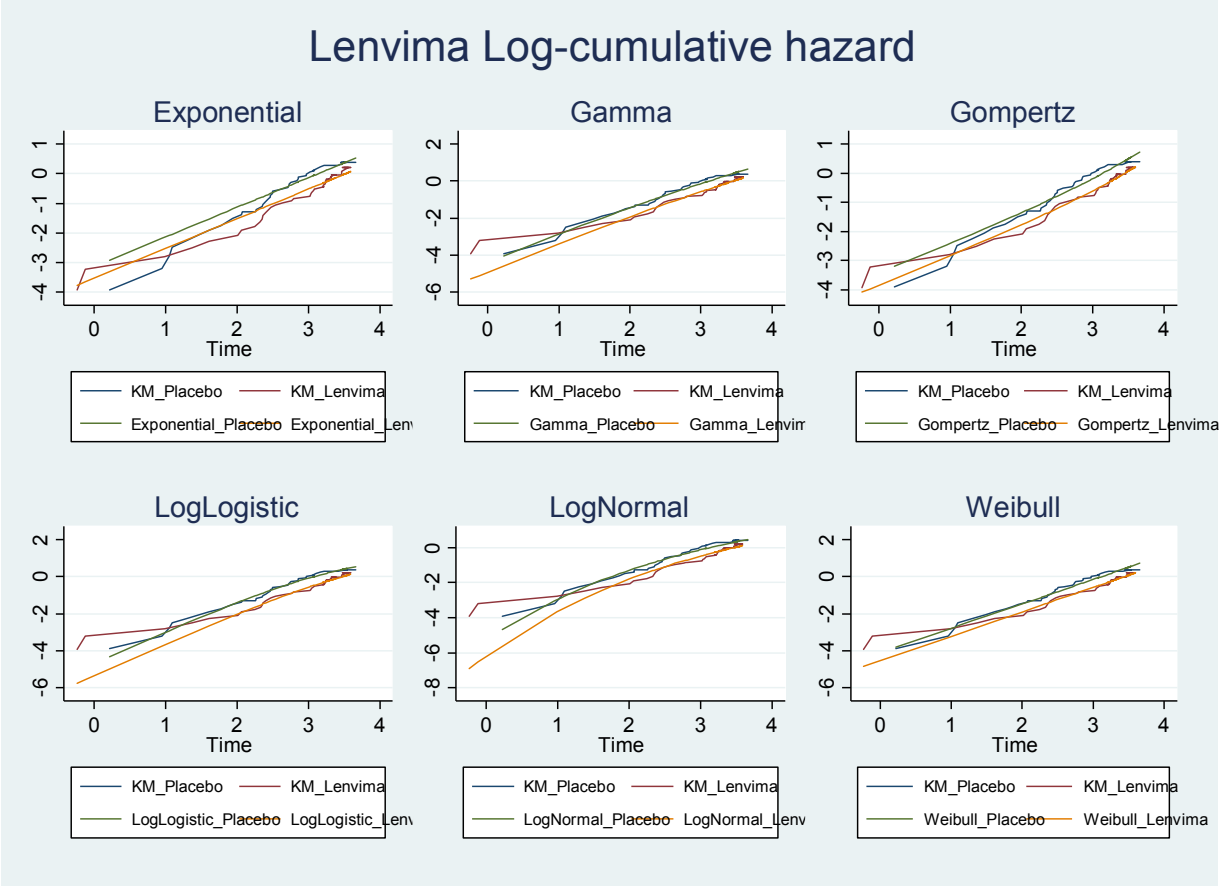
show a significant result (p-value=0.4412), which indicates that the curves do not deviate from the PH assumption. However, the p-value alone is not sufficient evidence to suggest proportionality.

Figure 65 Proportional Hazard testing: Overall Survival



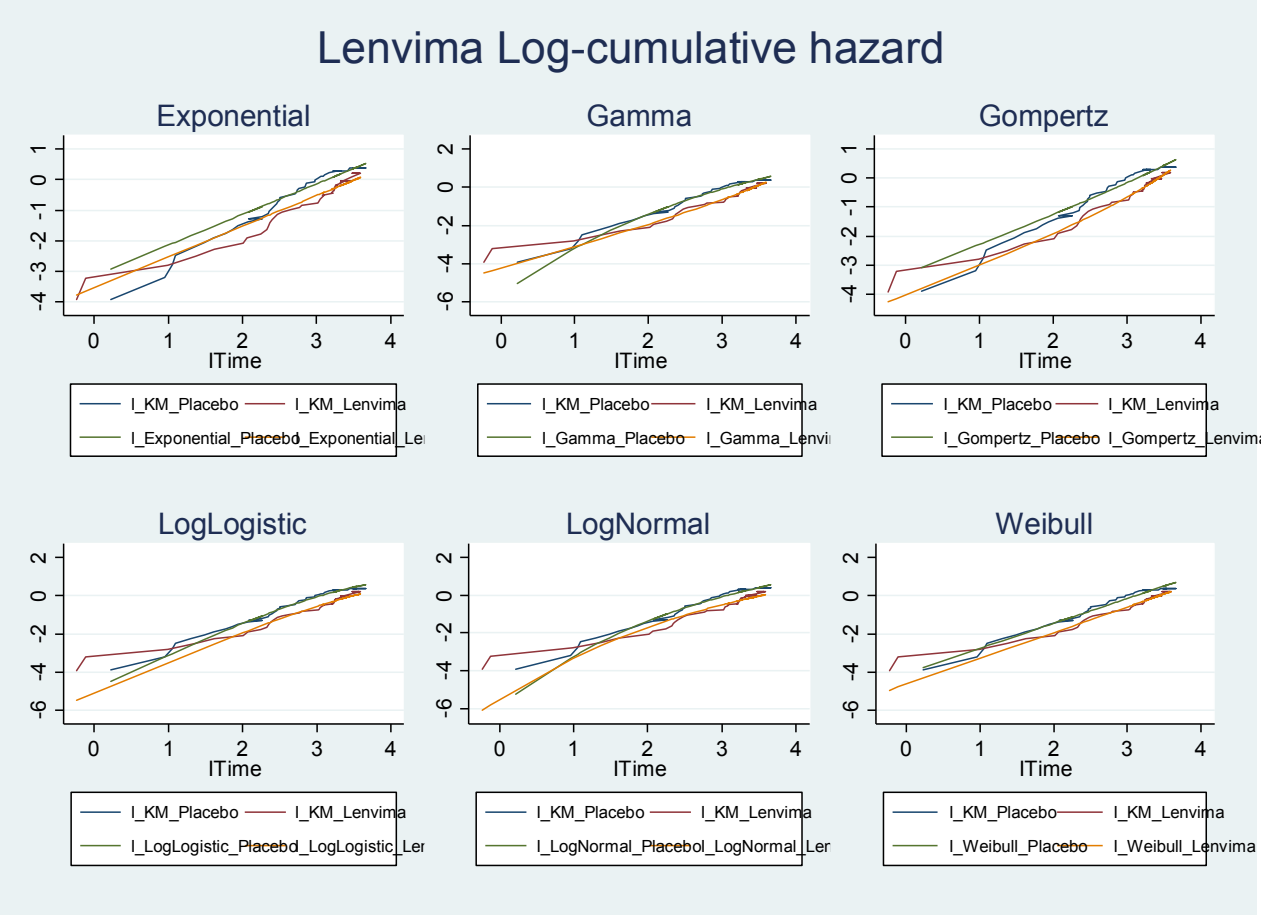
Criterion 2 – extrapolated hazard function fitting in time and between trial arms: A visual evaluation of the extrapolated hazard function fitting to the KM hazard function was performed. Figure 66 and Figure 67 present the proportional hazard models and present the hazard fitting for individual parametric models.

Figure 66 Parametric with treatment covariates - PH and AFT hazard fitting



The visual inspection in Figure 66 indicates that Gamma, Gompertz and Weibull seem to have a better fitting, but the fitting does not seem excellent in general.

Figure 67 Individual models – hazard fitting



In Figure 67, Gamma and log-normal curves for LEN+EVE versus placebo are crossing, which is not indicated by the data. Weibull and log-logistic curves for LEN+EVE versus placebo are almost crossing, which is not suggested by the data (especially in the low ln(time)). Exponential and Gompertz have very poor fitting in low ln(time). The visual inspection indicates none of the functional forms have a good fit.

Criterion 3 & 4– AIC/BIC and Uncertainty: Figure 68 presents the difference in mean OS survival estimates between the lenvatinib and placebo arms of Study 205 HOPE, summary statistics (based on a 120 months horizon), CIs of the marginal difference, and AIC/BIC criteria. The pre cut-off extrapolation can be compared to the Kaplan-Meier results to see if the match is proper. Also, the post cut-off extrapolation can be compared to the pre cut-off extrapolation to see if the extrapolation seems realistic. The total difference shows the amplitude of the OS gain for this extrapolation technique. The lower and upper CI can demonstrate the

uncertainty related to the extrapolation technique. The AIC and BIC statistics are the most commonly used fitting statistics for this type of extrapolation. Minimising the AIC-BIC will create the best match to the data.

Figure 68 Extrapolation uncertainty and fitting

Model type	Model class	Functional form	OS Pre Cut-off	OS Post Cut-off Extrapolated tail	Total Diff. in OS	Lower Bound CI	Higher Bound CI	Fitting Statistics (AIC/BIC)
Kaplan-Meier			5.72		5.72	-0.17	8.79	
Plots are Parallel	(1) PH Parametric models with treatment covariate	Weibull	5.04	3.01	8.05	0.02	16.09	245.7 / 258.8
		Exponential	4.55	5.97	10.52	-2.53	25.32	255.3 / 265.8
		Gompertz	4.91	1.34	6.25	0.08	13.44	248.1 / 261.2
Plots are not Parallel	(2) AFT Parametric models with treatment covariates	Log-Normal	4.32	4.85	9.16	-2.72	26.11	256.3 / 269.3
		Log-Logistic	5.26	4.58	9.84	0.02	26.12	247.6 / 260.7
		Gamma	5.04	3.05	8.10	-0.15	16.36	247.7 / 263.4
	(3) Individual parametric models	Weibull	5.56	2.97	8.52	0.42	36.17	246.1 / 261.5
		Exponential	5.15	6.91	12.06	0.51	57.77	255.5 / 267.1
		Gompertz	5.73	0.30	6.03	1.60	27.56	247.7 / 263
		Log-Normal	5.19	9.08	14.27	9.27	61.37	258.8 / 274.2
		Log-Logistic	5.57	5.65	11.22	4.93	51.03	250.1 / 265.4
		Gamma	4.70	-2.02	2.68	N.A.	N.A.	260.2 / 275.6
Plots are not Straight Lines: Consider piecewise Models	(4) SF + parametric tail extrapolation	Weibull	4.88	2.11	6.99	-0.27	13.32	245.7 / 258.8*
		Exponential	4.88	4.50	9.39	-0.27	18.33	256.3 / 269.3*
		Gompertz	4.88	0.90	5.78	-0.44	10.98	247.6 / 260.7*
		Log-Normal	4.88	4.28	9.16	-1.90	19.64	255.3 / 265.8*
		Log-Logistic	4.88	3.08	7.97	-2.73	18.05	247.7 / 263.4*
		Gamma	4.88	2.14	7.02	-0.28	13.38	248.1 / 261.2*

*Assumed the same as Parametric models

Parametric models with a treatment covariate do not show unrealistically low or high extrapolation gain, but seem to be quite uncertain with large confidence wings (with the exception of the Weibull and Gompertz forms). AIC/BICs quite consistent between the functional forms and the model types, with little variation.

Individual Parametric models show a large variety of extrapolation results, some unrealistically low (negative/crossing curves) and some too large (above 10 months). The confidence interval wings seem much larger than with the parametric models with treatment covariate.

Piecewise models seem to offer a stable and modest extrapolated OS benefit with much narrower confidence intervals. AIC/BIC cannot directly be applied here as they would be 0, but the AIC/BIC of the parametric curves can be used as a proxy.

Criterion 5 – similitude of pre-extrapolation marginal gain and realism of the extrapolated marginal gain: Criterion 5 is a “rule of thumb” designed to evaluate the robustness of the marginal survival gain of the extrapolation in comparison with that shown in the pre-extrapolation KM. The marginal survival gain prior or post the trial cutoff is divided by the time prior or post the trial cutoff, respectively. The resulting ratio in the post-trial period should be equal or inferior to the ratio in the pre-extrapolation period, that is, if the ratio is much higher after the cutoff, it suggests that the marginal gain is exaggerated in the post-cutoff period (resulting in a “long” and/or “thick” tail). The ratios that serve as the basis for evaluating Criterion 5 are shown in Figure 69.

Figure 69 Ratios for Evaluating Criterion 5 - OS

Model type	Model class	Functional form	Ratio of gain after/before cut off	Gain per month before cut off	Gain per month after cut off**
Kaplan-Meier				0.15	
Plots are Parallel	(1) PH Parametric models with treatment covariate	Weibull	0.60	0.14	0.04
		Exponential	1.31	0.12	0.07
		Gompertz	0.27	0.13	0.02
Plots are not Parallel	(2) AFT Parametric models with treatment covariates	Log-Normal	1.12	0.12	0.06
		Log-Logistic	0.87	0.14	0.06
		Gamma	0.61	0.14	0.04
	(3) Individual parametric models	Weibull	0.53	0.15	0.04
		Exponential	1.34	0.14	0.08
		Gompertz	0.05	0.15	0.00
		Log-Normal	1.75	0.14	0.11
		Log-Logistic	1.01	0.15	0.07
		Gamma	-0.43	0.13	-0.02
Plots are not Straight Lines: Consider Piecewise Models	(4) SF + parametric tale extrapolation	Weibull	0.43	0.13	0.03
		Exponential	0.92	0.13	0.05
		Gompertz	0.18	0.13	0.01
		Log-Normal	0.88	0.13	0.05
		Log-Logistic	0.63	0.13	0.04
		Gamma	0.44	0.13	0.03

*Assumed the same as Parametric models
**Horizon of 120 months (10 years)

The rule of thumb is satisfied by all parametric functional forms when a treatment covariate is used. On the other hand, the ratio of gain before/after cut-off is larger than 1 for exponential and log-normal indicating a potentially optimistic extrapolation. Gompertz has very low post cut-off extrapolation and pre extrapolation estimates are much lower than the Kaplan-Meier, so it is deemed too conservative.

The rule of thumb is also satisfied for individual models, except for Gamma and log-logistic which have negative post cut-off extrapolation. This negative extrapolation is not suggested by the data and should be discarded. Gompertz has very low post cut-off extrapolation and pre extrapolation estimates are much lower than the Kaplan-Meier, so it is deemed too conservative.

For piecewise models, the rule of thumb is satisfied by all functional forms.

The following table presents the summary of the decision criteria approach for OS.

Figure 70 Criterion results for OS

Model class		Weibull	Log-Normal	Log-Logistic	Exponential	Gamma	Gompertz
(1) PH Parametric models with treatment covariate & (2) AFT Parametric models with treatment covariates	C1 – PT assumption	Mixed evidence on the deviance. Lines are not really parallel nor straight, but the PT global test does indicate non-deviance to the PH test.					
	C2 – hazard fitting	X				X	X
	C3 – AIC	1st	6th	2nd	5th	3rd	4th
	C3 – BIC	1st	6th	2nd	5th	4th	3rd
	C4 – uncertainty	X				X	X
	C5 – rule of thumb	X		X		X	
(3) Individual parametric models	C1 – PT assumption	Lines are not straight and one convergent segment is followed by a divergent segment in the log-cumulative hazard plot, which could generate a crossing in the individual parametric curves. This crossing would not be suggested by the data					
	C2 – hazard fitting	X		X			
	C3 – AIC	1st	5th	3rd	4th	6th	2nd
	C3 – BIC	1st	5th	3rd	4th	6th	2nd
	C4 – uncertainty						
	C5 – rule of thumb	X	X				
(4) SF + parametric tale extrapolation	C1 – PT assumption	Piecewise models are particularly relevant to this context, as the log-cumulative hazard plots seem not straight and not parallel					
	C2 – hazard fitting	X				X	X
	C3 – AIC	1st	6th	2nd	5th	3rd	4th
	C3 – BIC	1st	6th	2nd	5th	4th	3rd
	C4 – uncertainty	X	X	X	X	X	X
	C5 – rule of thumb	X	X	X	X	X	X

Note: We have considered the uncertainty criteria to be respected when the CIs are within the CI- of the Kaplan-Meier and twice the CI+ of the Kaplan-Meier.

Parametric model with treatment covariate:

- Relatively weak PH assumption due to divergence followed by convergence.
- Hazard fitting is proper for Gamma, Gompertz and Weibull
- AIC/BIC is good for Weibull and log-logistic
- Uncertainty is very high in general. Weibull, Gamma and Gompertz are the most robust estimates
- Rule of thumb is satisfied by Weibull, LL and Gamma

- Gompertz and Weibull are recommended for this model class

Individual models:

- Convergence of the curve is likely to result in crossing of the extrapolation, which is not suggested by the data.
- Hazard fitting is proper for Weibull and log-logistic
- AIC/BIC is good for Gompertz, Log-logistic and Weibull
- Uncertainty is very high with only log-logistic seen as significant
- Rule of thumb is satisfied except for Weibull and Log-normal
- Weibull and Gompertz for this model class

Piecewise models

- Non-parallel and non-straight lines are a good sign of the piecewise superiority
- Hazard fitting is perfect prior to cut off and proper for Weibull, Gompertz and Gamma after cutoff
- AIC/BIC is perfect prior to cut off and proper for Weibull and log-logisitc after cut-off
- Uncertainty is relatively low for all estimates
- Rule of thumb is satisfied by all functional forms.

Weibull (basecase scenario) and Gompertz (additional scenario) are recommended for this model class

The use of piecewise model is therefore used in the base case of the economic analysis for OS to limit the uncertainty in the extrapolations, reduce the risk of high post cut-off extrapolated gain, increase fitting prior to cut-off, and reduce the risk of crossing of survival curves. Weibull (basecase scenario), Gompertz (additional scenario) and log-logistic (additional scenario) are recommended for this model class.

Progression Free Survival

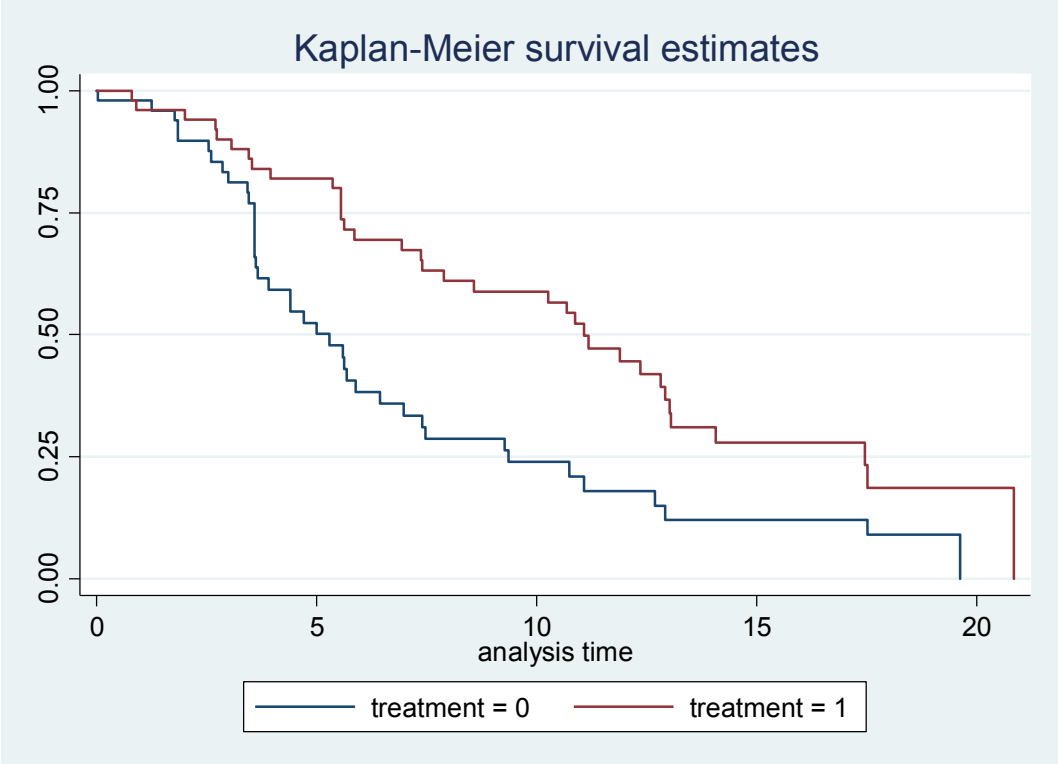
Figure 71 presents the Progression Free Survival Kaplan-Meier for the EMA “third data cut” which is used for the base case economic analysis. The data is quite complete in general as most of the events were recorded. The curve is ending with

some statistical plateau especially after month 10, but the importance or severity of this bias seems limited in this analysis. Eisai generated an EMA PFS flag called “Progression-Free Survival follow EMA suggestion”, and this flag was used in this analysis.

Need for extrapolation: About 6% of the patients did not progress in the LEN+EVE arm versus 0% in the EVE arm at the end of the trial. The extrapolation is likely to have a very modest impact on the cost-effectiveness. The following section analyses the extrapolation result for the PFS partition, though some would argue that the need for extrapolation is small. It is recommended to appl extrapolation when more than 10% are censored in the analysis.

Cut-off for extrapolation: For piecewise estimates, a cut-off must be selected where the data will be extrapolated. Based on the Kaplan-Meier analysis, it is recommended to use the last event (trial cut-off) as the extrapolation starting point because of the convergence of the curves between month 10 and 20. The smaller the distance between the curves, the smaller the uncertainty will be in the extrapolations.

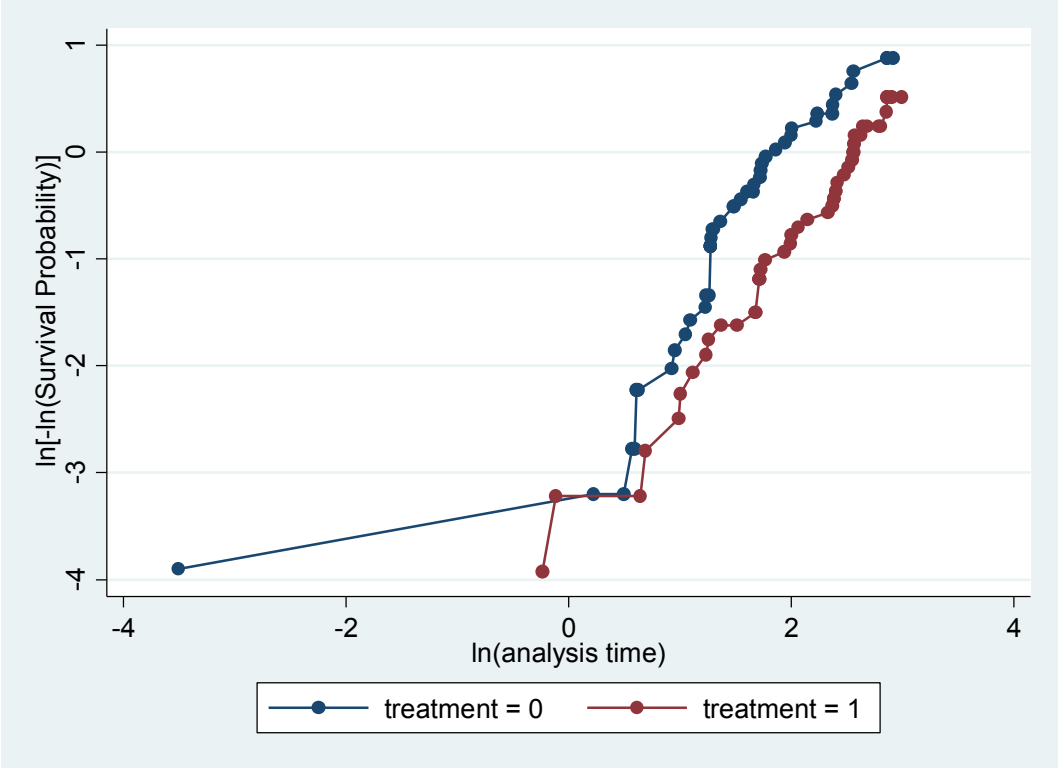
Figure 71 Kaplan-Meier: Progression Free Survival



The curves seem to diverge for the first 15 months and then converge thereafter. Visual inspection suggests that a proportional hazard with treatment covariate technique is unlikely to be the best technique to replicate curve patterns.

Criterion 1 – Proportional treatment/Proportional Hazard (PT) assumption testing: The log-cumulative hazard plots were analysed to detect the hazard patterns and identify the optimal model class (Figure 72). For PFS, the lines are not relatively straight or parallel. Additionally, the hazard plots for both treatment arms cross near X=0. They also converge toward the middle of the curve. Therefore, the validity of all models should be checked using the other decision making criteria. The global proportional hazard test based on residuals does not show a significant result (p-value=0.5461), which indicates that the curves do not deviate from the PH assumption. However, the p-value alone is not sufficient evidence to suggest proportionality.

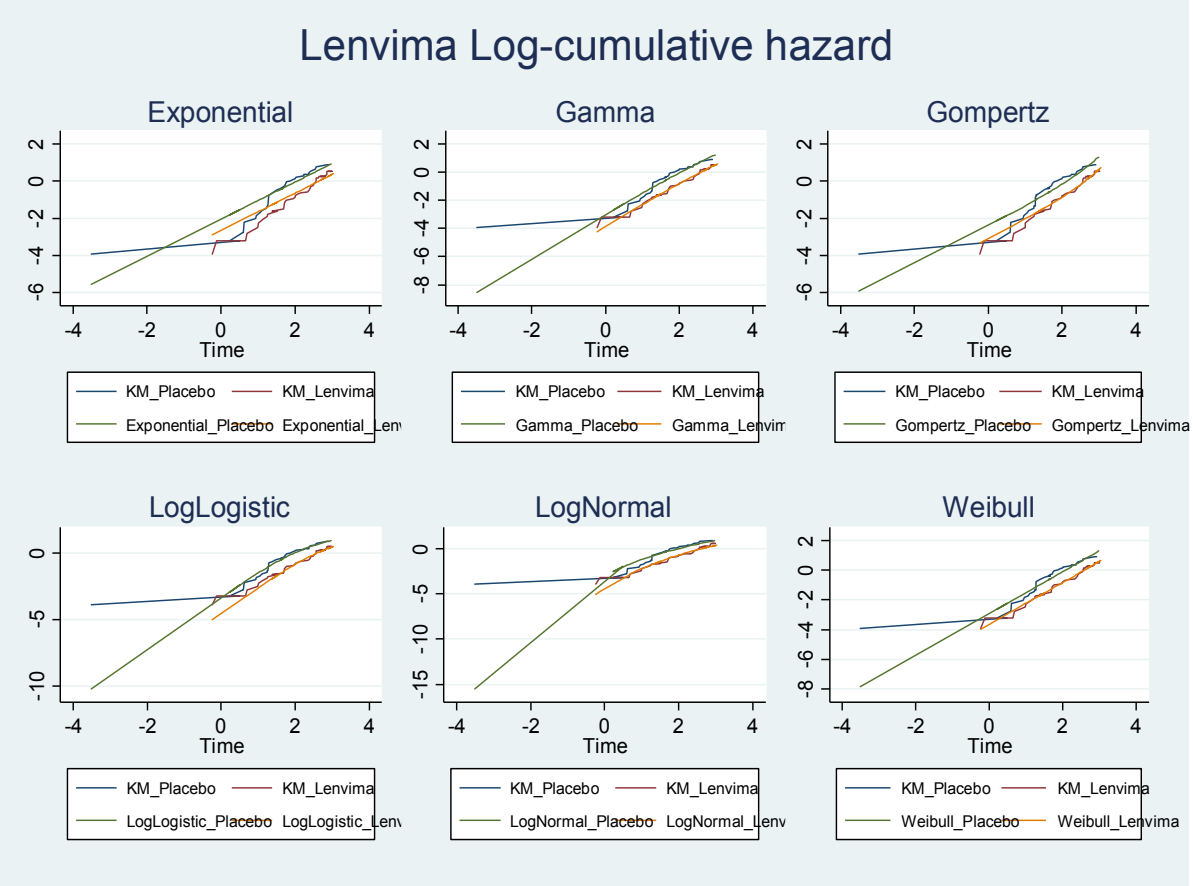
Figure 72 Proportional Hazard testing Overall Survival



Criterion 2 – extrapolated hazard function fitting in time and between trial arms: A visual evaluation of the extrapolated hazard function fitting to the KM hazard

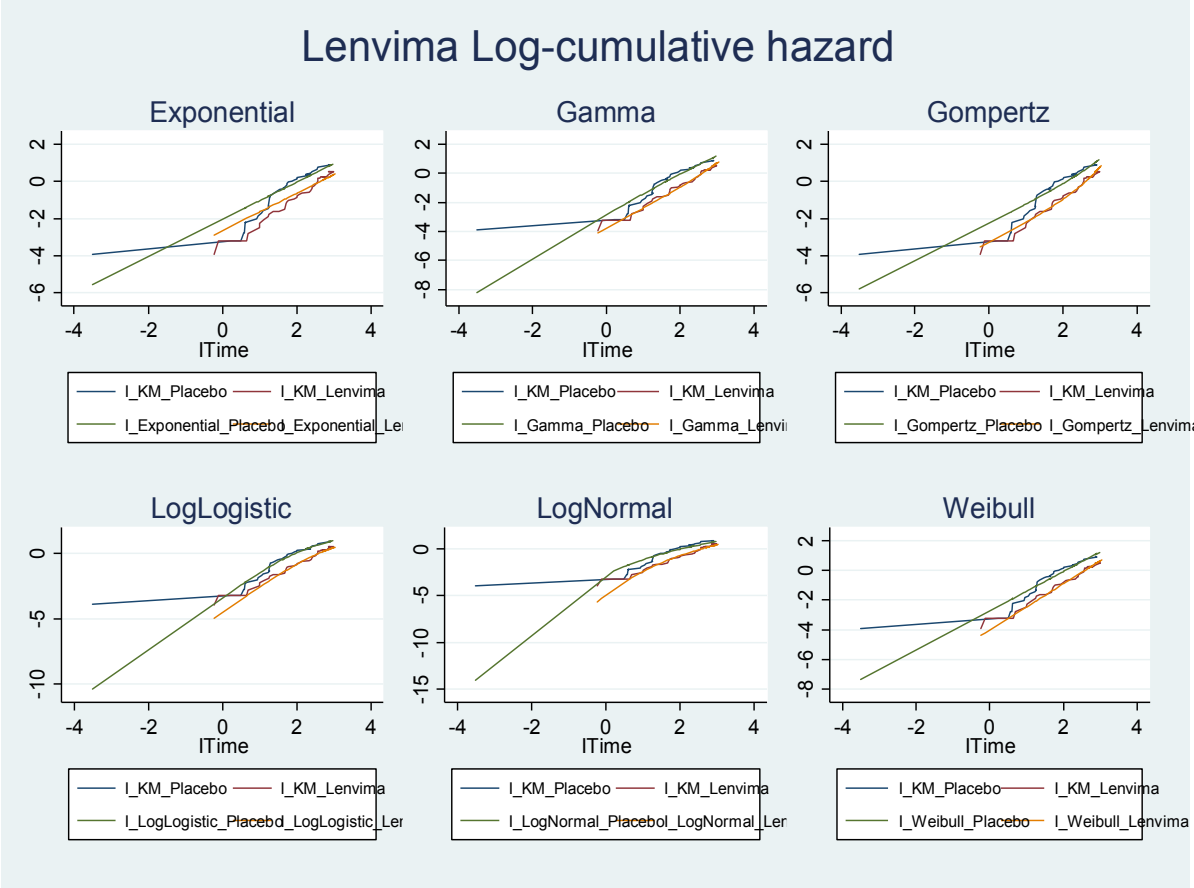
function was performed. Figure 73 and Figure 74 present the proportional hazard models and present the hazard fitting for individual parametric models.

Figure 73 Parametric with treatment covariates - PH and AFT hazard fitting



The visual inspection in Figure 73 indicates that Gamma and Weibull seem to have a better fit, but the fits do not seem excellent in general.

Figure 74 Individual models – hazard fitting



In Figure 74, Exponential, Gompertz and log-normal have very poor fits, especially in low ln(time). The visual inspection indicates that none of the functional forms have a good fit, but Weibull or Gamma should be used if needed.

Criterion 3 & 4– AIC/BIC and Uncertainty: Figure 75 presents the difference in mean PFS survival estimates between the lenvatinib and placebo arms of Study 205 HOPE, summary statistics (based on a 120 months horizon), CIs of the marginal difference, and AIC/BIC criteria. The pre cut-off extrapolation can be compared to the Kaplan-Meier results to see if the match is proper. Also, the post cut-off extrapolation can be compared to the pre cut-off extrapolation to see if the extrapolation seems realistic. The total difference shows the amplitude of the OS gain for this extrapolation technique, and the lower and upper CI can demonstrate the uncertainty related to the extrapolation technique. The AIC and BIC statistics are the most commonly used fitting statistics for this type of extrapolation. Minimizing the AIC-BIC will create the best match to the data.

Figure 75 Extrapolation uncertainty and fitting

Model type	Model class	Functional form	PFS Pre Cut-off	PFS Post Cut-off Extrapolated tail	Total Diff. in PFS	Lower Bound CI	Higher Bound CI	Fitting Statistics (AIC/BIC)
Kaplan-Meier			4.17		4.17	1.45	6.74	
Plots are Parallel	(1) PH Parametric models with treatment covariate	Weibull	3.87	0.81	4.68	1.46	7.89	244.3 / 257.4
		Exponential	3.70	2.42	6.12	0.99	11.26	255.1 / 265.5
		Gompertz	3.74	0.36	4.09	1.32	7.13	248.1 / 261.2
Plots are not Parallel	(2) AFT Parametric models with treatment covariates	Log-Normal	4.11	3.40	7.52	2.15	13.48	258.9 / 272
		Log-Logistic	4.35	2.42	6.77	2.81	11.83	243 / 256.1
		Gamma	3.97	0.98	4.95	1.52	8.38	245.8 / 261.5
	(3) Individual parametric models	Weibull	3.93	0.44	4.37	1.35	15.16	243.5 / 258.9
		Exponential	3.69	2.44	6.13	1.89	25.35	255.2 / 266.7
		Gompertz	3.86	0.09	3.95	1.98	13.50	247 / 262.4
		Log-Normal	3.54	1.34	4.88	2.06	20.41	261.9 / 277.3
		Log-Logistic	4.09	1.98	6.08	2.95	22.86	245.5 / 260.9
		Gamma	3.93	0.39	4.32	1.37	14.80	247.5 / 266.7
Plots are not Straight Lines: Consider Piecewise Models	(4) SF + parametric tale extrapolation	Weibull	4.17	0.36	4.53	1.46	8.56	244.3 / 257.4*
		Exponential	4.17	0.77	4.93	1.47	10.63	255.1 / 265.5*
		Gompertz	4.17	0.19	4.36	1.46	7.72	248.1 / 261.2*
		Log-Normal	4.17	1.23	5.40	1.48	12.99	258.9 / 272*
		Log-Logistic	4.17	1.20	5.37	1.48	12.84	243 / 256.1*
		Gamma	4.17	0.42	4.58	1.46	8.86	245.8 / 261.5*

*Assumed the same as Parametric models

Parametric models with treatment covariate do not show unrealistically low or high extrapolation gain, with high uncertainty noted only for exponential. Fitting statistics are very similar between PH models and individual models, and the PFS estimates are also very close.

Individual Parametric models do not show unrealistically low or high extrapolation gain. The confidence interval wings seems much larger for the parametric models without a treatment covariate than the models with a treatment covariate, with only Gompertz under the threshold set for the criteria.

Piecewise models seem to offer a stable and modest extrapolated PFS benefit with much narrower confidence intervals. AIC/BIC cannot directly be applied here as they would be 0, but the AIC/BIC of the parametric curves can be used as a proxy.

Criterion 5 – similitude of pre-extrapolation marginal gain and realism of the extrapolated marginal gain: Criterion 5 is a "rule of thumb" designed to evaluate the robustness of the marginal survival gain of the extrapolation in comparison with that shown in the pre-extrapolation KM. The marginal survival gain prior or post the trial cutoff is divided by the time prior or post the trial cutoff, respectively. The resulting ratio in the post-trial period should be equal or inferior to the ratio in the pre-extrapolation period, that is, if the ratio is much higher after the cutoff, it suggests that the marginal gain is exaggerated in the post-cutoff period (resulting in a "long" and/or "thick" tail). The ratios that serve as the basis for evaluating Criterion 5 are shown in Figure 76.

Figure 76 Ratios for Evaluating Criterion 5 - PFS

Model type	Model class	Functional form	Ratio of gain after/before cut off	Gain per month before cut off	Gain per month after cut off**
Kaplan-Meier				0.20	
Plots are Parallel	(1) PH Parametric models with treatment covariate	Weibull	0.21	0.18	0.01
		Exponential	0.65	0.18	0.02
		Gompertz	0.10	0.18	0.00
Plots are not Parallel	(2) AFT Parametric models with treatment covariates	Log-Normal	0.83	0.20	0.03
		Log-Logistic	0.56	0.21	0.02
		Gamma	0.25	0.19	0.01
	(3) Individual parametric models	Weibull	0.11	0.19	0.00
		Exponential	0.66	0.18	0.02
		Gompertz	0.02	0.18	0.00
		Log-Normal	0.38	0.17	0.01
		Log-Logistic	0.48	0.19	0.02
		Gamma	0.10	0.19	0.00
Plots are not Straight Lines: Consider Piecewise Models	(4) SF + parametric tale extrapolation	Weibull	0.09	0.20	0.00
		Exponential	0.18	0.20	0.01
		Gompertz	0.05	0.20	0.00
		Log-Normal	0.30	0.20	0.01
		Log-Logistic	0.29	0.20	0.01
		Gamma	0.10	0.20	0.00

*Assumed the same as Parametric models
**Horizon of 120 months (10 years)

The rule of thumb is satisfied by all parametric functional forms when a treatment covariate is used. The rule of thumb is also satisfied for all individual models. For piecewise models, the rule of thumb is satisfied by all functional forms.

The following table presents the summary of the decision criteria approach for PFS.

Figure 77 Criterion results for PFS

Model class		Weibull	Log-Normal	Log-Logistic	Exponential	Gamma	Gompertz
(1) PH Parametric models with treatment covariate & (2) AFT Parametric models with treatment covariates	C1 – PT assumption	Mixed evidence on the deviance. Lines are not really parallel nor straight, but the PT global test does indicate non-deviance to the PH test.					
	C2 – hazard fitting	X				X	
	C3 – AIC	2nd	6th	1st	5th	3rd	4th
	C3 – BIC	2nd	6th	1st	5th	4th	3rd
	C4 – uncertainty	X	X	X			X
	C5 – rule of thumb	X	X	X	X	X	X
(3) Individual parametric models	C1 – PT assumption	Lines are not straight and one convergent segment is followed by a divergent segment in the log-cumulative hazard plot, which could generate a crossing in the individual parametric curves. This crossing would not be suggested by the data					
	C2 – hazard fitting	X				X	
	C3 – AIC	1st	6th	2nd	5th	4th	3rd
	C3 – BIC	1st	6th	2nd	4th-5th	4th-5th	3rd
	C4 – uncertainty						X
	C5 – rule of thumb	X	X	X	X	X	X
(4) SF + parametric tale extrapolation	C1 – PT assumption	Piecewise models are particularly relevant to this context, as the log-cumulative hazard plots seem not straight and not parallel					
	C2 – hazard fitting	X				X	X
	C3 – AIC	2nd	6th	1st	5th	3rd	4th
	C3 – BIC	2nd	6th	1st	5th	4th	3rd
	C4 – uncertainty	X	X	X	X	X	X

Model class		Weibull	Log-Normal	Log-Logistic	Exponential	Gamma	Gompertz
	C5 – rule of thumb	X	X	X	X	X	X

Note: We have considered the uncertainty criteria to be respected when the CIs are within the CI- of the Kaplan-Meier and twice the CI+ of the Kaplan-Meier.

Parametric model with treatment covariate

- Relatively weak PH assumption due to divergence followed by convergence.
- Hazard fitting is proper for Gamma, Weibull.
- AIC/BIC is good for Log-Logistic and Weibull.
- Uncertainty is high for exponential and gamma.
- Rule of thumb is satisfied by all functional forms.
- Weibull is recommended for this model class.

Individual models

- Convergence of the curve is likely to result in crossing of the extrapolation, which is not suggested by the data.
- Hazard fitting is proper for Weibull and Gamma.
- AIC/BIC is good for Gompertz, Log-logistic and Weibull.
- Uncertainty is very high with only Gompertz seen as significant.
- Rule of thumb is satisfied by all functional forms.
- Gompertz and Weibull for this model class.

Piecewise models

- Non-parallel and non-straight lines are a good sign of the piecewise superiority
- Hazard fitting is perfect prior to cut off and proper for Weibull, Gompertz and Gamma after cutoff.
- AIC/BIC is perfect prior to cut off and proper for Log-Logistic and Weibull after cut-off.
- Uncertainty is relatively low for all estimates.
- Rule of thumb is satisfied by all functional forms.
- Weibull and Gompertz are recommended for this model class.

The use of piecewise model is therefore used in the base case of the economic analysis for PFS to reduce the risk of high post cut-off extrapolated gain, increase

fitting prior to cut-off, and reduce the risk of crossing of survival curves. Weibull (basecase analysis) is recommended for this model class. Weibull was the only distribution form believed to have sufficient fitting and low AIC/BIC at the same time.

As stated above, based on this selection process, it was determined that a piecewise extrapolation using a Weibull functional form was the best fit for both OS and PFS extrapolation.

Figure 78 presents the extrapolated PFS curves and Figure 79 presents the extrapolated OS curves using a piecewise Weibull approach. Extrapolation cut-offs for the piecewise models were based on the last events (for OS: 37 months for LEN+EVE and 39 months for everolimus; for PFS: 21 months for LEN+EVE and 20 months for everolimus).

In general, most benefit was achieved before the cut-off period for all treatments, showing strong consistency in the results.

Figure 78 Extrapolated PFS curves

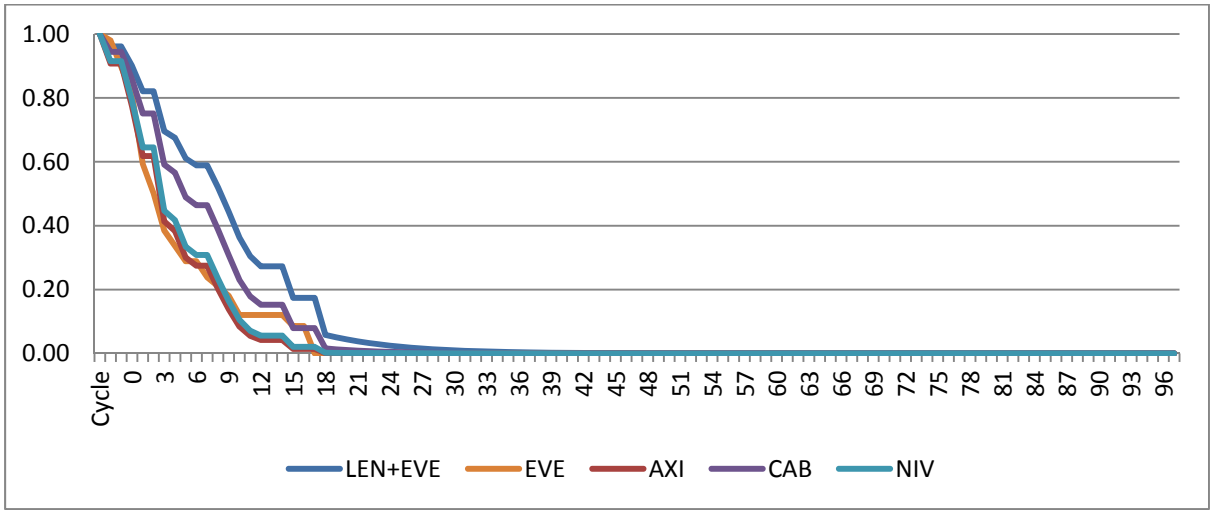
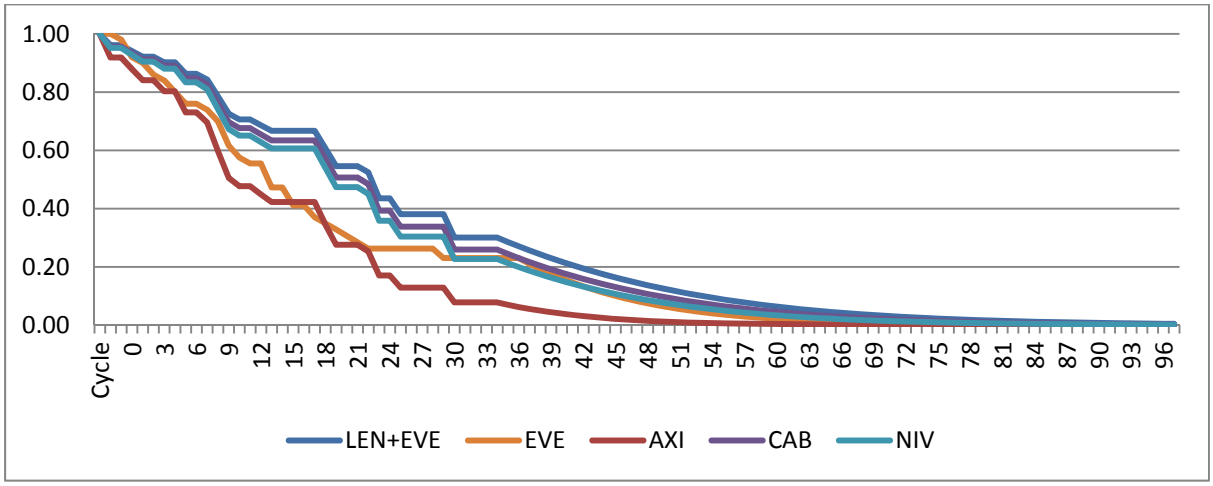


Figure 79 Extrapolated OS curves



5.4 Measurement and valuation of health effects

The economic endpoints used in the model were quality-adjusted life years (QALYs) and life years saved (LYs). Overall LYs were calculated as the sum of OS at each cycle (month). QALYs were calculated as the sum of the utility-weighted time in each health state.

Health-related quality-of-life data from clinical trials

No within-trial HRQoL data were available from the clinical trials, so information on utility values were obtained from previous NICE submissions, as identified in a systematic literature review – see below. In a scenario analysis, utility values were obtained from a separate vignette utility study. Further information is outlined below).

Mapping

Mapping was not applicable, as within-trial HRQoL data were not available from the clinical trials.

Health-related quality-of-life studies

A systematic literature review was carried out in order to identify relevant HRQoL studies for lenvatinib in combination with everolimus and relevant comparators (which include those listed in the scope and in the decision problem (Figure 1) ie

axitinib, everolimus, nivolumab and cabozantinib) for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Search strategy

The following databases were screened in line with standard methodology:

- Embase + MEDLINE;
- the Cochrane Library; and
- MEDLINE In-process and Other Non-indexed Citations (PubMed).

The search strategies are provided in the Systematic Literature Review Report Appendix 8.3.

Study selection

The searches were limited to records for English language articles and publications that are reviews (except systematic reviews, meta-analyses and pooled analyses), case reports, editorials, letters, notes/comments and errata were excluded, where the indexing allowed.

Figure 80 summarises the inclusion and exclusion criteria, language restrictions and the study selection process.

The PRISMA flow diagram of the number of studies included and excluded at each stage is shown in Figure 81.

The complete reference list for excluded studies is provided in the Systematic Literature Review Report (Appendix 8.3).

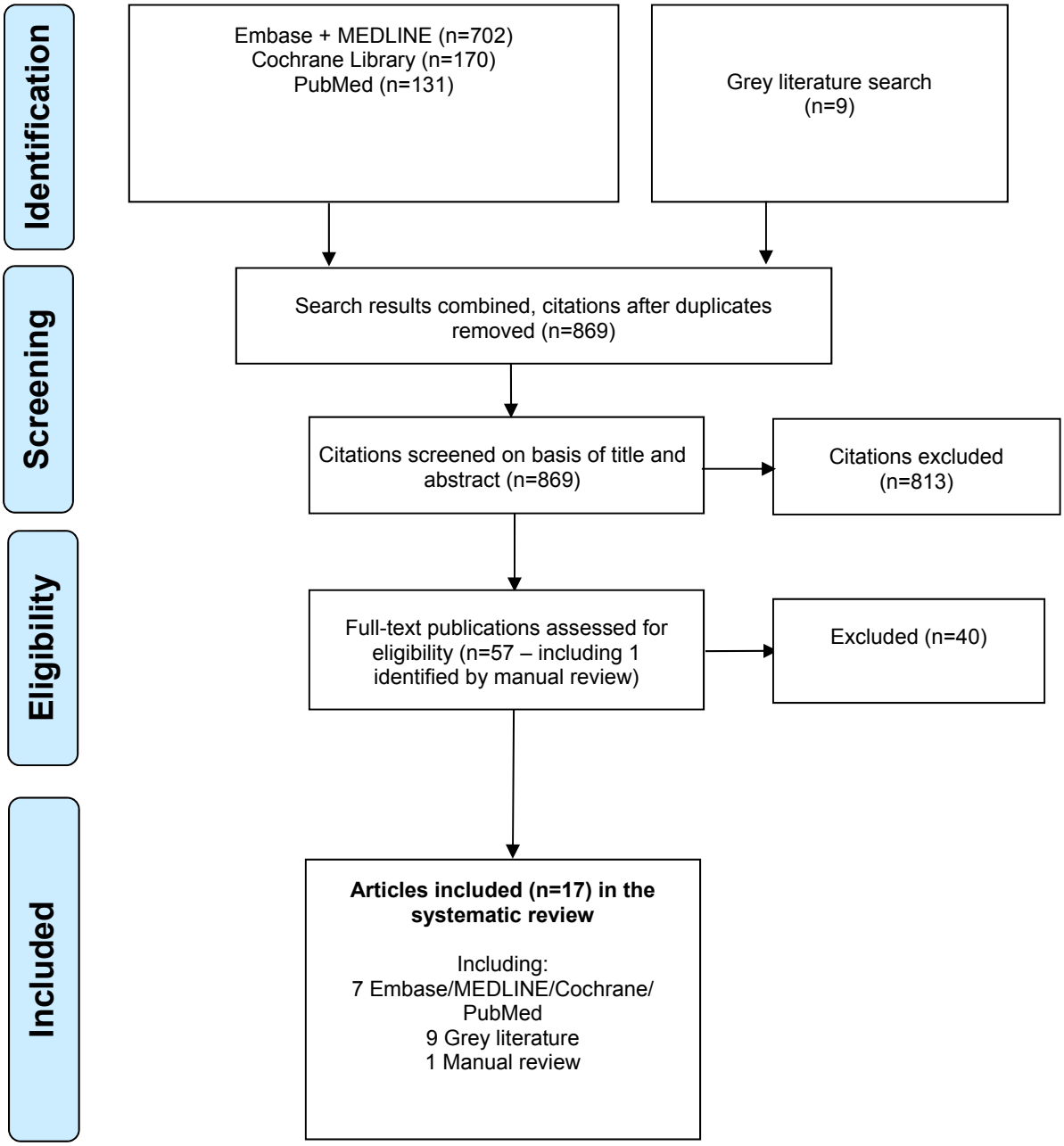
The comparators listed in the systematic literature search exceeded that in the final decision problem, in which comparators were limited to axitinib, nivolumab, everolimus and cabozantinib. (**Error! Reference source not found.**).

Figure 80 Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	▪ Lenvatinib ▪ Cabozantinib ▪ Nivolumab ▪ Temsirolimus ▪ Everolimus ▪ Pazopanib ▪ Sunitinib ▪ Sorafenib ▪ Bevacizumab ▪ Axitinib	Not second line a/mRCC treatment after one prior anti-VEGF therapy Surgical /Radiotherapy /Diagnostic intervention
Outcomes	▪ Health related quality of life ▪ Utility values ▪ Weightings ▪ Preference ▪ Health Status ▪ Specific quality of life instruments	
Study design	Systematic reviews Meta-analysis Pooled analyses	Reviews, case reports, editorials, letters, notes/comments, errata
Language restrictions	English	Non-English language

Abbreviations: a/mRCC, Advanced or metastatic renal cell carcinoma; VEGFR, Vascular endothelial growth factor receptor

Figure 81 PRISMA Study Attrition Diagram for Systematic Literature Review of a/mRCC: Economic Studies



Description of identified studies

As highlighted in Figure 81, the systematic review on the HRQoL of lenvatinib and the relevant comparators identified 17 separate citations, which are listed in Section 5.3 of the Systematic Literature Review Report (Appendix 8.3).

Of these 17 studies, 9 were HTA submissions and eight were publications. A quality assessment of the 17 studies is provided in Table 4.4.1 of the Systematic Literature Review Report (Appendix 8.3) and each study is summarised in Figure 82.

Upon review of the studies and in line with recent draft NICE committee recommendations during the review of cabonzatinib (GID-TA10075), the utilities values used in the axitinib NICE submission from the AXIS study were presented in the basecase.

Figure 82 Overview of outcomes of HRQoL studies

General data						Patient Characteristics	Results	
Author (year)	Study design	Country	Patient Number	Follow-up/ Observation period	Intervention(s)	Details	QoL Results	All HRQoL scales reported
NICE appraisal committee (includes additional detail from Thompson et al, 2010) (2009)	HTA appraisal based on a CUA and evidence from a phase 3 RCT (sorafenib) or a single arm phase 2 trial (sunitinib) and a pooled analysis of a review and Medicare data (BSC).	UK	NA	NA	Sorafenib or sunitinib	Patients with advanced RCC in whom immunotherapy has failed.	Sorafenib utility (from unpublished survey of physicians) Manufacturer; Same for sorafenib and BSC: Progression-free survival 0.737 Progressed disease 0.548 Sunitinib utility (EQ-5D from single arm Phase 2 trial) Manufactuer; Progression-free survival; sunitinib 0.803 vs BSC 0.758 Progressed disease; sunitinib 0.758 vs BSC 0.683 ERG re-analysis (trial data and UK EQ-5D tariffs); Same for all treatments: Progression-free survival 0.76 Progressed disease 0.68 No disutility Sorafenib FACT-G and FKSI There was no significant difference between the placebo and sorafenib groups over the first 32 weeks of treatment.	FACT-G, FKSI, EQ-5D

General data						Patient Characteristics	Results	
NICE appraisal committee (includes additional detail from Pitt et al, 2009) (2011)	HTA appraisal based on a CUA and evidence from a phase 3 RCT	UK	NA	NA	Everolimus plus BSC	Adults aged ≥ 18 years with aRCC whose cancer had progressed on or within 6 months of receiving VEGF-targeted therapy (sunitinib, sorafenib, and/or bevacizumab)	Utility (trial data and UK EQ-5D tariffs) Same for everolimus and BSC: Stable disease without AEs 0.76 Stable disease with AEs 0.71 Progressed disease 0.68 Death 0 Disutility for AE -0.05 EORTC, FKSI-DRS Time to deterioration in functioning/symptoms was delayed with everolimus plus BSC by 3.5 months.	EORTC QLQ-C30, FKSI-DRS, EQ-5D
NICE appraisal committee (includes additional detail from Riemsma et al, 2012) (2015)	HTA appraisal based on a CUA and evidence from an RCT (AXIS), with additional studies for an indirect comparison of axitinib with BSC.	UK	NA	NA	Axitinib	Patients with aRCC in whom treatment with sunitinib or cytokines has failed.	Utility (AXIS) Same for axitinib and BSC Manufacturer; Progression-free 0.69 (average on-treatment) Progressed disease 0.61 (average end of treatment) ERG re-analysis; Progression-free 0.73 (average on-treatment) Progressed disease 0.61 (average end of treatment) No disutility FSKI-15, EQ-5D and FKSI-DRS Mean scores were similar between axitinib and sorafenib until EOT.	FKSI-15, FKSI-DRS, EQ-5D

General data						Patient Characteristics	Results	
NICE appraisal committee Papers (2016)	HTA evaluation	UK	NA	NA	Nivolumab	Patients with previously treated advanced or mRCC.	Utility: Manufacturer, ERG re-analysis, additional analysis for ACM respectively (data from CheckMate 025, AXIS, TA333, oncologist and'best available evidence for AE) Pre-progression, nivolumab 0.80, 0.80, 0.73 Post-progression, nivolumab 0.73, 0.73, 0.64 Pre-progression, everolimus 0.76, 0.76, 0.69 Post-progression, everolimus 0.70, 0.70, 0.61 Pre-progression, axitinib 0.69, 0.76, 0.69 Post-progression, axitinib 0.61, 0.70, 0.61 Pre-progression, BSC 0.69, 0.76, 0.69 Post-progression, BSC 0.61, 0.70, 0.61 No disutility for base-case. In SA - pneumonitis -0.15, diarrhoea -0.1, anaemia -0.081, pneumonia -0.13 EQ-5D (from CheckMate 025 trial) Median change in utility from baseline showed a statistically significant benefit of nivolumab compared with everolimus for weeks 8-12, 24-44, 52-68 and 80. 53% of patients treated with nivolumab experienced meaningful EQ-5D VAS improvement compared with 39% of patients treated with everolimus (p=0.005). FKSI-DRS 55% of patients in the nivolumab group experienced 'meaningful' FKSI-DRS improvement compared with 37% of patients in the everolimus group at week 104 (p<0.001).	EQ-5D, FKSI-DRS

General data						Patient Characteristics	Results	
Scottish Medicines Consortium (SMC 595/10) (2014)	HTA evaluation	Scotland	NA	NA	Everolimus	Advanced mRCC after failure of VEGF treatment.	Utility (based on UK TTO, adjusted for AEs based on RECORD-1 trial) Stable disease without AEs 0.795 Stable disease with AEs everolimus 0.610 (-0.185 disutility) Stable disease with AEs axitinib 0.575 (-0.22 disutility) Disease progression 0.355 FKSI-DRSI and EORTC QLQ-C30 (based on trial data) Similar HRQoL for everolimus and BSC.	EORTC QLQ-C30, FKSI-DRSI, TTO
Scottish Medicines Consortium (SMC 855/13) (2013)	HTA evaluation	Scotland	NA	NA	Axitinib	Patients with a RCC whose cancer had progressed after first line therapy with either sunitinib or a cytokine.	Utility (EQ-5D; based on AXIS trial) Same for axitinib and BSC Progression free survival 0.69 Progressed disease 0.61 No disutility	Not reported

General data						Patient Characteristics	Results	
Scottish Medicines Consortium (SMC 1188/16)	HTA evaluation	Scotland	NA	NA	Nivolumab	Patients with aRCC after prior therapy in adults.	Utility (EQ-5D; based on CheckMate 025 trial and weighted values from AXIS trial) Progression-free nivolumab 0.80 Progression-free everolimus 0.76 Progression-free axitinib 0.69 Post-progression nivolumab 0.73 Post-progression everolimus 0.70 Post-progression axitinib 0.61 FKSI-DRSI A meaningful symptom improvement occurred in 55% of patients in the nivolumab group compared to 37% of patients in the everolimus group. EQ-5D VAS A meaningful symptom improvement occurred in 53% of patients in the nivolumab group compared to 39% of patients in the everolimus group.	EQ-5D, EQ-5D VAS, FSKI-DRS

General data						Patient Characteristics	Results	
pan-Canadian Oncology Drug Review (2016)	HTA evaluation	Canada	NA	NA	Nivolumab	Patients with locally advanced or mRCC who have received at least one prior anti-angiogenic therapy.	Manufactuter submission Utility (EQ-5D: based on Checkmate 025 trial) Progression free with response 0.887 Progression free no response 0.835 Progressed disease 0.806 EGP re-analysis Progression free with response 0.69-0.887 Progression free no response 0.69-0.835 Progressed disease 0.61-0.806 No disutility FSKI-DRS (based on Checkmate 025) The median changes from baseline were statistically better in the nivolumab group, compared with everolimus ($p<0.05$).	EQ-5D, FSKI-DRS
PBAC (2012)	HTA evaluation	Australia	NA	NA	Sorafenib	Patients with stage IV clear cell renal carcinoma who have failed therapy with first line treatment.	Utility weights were literature-based, with the utility difference between sorafenib and placebo being the midpoint of calculated utility values for progressed and non-progressed patients (values not reported).	Not reported

General data						Patient Characteristics	Results	
Cella D et al. (2016)	Phase 3 OL RCT (CHECKMATE-025; NCT01668784)	International (24 countries across North America, Europe, Australia, South America, Asia)	706/821 patients had baseline HRQoL data (86%) Nivolumab: 362 Everolimus 344	Study stopped early as it met its primary objective. Minimum follow-up time was 14 months, median follow-up for survival was nivolumab 18.3 months and everolimus 17.2 months.	Nivolumab: 3mg/kg every 2 weeks (28-day cycle) Everolimus: 10mg once per day (28-day cycle)	Patients aged ≥ 18 years, with aRCC, measurable disease, Karnofsky PS ≥70 and had received one or two anti-angiogenic therapies for advanced RCC (no more than 3 prior systemic therapies in total (including cytokines and cytotoxic chemotherapy).	Utility (EQ-5D) Baseline, mean (SD) Nivolumab 0.78 (0.24) vs everolimus 0.78 (0.21) Average (on-treatment), LSM; Difference: 0.04 95% CI 0.02 to 0.07; p=0.003 FKSI-DRS Nivolumab patients had an improvement from baseline. Everolimus patients had a deterioration from baseline.	FKSI-DRS, EQ-5D index and VAS
Cella D et al. (2013)	Phase 3 OL RCT (AXIS; NCT00678392)	Not reported	723 patients Axitinib: 361 Sorafenib: 362	Treated until progression, toxicity, withdrawal or death.	Axitinib: 5mg b.i.d. increased to 7mg b.i.d. and again to 10mg b.i.d. if tolerated Sorafenib: 400mg b.i.d. reduced to 400mg q.d. or EOD if not tolerated	Patients aged ≥ 18 years, with aRCC after failure of one first-line systemic regimen, evidence of measurable disease and ECOG PS of 0 or 1.	Utility (EQ-5D), mean (SD) Baseline: not reported Average "post-treatment" Axitinib 0.71 vs Sorafenib 0.69 Difference 0.02; 95% CI -0.01 to 0.05; p=0.193 Observed EQ-5D means were similar until EOT, after which there was a drop when patients typically experienced disease progression. FKSI-15 and FKSI-DRS Mean scores were similar between axitinib and sorafenib until EOT.	FKSI-15, FKSI-DRS, EQ-5D index

General data						Patient Characteristics	Results	
Beaumont JL et al. (2011)	Phase 3, DB, placebo controlled RCT (RECORD-1; NCT00410124)	Not reported	Everolimus: 277 patients enrolled, 242 analysed Placebo, 139 patients enrolled, 128 analysed	All of the longitudinal models were performed using only the first 8 months of follow-up.	Everolimus	Adults aged ≥ 18 years with mRCC that showed a clear-cell component and had progressed on or were within 6 months of stopping treatment with sunitinib and/or sorafenib.	There was little difference between everolimus and placebo in global quality of life trends.	EORTC QLQ-C30, FKSI-DRS
Trask PC et al. (2011)	Phase 3, OL, MC, single arm trial	USA	62 patients enrolled	Median of 6.3 months of treatment; range 0.2-33.6 months)	Axitinib	Adults aged ≥ 18 years with mRCC, prior nephrectomy, ECOG PS ≤ 1, and prior failed treatment with sorafenib.	Longer PFS and OS were associated with higher (more favorable) baseline FKSI-15 and FKSI-DRS.	FKSI-15, FSKI-DRS
Karakiewicz PI et al. (2016)	OL, single arm, MC trial (NCT01473043)	Canada and Australia	15 patients enrolled	Median time on axitinib was 118.0 days (range: 3.5-645,0 days)	Axitinib	Adults aged ≥ 18 years with mRCC with a component of clear-cell subtype who failed a prior single line of therapy with any of: interleukin-2, interferon, bevacizumab, sunitinib, pazopanib, tivozanib, temsirolimus, or everolimus.	Utility (EQ-5D), mean Baseline: 0.7947 EOT: 0.711 EuroQol VAS mean Baseline: 73.3 EOT: 66.8	EQ-5D, Euro-Qol VAS

General data						Patient Characteristics	Results	
Thompson Coon J et al. (PenTAG). (2008)	Systematic review and economic evaluation	UK	NA	NA	Sorafenib	Patients with RCC as a second line treatment and unsuitable for IFN	Utility (SE) (derived from Pfizer submission) Progression free survival 0.76 (0.03) Progressed disease 0.68 (0.04) No disutility	Not reported
Chandiwana D et al. (2014)	Economic evaluation	UK	NA	NA	Everolimus Axitinib	Patients with advanced mRCC who had failed previous therapy with sunitinib.	Utility (TTO; calculated based on Swinburn et al, 2010) Same for everolimus and axitinib Stable disease 0.795 Stable disease with AEs (everolimus) 0.610 (-0.185 disutiliy) Stable disease with AEs (axitibnib) 0.575 (-0.22 disutility) Progressed disease 0.355 Death 0.00	TTO
Ozono S et al. (2014)	Phase 2 OL MC single-arm trial (UMIN000004742)	Japan	57 patients enrolled, 49 patients analysed	Interim analysis (49 patients with median of 4.4 months of treatment)	Everolimus	RCC with clear cell component, patients who received one TKI as first line therapy, did not receive cytokine and chemotherapy and ECOG PS 0-1	EORTC QLQ-C30, FKSI-DRS All QOL scores were not changed at 2 months, while dyspnea and global health scores were worsened at 4 months.	EORTC QLQ-C30, FKSI-DRS, EQ-5D

Source: Systematic Literature review (Appendix 8.3)

Abbreviations: ACM, Appraisal Committee Meeting; AE, adverse events; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technology in Health; CUA, cost utility analysis; ECOG, Eastern Cooperative Oncology Group; EGP, Economic Guidance Panel; EORTC, European Organisation for Research and Treatment; EOT, end of treatment; EQ-5D, Euroqol - 5 dimension; ERG, Evidence Review Group; FKSI, Functional Assessment of Cancer Therapy-Kidney Symptom Index; FACT-G, Functional Assessment of Cancer Therapy: General; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index - Disease Related Symptoms; HRQoL, Health-related quality of life; HTA, Health Technology Assessment; IFN, interferon; MC, multi-centre; mRCC, metastatic renal cell carcinoma; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; OL, open-label; ORR, overall response rate; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; PS, performance status; QLQ-C30, Quality of Life Questionnaire-C30; QOL, quality of life; RCC, renal cell carcinoma; SA, Scenario analysis; SE, standard error; SMC, Scottish Medicines Consortium; TKI, tyrosine kinase inhibitor; TTO, time trade off; UK, United Kingdom; VEGF, Vascular Endothelial Growth Factor

Adverse reactions

Adverse reactions can have a significant impact on health-related quality of life. This is particularly pertinent when assessing drugs used in oncology, where patients may experience severe toxicities and reactions as a result of the therapies they take. In our economic model, adverse events reported in the respective comparators' clinical trials were used directly in the utility calculations (explained in the Section below).

Health-related quality-of-life data used in cost-effectiveness analysis

Base case utility values

Since no utility values were presented in the clinical trials, utility values were obtained from the AXIS clinical trial (Rini, et al., 2011) assessing axitinib versus sorafenib in advanced renal cell carcinoma. In brief, this study included patients coming from 175 sites (hospitals and outpatient clinics) in 22 countries aged 18 years or older with confirmed renal clear-cell carcinoma who progressed despite first-line therapy containing sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines. The population here was determined to be comparable to the target population of this economic model.

Patient-reported outcomes were assessed using the EuroQoL (EQ-5D) tool and were completed at screening during the AXIS trial, after every 4 weeks of therapy, at end of study treatment, and at follow-up (28 days after end of therapy). To avoid potential bias, questionnaires were completed before patients discussed their disease status with health-care professionals. The EQ-5D is a preference-based generic health status measure and comprises two components, an index score with five items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale score for overall health state.

The mean utility value for the progression-free health state was 0.69, based on the average of the EQ-5D index value at each time point in the AXIS trial and weighted by the number of patients still on treatment at that time point. The utility value for the progressed disease health state was 0.61, based on the weighted average of the mean utility at the end of treatment.

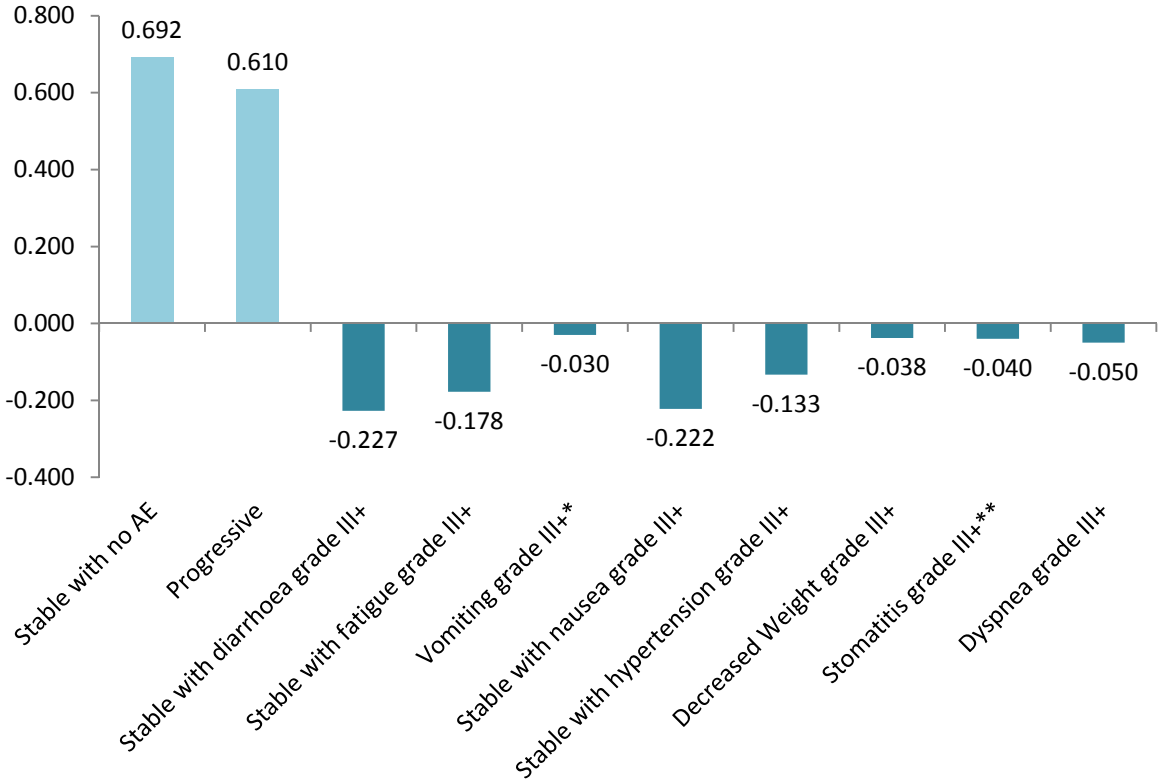
In the economic model basecase, incremental impact of health states on utilities was derived compared to a base state of stable/no response with no adverse events (Figure 83). Although the utility scores of the base case state were equal to the utility scores of the AXIS trial, there was a need to calculate the treatment-specific utility scores for each health state taking into consideration the dis-utilities for AEs and the rate of AEs in each treatment arm.

Additional dis-utility values for several other AEs that were not included in the AXIS study were obtained from other published literature: vomiting (Grade 3+) was obtained from Shabbarudin, et al., 2013 (Shabaruddin, n.d.), while dyspnoea (Grade 3+) was obtained from Doyle, et al., 2008 (Doyle, 2008), and decreased weight (Grade 3+) was obtained from Hudgens, et al., 2014 (Hudgens, 2014) (using decreased appetite as a proxy).

Figure 83. **Mean observed utilities for mRCC health states and calculated incremental disutilities**

Health State	Mean utility	Disutility of AEs	Source
Stable with no AE	0.692	NA	AXIS clinical trial (Rini, et al., 2011)
Progressive	0.610	NA	AXIS clinical trial (Rini, et al., 2011)
Stable with diarrhoea grade III+	0.465	-0.227	AXIS clinical trial (Rini, et al., 2011)
Stable with fatigue grade III+	0.514	-0.178	AXIS clinical trial (Rini, et al., 2011)
Vomiting grade III+	NR	-0.030	NR
Stable with nausea grade III+	0.470	-0.222	AXIS clinical trial (Rini et al. 2011)
Stable with hypertension grade III+	0.559	-0.133	AXIS clinical trial (Rini, et al., 2011)
Decreased Weight grade III+	NR	-0.038	Using (Hudgens, 2014) decreased appetite as a proxy
Stomatitis grade III+**	NR	-0.040	(Shabaruddin, n.d.)
Dyspnea grade III+	NR	-0.050	(Doyle, 2008)

Figure 84 Unadjusted utility scores used in the model



Final Health State Utilities for the base case

This derivation of the final utility was conducted through a stepwise approach, as follows: the incremental dis-utility for AEs for each product was first calculated by multiplying the disutility for each AE by the product specific rate for each AE (Figure 89). Then this resultant AE dis-utility was deducted from the initial utility for each health state. The AE rates were available for patients from the clinical studies. Hence, the results health states utilities were different for patients on each treatment (Figure 86).

Figure 85 AE prevalence used in utility calculations

	LEN+EVE	EVE	AXI	CAB	NIV
Adverse events prevalence					
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%
Disutility	**-0.013**	**-0.003**	**-0.010**	**-0.011**	**-0.002**

Note: Based on clinical trial results

Figure 86 Summary of utility values for base case cost-effectiveness analysis

	LEN+EVE	EVE	AXI	CAB	NIV
Stable disease state with treatment	0.68	0.69	0.68	0.68	0.69
Stable disease state without treatment	0.69	0.69	0.69	0.69	0.69
Progressive state	0.61	0.61	0.61	0.61	0.61

*Patients in progressive state are assumed to not be on therapy, so dis-utilities for treatment does not apply (dis-utilities were only applied for primary treatment).

Utility values used in scenario analysis

Since no utility values were presented in the clinical trials, a vignette-based study was identified which collected utility data on mRCC from the UK general public (Swinburn, 2010) and these results were presented as a scenario in the cost effectiveness model. Health state descriptions (vignettes) for mRCC treatment response and AE health states were informed by literature review, and by qualitative work conducted with mRCC patients and interviews with four clinicians and one oncology nurse with mRCC treatment experience.

A list of health states and descriptions, some including adverse events selected by the experts as the most common and relevant to the HRQoL of patients with mRCC, was finalised using feedback provided by the clinical experts and mRCC patients undergoing therapy. The states were as follows: Stable with no AE; Progressive; Stable with Anemia Grade 3; Stable with Diarrhoea Grade 1/2; Stable with Diarrhoea Grade 3; Stable with Fatigue Grade 3; Stable with Palmar-plantar

erythrodysaesthesia (PPE) syndrome Grade 3; Stable with Mucositis Grade 1/2; Stable with Mucositis Grade 3; Stable with Nausea Grade 1/2; Stable with Nausea Grade 3; Stable with Hypertension Grade 3.

The health states were piloted with six members of the general public in order to determine comprehensibility. Participants completed both a ranking exercise and TTO interview to assess the extent of any difficulties experienced in completing the ratings tasks. No significant issues arose from the piloting process and so the health states were finalised.

Mean TTO utilities and descriptive distribution statistics were calculated for each health state from the interview data.

Vignette Study Results

Mean utility values derived from the TTO interviews indicate how participants in the study differentiated between the mRCC health states (Figure 87). As demonstrated by no overlap in the 95% confidence intervals for the health states which included a grade III adverse event (diarrhoea or fatigue) mean utility values were significantly lower than for the stable health state without the adverse event.

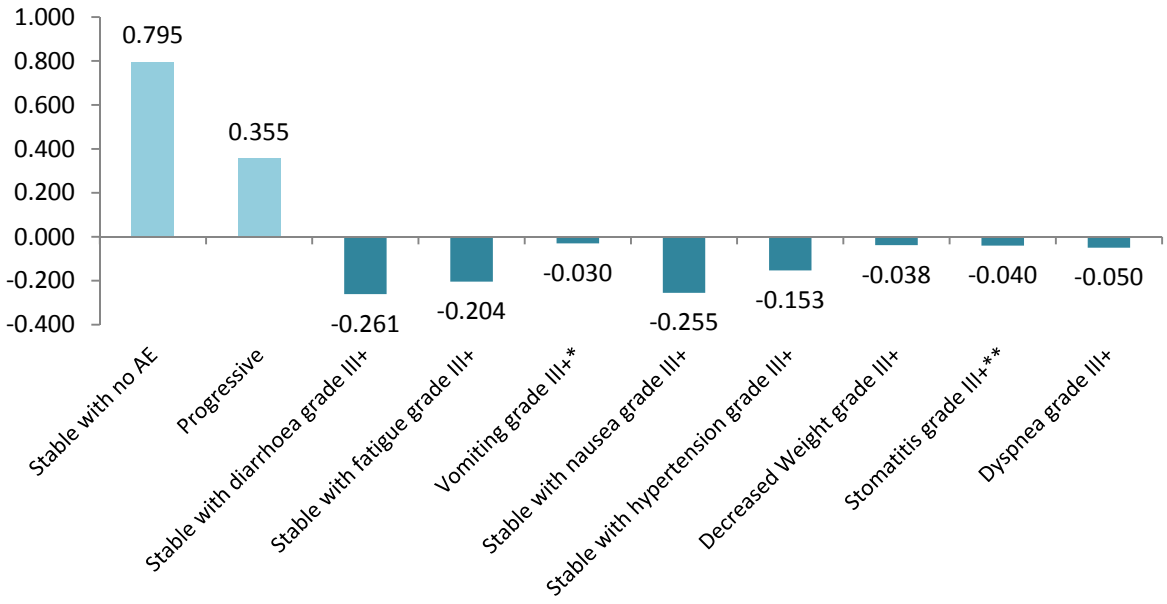
The incremental impact of health states on utilities was then derived compared to a base state of stable with no adverse events (Figure 87). Although the utility scores of the base case state were equal to the health state scores of the vignette, there was a need to calculate the treatment-specific utility scores for each health state taking into consideration the dis-utilities for AEs and the rate of AEs in each treatment arm.

Additional dis-utility values for several other AEs that were not included in the vignette, but which were AEs identified in the HOPE 205 study, were obtained from other published literature: vomiting, decreased weight, and stomatitis (all Grade 3+) were obtained from (Shabaruddin, n.d.), while dyspnoea (Grade 3+) was obtained from (Doyle, 2008)

Figure 87 Mean observed utilities for mRCC health states and calculated incremental disutilities

Health State	Mean utility	Disutility of AEs	Source
Stable with no AE	0.795	NA	(Swinburn, 2010)
Progressive	0.355	NA	(Swinburn, 2010)
Stable with diarrhoea grade III+	0.534	-0.261	(Swinburn, 2010)
Stable with fatigue grade III+	0.591	-0.204	(Swinburn, 2010)
Vomiting grade III+*	NR	-0.030	(Shabaruddin, n.d.)
Stable with nausea grade III+	0.540	-0.255	(Swinburn, 2010)
Stable with hypertension grade III+	0.642	-0.153	(Swinburn, 2010)
Decreased Weight grade III+	NR	-0.038	Using Hudgens et al (2014) (Hudgens, 2014) decreased appetite as a proxy
Stomatitis grade III+**	NR	-0.040	(Shabaruddin, n.d.)
Dyspnea grade III+	NR	-0.050	(Doyle, 2008)

Figure 88 Unadjusted utility scores used in the model



Final Health State Utilities for the scenario

This derivation of the final utility was conducted through a stepwise approach, as follows: the incremental dis-utility for AEs for each product was first calculated by multiplying the disutility for each AE by the product specific rate for each AE (Figure

89). Then this resultant AE dis-utility was deducted from the initial utility for each health state. The Grade 3 and 4 AE rates were available for patients from the clinical studies. Hence, the results health states utilities were different for patients on each treatment. (Figure 90)

Figure 89 AE prevalence used in utility calculations

	LEN+EVE	EVE	AXI	CAB	NIV
Adverse events prevalence					
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%

Sources: LEN+EVE (Eisai Ltd., 2015), Everolimus (Eisai Ltd., 2015), Axitinib (Motzer, et al., 2013), Cabozantinib (Choueiri, et al., 2016), Nivolumab (Motzer, et al., 2015)
Note: All prevalence values reported are for treatment emergent adverse events, except for axitinib and nivolumab which are treatment-related adverse events

Figure 90 Summary of utility values for scenario analysis

	LEN+EVE	EVE	AXI	CAB	NIV
Stable disease state with treatment	0.76	0.79	0.78	0.78	0.79
Stable disease state without treatment	0.80	0.80	0.80	0.80	0.80
Progressive state	0.36	0.36	0.36	0.36	0.36

*Patients in progressive state are assumed to not be on therapy, so dis-utilities for treatment does not apply (dis-utilities were only applied for primary therapy).

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

As described previously in Section 5.1, a systematic review was carried out in order to identify relevant cost-effectiveness studies for lenvatinib in combination with everolimus and relevant comparators (which include those listed in the scope and in the decision problem (Figure 1) ie axitinib, everolimus, nivolumab and cabozantinib) for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

In further detail, the systematic literature review (see Table 5.5.1 in Appendix 8.3) identified the following studies that included resource utilisation and costs for the management of advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy:

Figure 91 List of included studies from Embase/ MEDLINE/ Cochrane library

	Reference
1	NICE (2011). "Everolimus for the second-line treatment of advanced RCC (TA219)". HTA submission. https://www.nice.org.uk/guidance/ta219. Review of NICE TA219: Pitt, M, Crathorne, L, Moxham, T, Bond, M and Hyde, C (2010) "Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis (Structured abstract)." Health Technology Assessment Database(3): 41.
2	NICE (2015). "Axitinib for treating advanced RCC after failure of prior systemic treatment (TA333)". HTA submission. https://www.nice.org.uk/guidance/ta333. Riemsma R, Al M, Corro Ramos I, Deshpande S et al. (2012). "Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment: a Single Technology Appraisal." York:Kleijnen Systematic Reviews Ltd (October 2012)
3	NICE (2016). "Nivolumab for treated or metastatic renal cell carcinoma [ID853]". HTA submission. https://www.nice.org.uk/guidance/gid-ta10037/consultation/html-content
4	SMC (2013). "Axitinib (Inlyta) resubmission 855/13 SMC Advice. http://www.scottishmedicines.org.uk/SMC_Advice/Advice/855_13_axitinib_Inlyta/axitinib_Inlyta_Resubmission
5	SMC (2007). "Sunitinib 50mg capsule (Sutent) 343/07 SMC advice" https://www.scottishmedicines.org.uk/files/sunitinib_Sutent_MRCC_343_07.pdf
6	Hoyle, M, Green, C, Thompson-Coon, J, Liu, Z, Welch, K, Moxham, T, et al. (2010). "Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma." Value in Health 13(1): 55-60.
7	Chandiwana, D, Perrin, A and Sherman, S (2014). "A cost effectiveness analysis of everolimus compared with axitinib in the treatment of metastatic renal cell carcinoma in the United Kingdom." Value in Health 17(7): A640.

A quality assessment of the above 9 studies is provided in Table 5.4.2 of the Systematic Literature Review Report (Appendix 8.3) and each study is summarised in Figure 54.

In order to reflect recent NICE guidance in this patient population, the type and frequency of resources utilised for routine medical monitoring across the pre and post progression period (i.e. "Stable disease" and "Progressive disease" health states) were predominantly based on the previous NICE STA submission for axitinib, TA333 (National Institute for Health and Care Excellence, NICE, 2015), in line with feedback received during the NICE submissions for nivolumab (National Institute for Health and Care Excellence, NICE, 2016) and cabozantinib (National Institute for Health and Care Excellence, NICE, 2017). Further details are provided below.

Overall resource utilisation and cost calculations associated with each treatment included drug costs, routine care costs, AE-related costs (grades 3/4), and mortality

costs. Costs were summed for each primary therapy to obtain its total cost. The included costs and their sources are summarised in Figure 92.

Figure 92 Cost sources

Cost	Source
Therapies	Monthly Index of Medical Specialities. mims.co.uk, accessed 25 01 2017 (MIMS, accessed 25 01 2017)
Routine care Adverse events	National Schedule of Reference Costs (2016-2015). NHS Trusts and NHS Foundation Trusts https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 (NHS, 2016) Personal Social Services Unit. PSSRU, 2016. **(PSSRU, 2016)**
Mortality	Georghiou, Theo, and Martin Bardsley. "Exploring the cost of care at the end of life." Report, Nuffield Trust, London (2014). (Georghiou, 2014)

Utilisation of primary therapy and the prevalence of AEs was based directly on patient-level data from the respective clinical trials.

Intervention and comparators' costs and resource use

Proportion of patients reaching each treatment cycle

As described previously in Section 5.2, in the economic model, treatment duration was modelled directly based on the patient level data for lenvatinib + everolimus and everolimus alone (based on the HOPE 205 clinical trial). For the other included comparators (axitinib, nivolumab, and cabozantinib), the proportion of patients reaching each treatment cycle were also based on the treatment partitions from the lenvatinib + everolimus patient level data (Figure 58), adjusted for the relative treatment durations from the respective trials. For example, for axitinib a relative treatment duration of 1.025 (derived from dividing 8.2 by 8.0) was applied to the lenvatinib + everolimus treatment cycle partition to equate the proportion of patients receiving axitinib treatment in each cycle. This same technique was applied for the other comparators. (Figure 58)

Primary therapy costs

Drugs costs were obtained from the Monthly Index of Medical Specialities (MIMS, accessed 25 01 2017)

The costs "per tablet" of treatment are summarised in Figure 93.

Figure 93 Tablet prices

Generic name	Strength per unit	Units per pack	Pack price (£)	Price per tab (£)
Lenvatinib	10	30	1437	47.90
Everolimus	5	30	2250	75.00
Everolimus	10	30	2673	89.10
Axitinib	5	56	3517	62.80
Cabozantinib	60	30	5143	171.43
Nivolumab	100	1	1097	1,097.00

Source: (MIMS, accessed 25 01 2017)

Daily cost of treatment is calculated according to the SPC dosing guidelines (eMC, Accessed 25 01 2017). The starting doses ie defined daily dose (DDD) for the treatments are outlined in Figure 94. Dose reduction assumptions in the model are based on the data from the corresponding clinical trials using mean values ie LEN+EVE (Eisai Ltd., 2015), Everolimus (Eisai Ltd., 2015), Axitinib (Rini, et al., 2011), Cabozantinib (Choueiri, et al., 2016), Nivolumab (Motzer, et al., 2015).

Consistent with the HOPE 205 individual patient level clinical trial data, it was assumed that the average patient had a weight of 80.8 kg. To obtain total costs per daily dose of each therapy, the total dose (mg) of treatment per cycle (including wastage and dose reduction) was divided by the size of pack/vial before being multiplied by the price per pack/vial:

$$Cost\ of\ a\ therapy\ per\ daily\ dose\ (oral) = \frac{(mg\ per\ cycle)}{(pack\ size)} x\ (price\ per\ pack)$$

$$Cost\ of\ a\ therapy\ per\ daily\ dose\ (IV) = KG\ x\ roundedup\left(\frac{mg}{kg}\right) x\ (price\ per\ vial)$$

Wastage was included in the drug costs, meaning it was assumed that no "pill-splitting" occurred (i.e. fractions of doses were rounded up to the nearest whole number). Additionally, dose reduction was accounted for in the drug cost of all comparators. Costs per cycle with dose reduction for each therapy were calculated by using the within-trial doses received. Wastage used the within-trial doses rounded up to the nearest possible whole pill or vial amount.

Figure 94 Drug dosing and costs (per day)

Therapy	Administration	DDD	Dose reduction	Number of tabs needed	Final dose (mg)	Drug cost per DDD
Lenvatinib +	Oral	18	[redacted]		14.0	[redacted]
Everolimus	Oral	5	[redacted]		5.0	
Axitinib	Oral	10	[redacted]	2.00	10.0	[redacted]
Cabozantinib	Oral	60	[redacted]	1.00	60.0	[redacted]
Nivolumab	IV	244	[redacted]	3.00	300.0	[redacted]
Everolimus	Oral	10	[redacted]	2.00	10.0	[redacted]

Abbreviations: DDD, Defined daily dose
Sources: LEN+EVE (Eisai Ltd., 2015), Everolimus (Eisai Ltd., 2015), Axitinib (Rini, et al., 2011), Cabozantinib (Choueiri, et al., 2016), Nivolumab (Motzer, et al., 2015). (MIMS, accessed 25 01 2017)

Apart from the cost of treatment, patients in the "Pre-Progression" health state also incur the costs of administration for oral and IV therapies.

Drug administration costs were based on NHS Reference Costs 2015 to 2016 (NHS, 2016). As a simplifying assumption, all chemotherapy was considered part of ongoing therapy, eliminating the need for separate initial and subsequent HRG codes.

Chemotherapy administration costs were estimated according to the HRG codes in the table below (Figure 95). Oral chemotherapy costs have been considered for LEN+EVE, everolimus, axitinib and cabozantinib. Simple parenteral chemotherapy costs have been considered for nivolumab.

Figure 95 Administration costs

Type of chemotherapies	UK (NHS) cost code	Average cost (£)	Source
Oral chemotherapy	SB11z	183.50	NHS ref costs 2015-16
Simple parenteral chemotherapy (first attendance)	SB12Z	236.19	NHS ref costs 2015-16

The estimation of the monthly total costs is provided below (Figure 96).

The daily treatment costs were adjusted and estimated for one Markov cycle since this economic evaluation is a Markov model. One Markov cycle length in this model was one month (30.4375 days): Therefore, Markov cycle treatment costs = daily treatment cost x 30.4375.

Figure 96 Drug costs per month

Comparator	Cost per DDD	Cycle Length	Doses per cycle	Type of admin. costs	Admin. cost per cycle (£)	Drug Cost per cycle (£)	Total Cost per month (£)
Lenvatinib + Everolimus	[redacted]	28	28	Oral	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	28	28	Oral	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	28	28	Oral	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	28	2	IV	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	28	28	Oral	[redacted]	[redacted]	[redacted]

Health-state unit costs and resource use

Costs were applied for each treatment phase. In addition to the drug costs (summarised above), routine care (i.e., non-medication costs) and mortality costs were included and are summarised below.

Routine Care Costs

As highlighted previously, the type and frequency of resources utilised for routine medical monitoring across the pre and post progression period (i.e. “Stable disease” and “Progressive disease” health states) were predominantly based on the previous NICE STA submission for axitinib, TA333 (National Institute for Health and Care Excellence, NICE, 2015), in line with feedback received during the NICE submissions for nivolumab (National Institute for Health and Care Excellence, NICE, 2016) and cabozantinib (National Institute for Health and Care Excellence, NICE, 2017) These resources were also validated through expert opinions (see below for further details).

For the Stable disease health state, the type and frequency of resource utilisation were taken from TA333 (National Institute for Health and Care Excellence, NICE,

2015), using the scenario analysis assuming oncology visits in line with feedback received during the clinical expert validation. In addition, for the Stable disease health state, GP visits were excluded in line with feedback from the NICE committee during the cabozantinib NICE assessment (National Institute for Health and Care Excellence, NICE, 2017).

For the Progressive disease health state, the type and frequency of resource utilisation were again taken from TA333 (National Institute for Health and Care Excellence, NICE, 2015), using the scenario analysis assuming oncology visits in line with feedback received during the clinical expert validation.

Costs were obtained from the NHS reference (2015-2016) costs (NHS, 2016), with the exception of GP visit costs and specialist community nurse visit, which were obtained from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2016) (PSSRU, 2016). These costs are presented in Figure 97.

As described above, the inputs were validated by 8 NHS England and Wales practising clinical experts. These were selected based on their expertise in RCC and their sites of practice included Leicester Royal Infirmary, Addenbrookes NHS Trust, Royal Free Hospital, Queen Elizabeth Hospital, Royal Surrey County Hospital, Southampton General Hospital and the Velindre Cancer Centre. The validation was conducted as part of an advisory board meeting. The clinical experts were presented with the resource utilisation estimates, related costs and the rationale around them. Following that, they were asked to confirm or rejects the inputs. In case of rejection, experts were asked to provide their rationale. The majority of the experts confirmed that the final inputs below generally reflect the current clinical practice in NHS England and Wales.

Figure 97 Routine care unit costs

Stable Disease Health Care Resource Use Costs					
Cost Item	Price per Item Unit (£)	DDD/Frequency per cycle	Proportion of Patients %	Cost per cycle	Source of unit costs
Oncologist Examination	162.84	1.00	100.00%	162.84	Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (Source NHS Reference costs 2015/16)
CT Scan	140.11	0.30	100.00%	42.03	RD27Z Computerised Tomography Scan of more than three areas (Source: NHS Reference costs 2015/16)
Blood Test	3.00	1.00	100.00%	3.00	DAPS05 NHS Reference costs 2015/16
Total Stable Disease Costs				207.87	
Progressive Disease Health Care Resource Use Costs					
Cost Item	Price per Item Unit (£)	DDD/Frequency per cycle	Proportion of Patients %	Cost per cycle	Source of unit costs
Oncologist Examination	162.84	1.00	100.00%	162.84	Cost of Consultant Medical oncology visit (Source NHS Reference costs 2015/16)
GP visit	36.00	1.00	100.00%	36.00	PSSRU 2016 Section10.3b page 145 GP unit cost Per surgery consultation lasting 9.22 minutes, including direct staff costs, with qualification costs
Specialist community nurse visit	43.00	1.50	100.00%	64.50	PSSRU 2016 Section10.2 page 143 Nurse (GP practice), unit costs, including qualifications
Pain medication	5.36	28.00	100.00%	150.08	TA333 (BNS Section 4.7.2 Opioid analgesics (morphine sulphate 1mg/ml, net price 50ml vial = £5.00 using NHS reference costs 2010/11), adjusted to 2015/16 prices using PSSRU 2016 Section 16.3 page 196, The HCHS index
Total Progressive Disease Costs				413.42	

Source: TA333 (Axitinib NICE guidance, company submission pages 161-163) and Nivolumab NICE company submission (page 178) and ERG report (pg 123) and cabozantinib ACD (pg 16)

Mortality costs

Mortality-related costs were obtained from Nuffield Trust (2014) (Georghiou, 2014) http://www.nuffieldtrust.org.uk/sites/files/nuffield/publication/end_of_life_care.pdf) data and included acute hospital care (all hospital contacts, emergency inpatient admissions, non-emergency inpatient admissions, outpatient visits, accident & emergency visits), local authority-funded social care, district nursing care, and GP visit costs. These were summed to obtain the cost per mortality event, and were then adjusted for inflation to 2016 values, based on PSSRU inflation rates (Figure 98). The overall mortality-associated cost for each comparator was calculated as the sum of the product of the cost per mortality and the estimated mortality (1- % OS) at each cycle (derived from the extrapolation):

$$Overall\ cost\ of\ mortality = \sum (cost\ per\ mortality) \times (1 - proportion\ of\ patients\ surviving\ at\ cycle\ n)$$

Figure 98 Mortality costs

Mortality cost	Cost element	2013 value in the UK (£)
Secondary (acute hospital care)	Cost of all hospital contacts	5,890
	Cost of emergency inpatient admissions	4,071
	Cost of non-emergency inpatient admissions	1,360
	Cost of outpatient visits	378
	Cost of A&E visits	80
Local authority funded social care	Cost of local authority-funded social care	444
District nursing	Cost of district nursing care	588
GP contacts	Cost of GP visits	365
Total used in the model (Inflation-adjusted for 2016)		7,450

Source: Nuffield Trust. (2014). Exploring the cost of care at the end of life. (Georghiou, 2014) http://www.nuffieldtrust.org.uk/sites/files/nuffield/publication/end_of_life_care.pdf

Adverse reaction unit costs and resource use

The Grade 3/4 AEs identified in Section 5.4 were included in the model, as lower grade AEs would likely not bear substantial costs. AE prevalence was derived from the respective clinical trial results for each comparator, as described previously in

Figure 89 and were considered constant over time. This is an assumption made in the absence of any evidence suggesting otherwise and being consistent with the methods employed in other models that estimate AEs.

The costs associated with the treatment of adverse events were obtained from the NHS Reference costs 2015/2016 (NHS, 2016) and/or the PSSRU Unit Costs of Health and Social Care 2016 report (PSSRU, 2016). The list of adverse events and the relevant costs associated with the management of these adverse events are listed in Figure 99. These costs were informed by the same 8 practising NHS clinicians from England and Wales described above who provided input at an advisory board. In the absence of specific input at this advisory board on the cost of treating hypertension associated with lenvatinib, costing information on hypertension was taken directly from the lenvatinib NICE evidence submission for differentiated thyroid cancer.

Figure 99 AE NHS reference costs

AE	Custom HRG Cost (£)	Source
Diarrhoea	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Fatigue/ Asthenia	658.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of F2F community nurse contact of £43 (Source: PSSRU 2016)
Vomiting	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Nausea	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Hypertension	850.67	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (£162.84) (Source NHS Reference costs 2015/16) + 2 follow up GP visits (£36) Source: PSSRU 2016
Decreased Weight	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Stomatitis	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Dyspnoea	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)

The prevalence for included AEs are shown in Figure 102. The AE prevalence used in the model were derived by adjusting the prevalence reported in the clinical trials to a "monthly frequency". This was done by first dividing the median duration of each AE (based on HOPE 205 clinical trial patient-level data and presented in Figure 100 by the duration of treatment for each comparator to obtain the average proportion of time patients are treated for each AE, for each comparator: (Figure 101)

$$Proportion\ of\ time\ treated\ for\ an\ AE = (median\ duration\ of\ AE) \div (median\ treatment\ duration)$$

Figure 100 AE Duration in days

AE	Duration in days	Source
Diarrhoea	25.51	Source: NCT01136733 LEN+EVE clinical trial patient-level data
Fatigue/Asthenia	49.39	
Vomiting	10.11	
Nausea	34.79	
Hypertension	28.34	
Decreased Weight	49.59	Assumed equal to decreased appetite (NCT01136733)
Stomatitis	37.477	Source: NCT01136733 LEN+EVE clinical trial patient-level data
Dyspnoea	33.56	

Figure 101 Proportion of time treated for AEs

AE	LEN+EVE	EVE	AXI	CAB	NIV
Treatment duration in the model (months)	8.00	4.10	8.20	8.30	5.50
Diarrhoea	10.47%	20.44%	10.22%	10.10%	15.24%
Fatigue/Asthenia	20.28%	39.57%	19.79%	19.55%	29.50%
Vomiting	4.15%	8.10%	4.05%	4.00%	6.04%
Nausea	14.29%	27.88%	13.94%	13.77%	20.78%
Hypertension	11.64%	22.71%	11.36%	11.22%	16.93%
Decreased Weight	20.37%	39.74%	19.87%	19.63%	29.62%
Stomatitis	15.39%	30.03%	15.02%	14.83%	22.39%
Dyspnoea	13.78%	26.89%	13.44%	13.28%	20.04%

The proportion of time treated for each AE was then multiplied by the % prevalence of that AE reported in the respective clinical trial (Figure 102) to obtain the monthly-adjusted prevalence of each AE.

Figure 102 AE prevalence from clinical trials

	LEN+EVE	EVE	AXI	CAB	NIV
Adverse events prevalence					
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%

Sources: LEN+EVE (Eisai Ltd., 2015), Everolimus (Eisai Ltd., 2015), Axitinib (Rini, et al., 2011)), Cabozantinib (Choueiri, et al., 2016), Nivolumab (Motzer, et al., 2016)
Note: All prevalence values reported are for treatment emergent adverse events, except for nivolumab which are treatment-related adverse events

AE costs per month (were derived by multiplying the AE prevalence (monthly-adjusted) by the corresponding cost in Figure 99:

$$Monthly\ AE\ cost = (AE\ prevalence)x(HRG\ cost)$$

Figure 103 Cost per month for AEs used in the model (£)

AE	LEN+EVE	EVE	AXI	CAB	NIV
Diarrhoea	152	15	85	101	10
Fatigue/Asthenia	65	0	66	72	16
Vomiting	60	0	8	15	0
Nausea	46	0	15	39	2
Hypertension	117	17	145	128	0
Decreased Weight	12	0	18	18	0
Stomatitis	0	12	6	12	0
Dyspnoea	12	49	0	18	5
Total cost	***464***	***94***	***344***	***404***	***32***

Miscellaneous unit costs and resource use

No other costs were included.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

Figure 104 summarises all the inputs and variables used in the economic model.

Figure 104 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
Utility values	**Value**	**SD**	
Basecase values (AXIS Study)			
"Pre-progression" or Stable disease health state	0.692	0.035 (5% value assumption	Section 5.4
"Post progression" or Progressive disease health state	0.610	0.031 (5% value assumption)	
Stable with diarrhoea grade III+	0.46	N/A	Section 5.4
Stable with fatigue grade III+	0.51	N/A	
Stable with nausea grade III+	0.47	N/A	
Stable with hypertension grade III+	0.56	N/A	
Stable with fatigue grade III+	0.591	N/A	
Drug & Acquisition Costs	**Cost (£) / Value**	**SD**	
Treatments			
Lenvatinib 4mg x 30	£1,437.00	N/A	Section 5.5
Lenvatinib 10mg x 30	£1,437.00	N/A	
Everolimus 5mg x 30	£2,250.00	N/A	
Everolimus 10mg x 30	£2,673.00	N/A	
Axitinib 5mg x 56	£3517.00	N/A	
Nivolumab 10mg/ml x 100ml	£1,097.00	N/A	
Cabozantinib 60mg x 30	£5,143.00	N/A	
Administration			
Oral chemotherapy	£184.00	N/A	Section 5.5
Simple parenteral chemotherapy (first attendance)	£236.00	N/A	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Resource Utilisation	**Cost (£)**		
Oncologist Examination	£162.84 at 1 visit per month	N/A	Section 5.5
CT Scan	£140.11 at 1 scan every 3 months	N/A	
Blood Test	£3.00 at 1 per month	N/A	
GP visit	£36.00 at 1 visit per month	N/A	
Specialist community nurse visit	£43.00 at 1.5 visits per month	N/A	
Pain medication	£5.86	N/A	
Mortality costs	£7,450	N/A	
AE Management	**Cost (£)**		
Grade 3/4 diarrhoea	£774.43	N/A	Section 5.5
Grade 3/4 fatigue/asthenia	£658.83	N/A	
Grade 3/4 vomiting	£774.43	N/A	
Grade 3/4 nausea	£774.43	N/A	
Grade 3/4 hypertension	£850.67	N/A	
Grade 3/4 decreased weight	£615.83	N/A	
Grade 3/4 stomatitis	£615.83	N/A	
Grade 3/4 dyspnoea	£615.83	N/A	

CI, confidence interval

Assumptions

The base case analysis is subject to several key assumptions which are discussed throughout Section 5. For reference, these key assumptions are summarised here. Uncertainties regarding these assumptions are explored in Section 5.8.

Effectiveness

1. OS and PFS for lenvatinib and everolimus is best characterised by a piecewise approach for extrapolation, where the Kaplan-Meier curve is used prior to the trial cut-off, followed by a parametric Weibull tail after the cut-off.
2. ITT OS HRs from the ITC reported in Section 4.10 are appropriate to estimate OS for cabozantinib and nivolumab.
3. Cross-over adjusted OS HRs from the ITC reported in Section 4.10 are appropriate to estimate OS for axitinib.

4. Main analysis as reported by trial PFS HRs from the ITC reported in Section 4.10 are appropriate to estimate PS for cabozantinib, nivolumab and axitinib.

Quality of life

1. The most suitable sources to estimate utilities are AXIS EQ-5D data.

Resource use and costs

1. Treatment duration for LEN+EVE, everolimus, axitinib, cabozanitib and nivolumab are based on the most up to date clinical trial data.
2. Once patients progress on primary treatment, it is assumed that they do not receive any further treatment.
3. Medical resource use costs are based on previous NICE submissions

5.7 Base-case results

Base-case incremental cost effectiveness analysis results

Figure 105 overleaf summarises the basecase results.

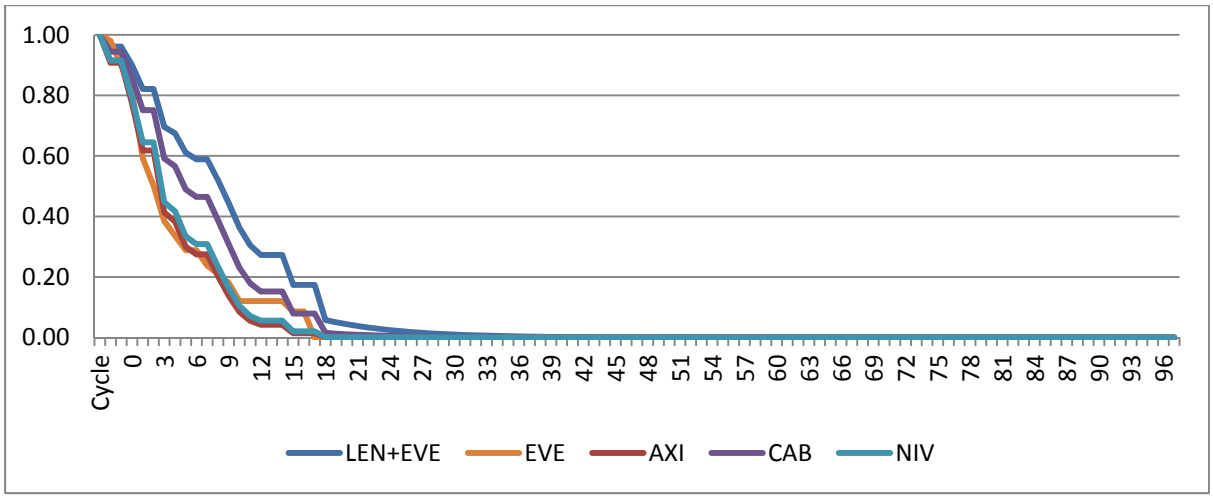
Figure 105 Base-case results; pairwise analysis, LEN+EVE versus comparators

Technology/ comparator	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
LEN+EVE	[redacted]	[redacted]	[redacted]				
Axitinib	54,470	1.38	0.85	[redacted]	[redacted]	[redacted]	32,906
Cabozantinib	73,079	2.10	1.31	[redacted]	[redacted]	[redacted]	1,683
Nivolumab	69,896	1.98	1.23	[redacted]	[redacted]	[redacted]	17,146
Everolimus	39,988	1.73	1.08	[redacted]	[redacted]	[redacted]	96,403

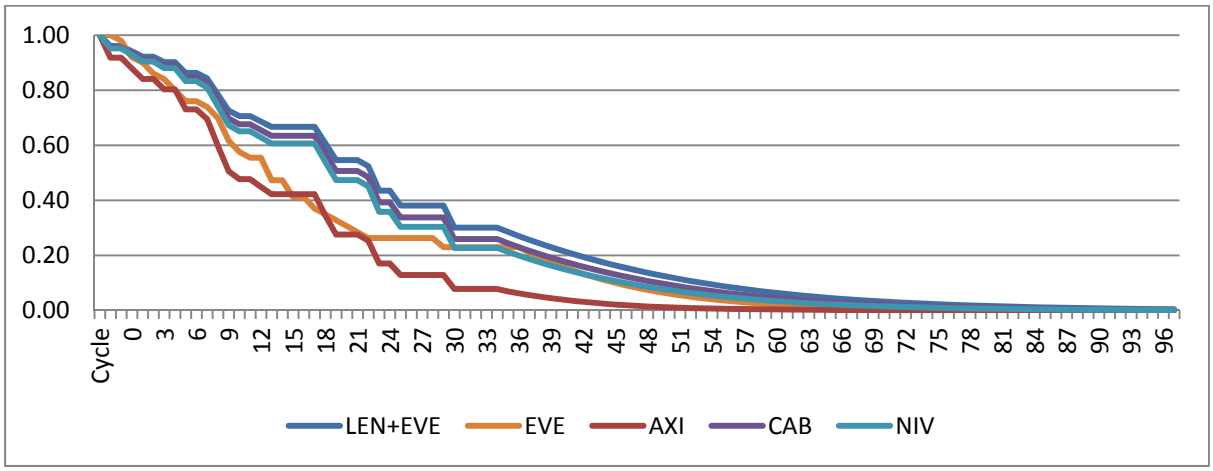
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Clinical outcomes from the model

Progression Free Survival



Overall Survival



Disaggregated results of the base case incremental cost effectiveness analysis

Figure 106 Summary of predicted resource use by category of cost

Item	Cost LEN+EVE	Cost Axitinib	Increment	Absolute increment	% absolute increment
Primary drug therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Item	Cost LEN+EVE	Cost Axitinib	Increment	Absolute increment	% absolute increment
Mortality costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 107 Summary of predicted resource use by category of cost

Item	Cost LEN+EVE	Cost Cabozantinib	Increment	Absolute increment	% absolute increment
Primary drug therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 108 Summary of predicted resource use by category of cost

Item	Cost LEN+EVE	Cost Nivolumab	Increment	Absolute increment	% absolute increment
Primary drug therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

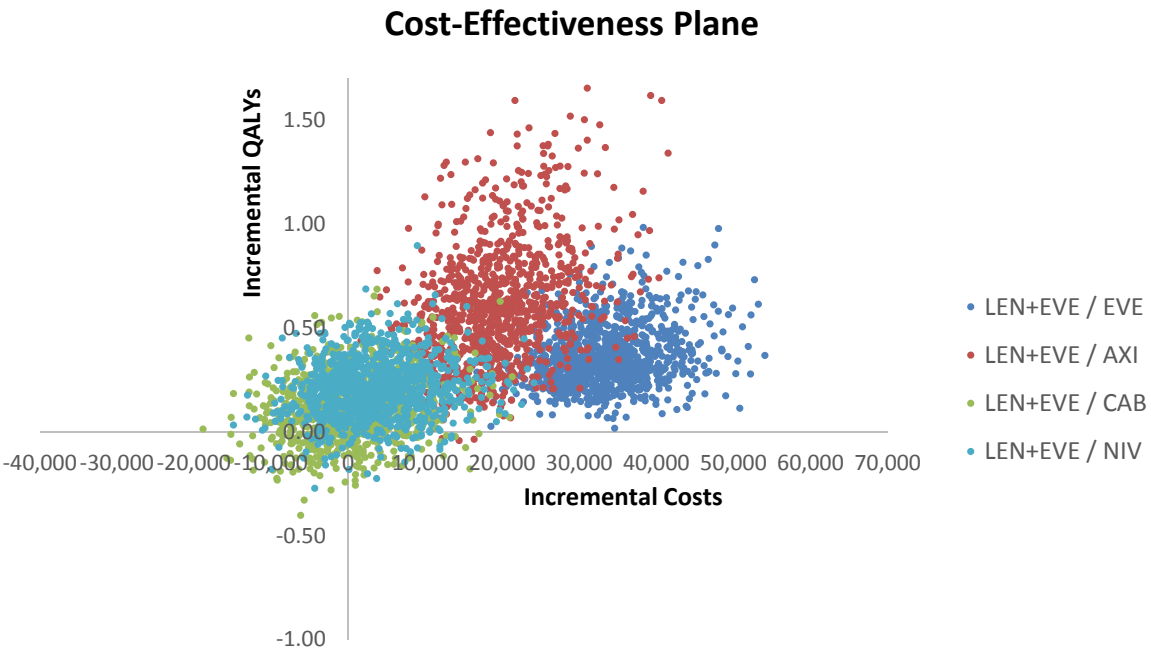
Figure 109 Summary of predicted resource use by category of cost

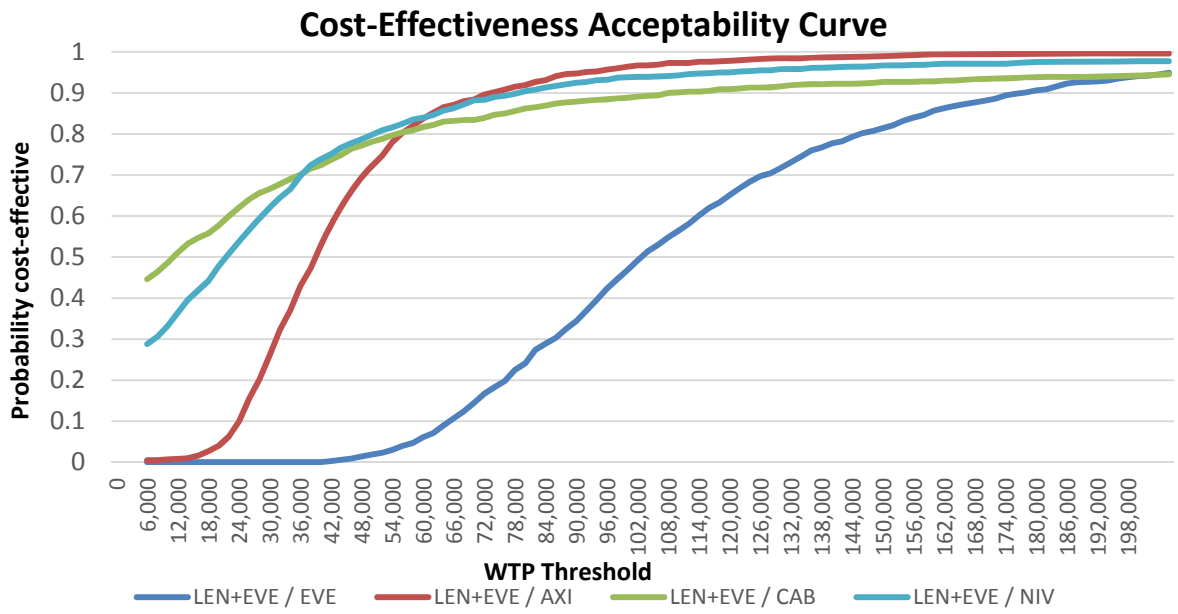
Item	Cost LEN+EVE	Cost Everolimus	Increment	Absolute increment	% absolute increment
Primary drug therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

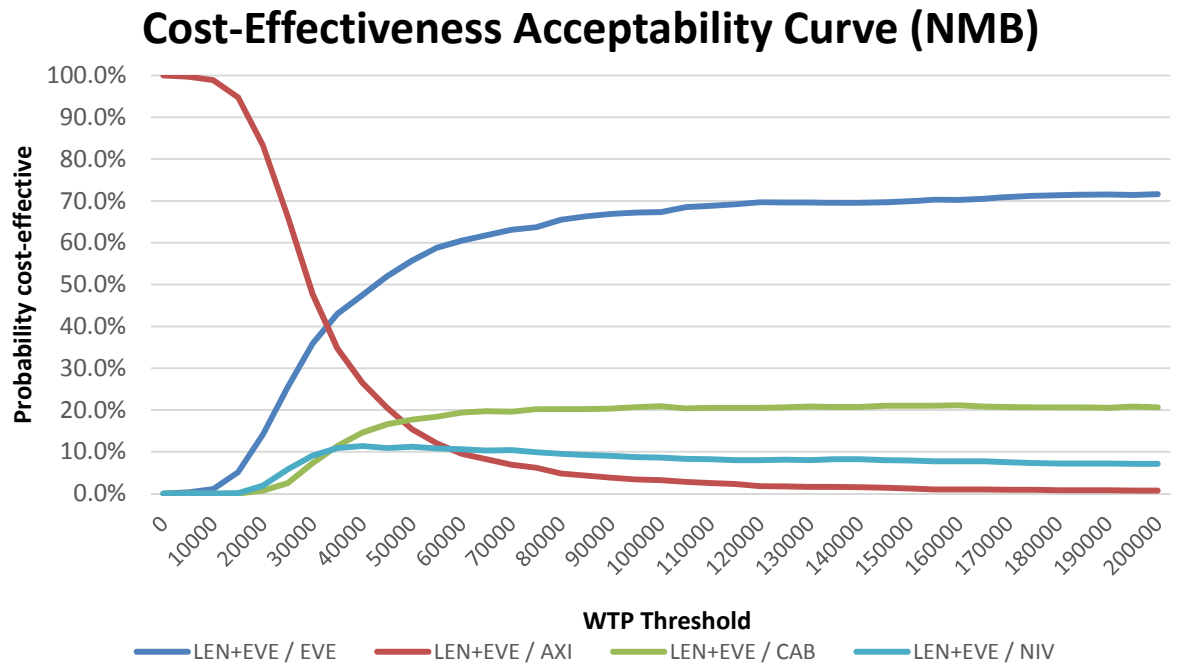
5.8 Sensitivity analyses

Probabilistic sensitivity analysis

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Mean ICER	[redacted]	[redacted]	[redacted]	[redacted]
Median ICER	[redacted]	[redacted]	[redacted]	[redacted]
% under 25,000	[redacted]	[redacted]	[redacted]	[redacted]
% under 50,000	[redacted]	[redacted]	[redacted]	[redacted]




Cost-Effectiveness Acceptability Curve
Probability cost-effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
6,000
12,000
18,000
24,000
30,000
36,000
42,000
48,000
54,000
60,000
66,000
72,000
78,000
84,000
90,000
96,000
102,000
108,000
114,000
120,000
126,000
132,000
138,000
144,000
150,000
156,000
162,000
168,000
174,000
180,000
186,000
192,000
198,000
WTP Threshold
LEN+EVE / EVE
LEN+EVE / AXI
LEN+EVE / CAB
LEN+EVE / NIV


Cost-Effectiveness Acceptability Curve (NMB)
Probability cost-effective
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
0
10000
20000
30000
40000
50000
60000
70000
80000
90000
100000
110000
120000
130000
140000
150000
160000
170000
180000
190000
200000
WTP Threshold
LEN+EVE / EVE
LEN+EVE / AXI
LEN+EVE / CAB
LEN+EVE / NIV

Deterministic sensitivity analysis

Figure 110 Tornado diagram LEN+EVE vs Axitinib

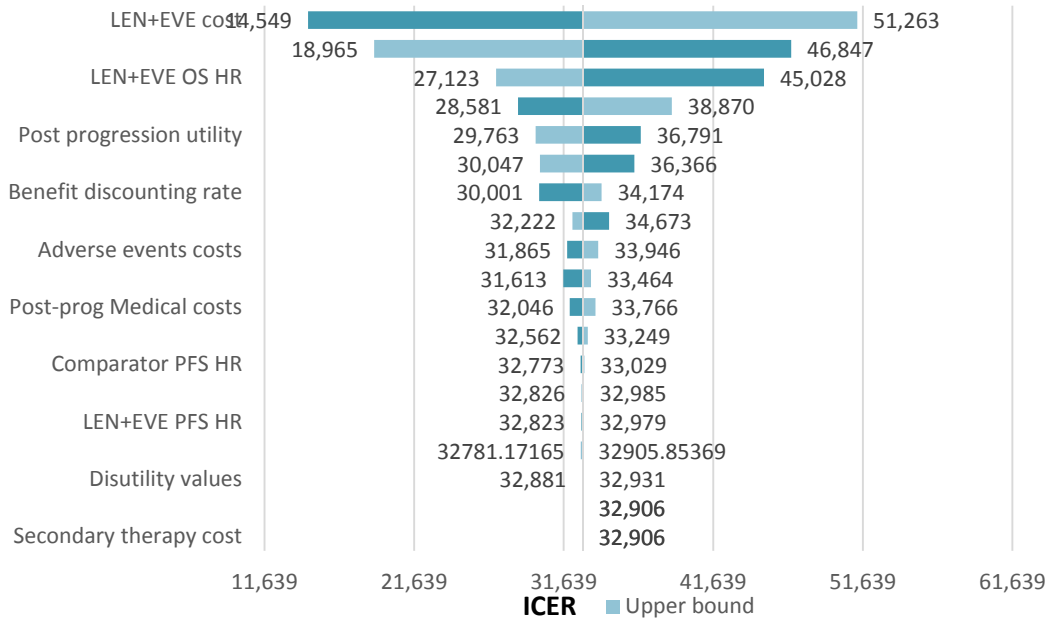


Figure 111 Tornado diagram LEN+EVE vs cabozantinib

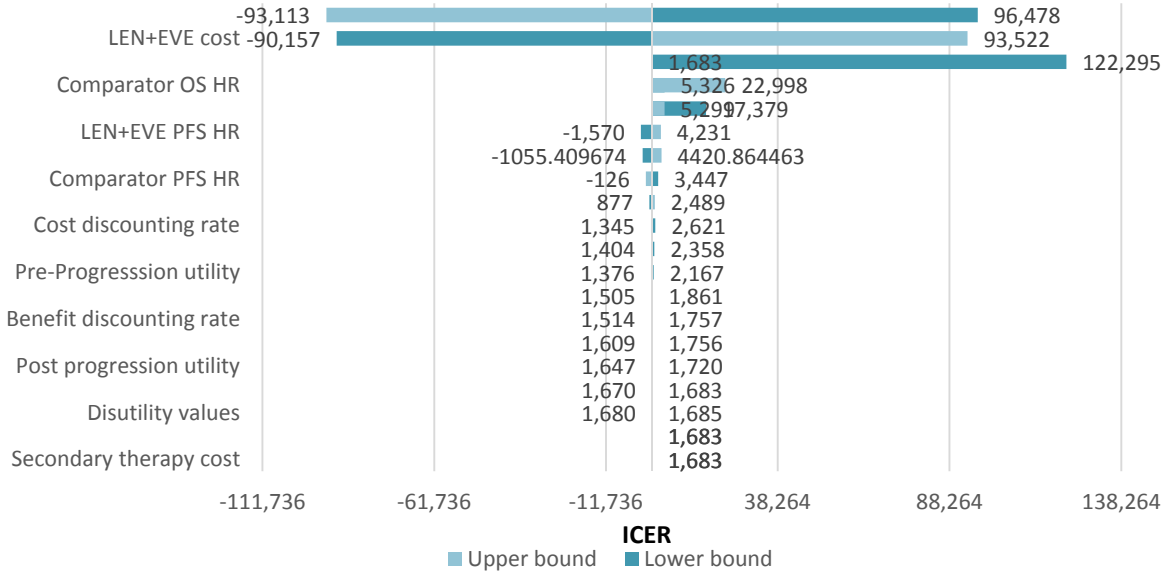


Figure 112 Tornado diagram LEN+EVE vs Nivolumab

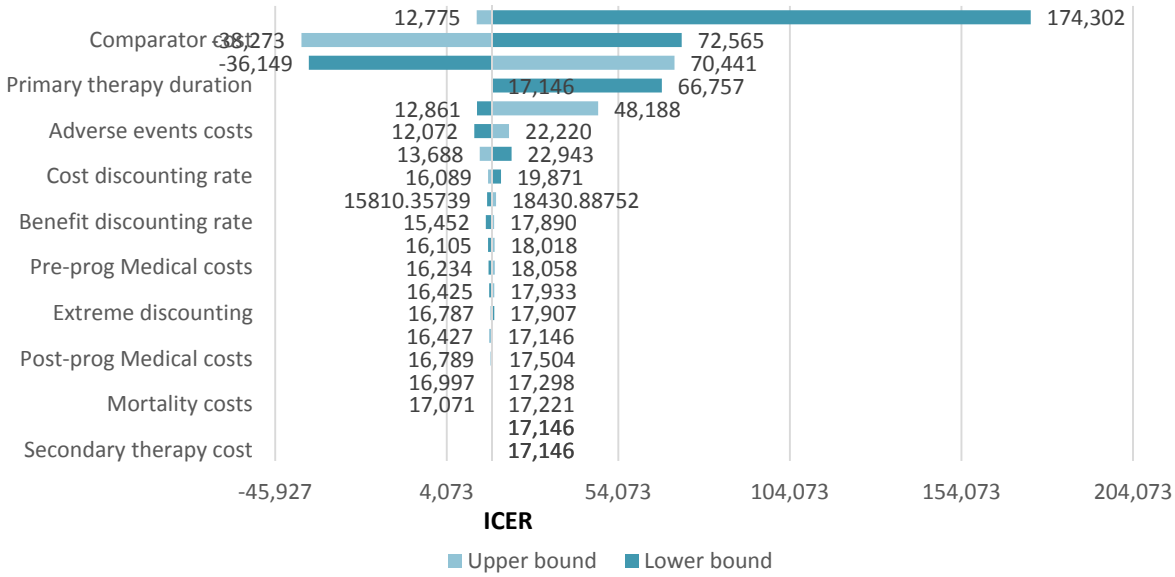
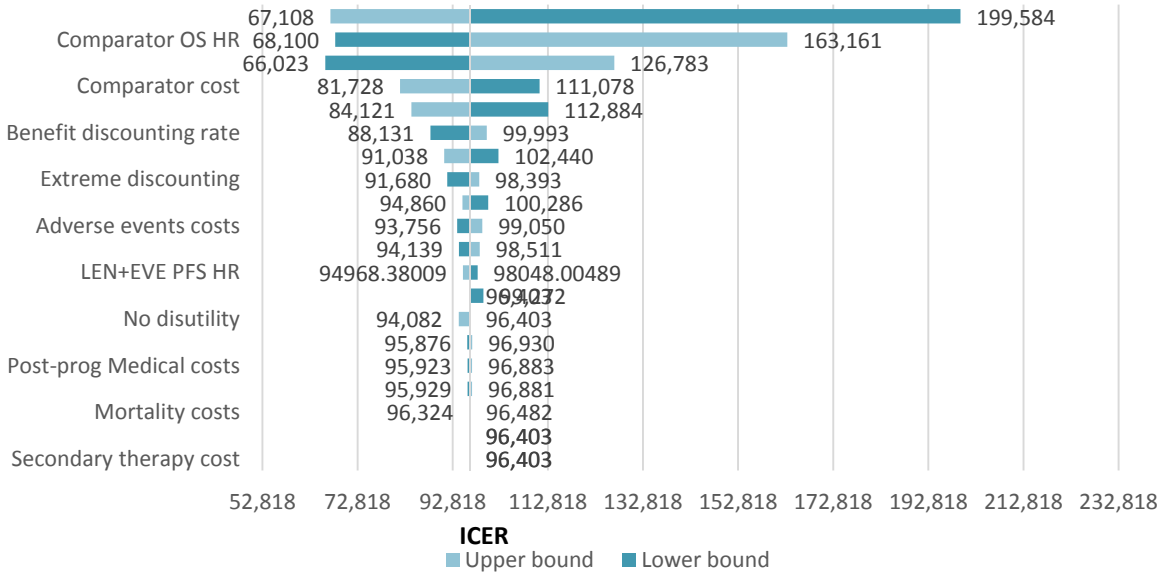


Figure 113 Tornado diagram LEN+EVE vs everolimus



Scenario analysis

Figure 114 LEN+EVE vs Axitinib

Parameter	Base case	Scenario	ICER
Treatment Duration	Clinical trial data	Switch at progression	£71,683
10% discount for everolimus in the combination			£67,154
20% discount for everolimus in the combination			£62,625
30% discount for everolimus in the combination			£58,096
40% discount for everolimus in the combination			£53,566
50% discount for everolimus in the combination			£49,037
60% discount for everolimus in the combination			£44,508
70% discount for everolimus in the combination			£39,979
Discount rate	3.5%	0%	£31,613
10% discount for everolimus in the combination			£27,988
20% discount for everolimus in the combination			£24,363
30% discount for everolimus in the combination			£20,739
40% discount for everolimus in the combination			£17,114
50% discount for everolimus in the combination			£13,489
60% discount for everolimus in the combination			£9,864
70% discount for everolimus in the combination			£6,240
Discount rate	3.5%	5%	£33,464
10% discount for everolimus in the combination			£29,472
20% discount for everolimus in the combination			£25,481
30% discount for everolimus in the combination			£21,490
40% discount for everolimus in the combination			£17,498
50% discount for everolimus in the combination			£13,507
60% discount for everolimus in the combination			£9,516
70% discount for everolimus in the combination			£5,524
OS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£37,306
10% discount for everolimus in the combination			£32,746
20% discount for everolimus in the combination			£28,186
30% discount for everolimus in the combination			£23,627
40% discount for everolimus in the combination			£19,067
50% discount for everolimus in the combination			£14,507
60% discount for everolimus in the combination			£9,947
70% discount for everolimus in the combination			£5,388

Parameter	Base case	Scenario	ICER
OS Extrapolation model	Piecewise - Weibull	Parametric - Gompertz	£38,860
10% discount for everolimus in the combination			£34,061
20% discount for everolimus in the combination			£29,261
30% discount for everolimus in the combination			£24,462
40% discount for everolimus in the combination			£19,663
50% discount for everolimus in the combination			£14,864
60% discount for everolimus in the combination			£10,064
70% discount for everolimus in the combination			£5,265
OS Extrapolation model	Piecewise - Weibull	Individual - Weibull	£34,674
10% discount for everolimus in the combination			£30,520
20% discount for everolimus in the combination			£26,366
30% discount for everolimus in the combination			£22,212
40% discount for everolimus in the combination			£18,058
50% discount for everolimus in the combination			£13,904
60% discount for everolimus in the combination			£9,750
70% discount for everolimus in the combination			£5,596
PFS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£32,897
10% discount for everolimus in the combination			£29,008
20% discount for everolimus in the combination			£25,120
30% discount for everolimus in the combination			£21,231
40% discount for everolimus in the combination			£17,343
50% discount for everolimus in the combination			£13,454
60% discount for everolimus in the combination			£9,566
70% discount for everolimus in the combination			£5,677
PFS Extrapolation model	Piecewise - Weibull	Parametric - Weibull	£32,885
10% discount for everolimus in the combination			£29,030
20% discount for everolimus in the combination			£25,175
30% discount for everolimus in the combination			£21,320
40% discount for everolimus in the combination			£17,465
50% discount for everolimus in the combination			£13,610
60% discount for everolimus in the combination			£9,755
70% discount for everolimus in the combination			£5,900
PFS Extrapolation model	Piecewise - Weibull	Individual - Gompertz	£32,895
10% discount for everolimus in the combination			£28,996

Parameter	Base case	Scenario	ICER
20% discount for everolimus in the combination			£25,098
30% discount for everolimus in the combination			£21,200
40% discount for everolimus in the combination			£17,301
50% discount for everolimus in the combination			£13,403
60% discount for everolimus in the combination			£9,504
70% discount for everolimus in the combination			£5,606
Utility values	Axis Study	Vignette Study	£38,734
10% discount for everolimus in the combination			£34,165
20% discount for everolimus in the combination			£29,596
30% discount for everolimus in the combination			£25,027
40% discount for everolimus in the combination			£20,458
50% discount for everolimus in the combination			£15,889
60% discount for everolimus in the combination			£11,320
70% discount for everolimus in the combination			£6,751
Everolimus Price	List Price	Generic (capecitabine as proxy)	-£87
10% discount for everolimus in the combination			-£669
20% discount for everolimus in the combination			-£1,251
30% discount for everolimus in the combination			-£1,834
40% discount for everolimus in the combination			-£2,416
50% discount for everolimus in the combination			-£2,998
60% discount for everolimus in the combination			-£3,580
70% discount for everolimus in the combination			-£4,163

Figure 115 LEV+EVE vs Cabozantinib

Parameter	Base case	Scenario	ICER
Treatment Duration	Clinical trial data	Switch at progression	£122,295
10% discount for everolimus in the combination			£99,303
20% discount for everolimus in the combination			£76,312
30% discount for everolimus in the combination			£53,320
40% discount for everolimus in the combination			£30,328
50% discount for everolimus in the combination			£7,336
60% discount for everolimus in the combination			-£15,656
70% discount for everolimus in the combination			-£38,648
Discount rate	3.5%	0%	£2,358

Parameter	Base case	Scenario	ICER
10% discount for everolimus in the combination			-£15,535
20% discount for everolimus in the combination			-£33,428
30% discount for everolimus in the combination			-£51,320
40% discount for everolimus in the combination			-£69,213
50% discount for everolimus in the combination			-£87,106
60% discount for everolimus in the combination			-£104,999
70% discount for everolimus in the combination			-£122,892
Discount rate	3.5%	5%	£1,404
10% discount for everolimus in the combination			-£18,670
20% discount for everolimus in the combination			-£38,745
30% discount for everolimus in the combination			-£58,819
40% discount for everolimus in the combination			-£78,894
50% discount for everolimus in the combination			-£98,968
60% discount for everolimus in the combination			-£119,042
70% discount for everolimus in the combination			-£139,117
OS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£194
10% discount for everolimus in the combination			-£24,008
20% discount for everolimus in the combination			-£48,210
30% discount for everolimus in the combination			-£72,412
40% discount for everolimus in the combination			-£96,615
50% discount for everolimus in the combination			-£120,817
60% discount for everolimus in the combination			-£145,019
70% discount for everolimus in the combination			-£169,222
OS Extrapolation model	Piecewise - Weibull	Parametric - Gompertz	-£126
10% discount for everolimus in the combination			-£25,360
20% discount for everolimus in the combination			-£50,593
30% discount for everolimus in the combination			-£75,826
40% discount for everolimus in the combination			-£101,060
50% discount for everolimus in the combination			-£126,293
60% discount for everolimus in the combination			-£151,526
70% discount for everolimus in the combination			-£176,760
OS Extrapolation model	Piecewise - Weibull	Individual - Weibull	£1,303
10% discount for everolimus in the combination			-£19,335
20% discount for everolimus in the combination			-£39,974

Parameter	Base case	Scenario	ICER
30% discount for everolimus in the combination			-£60,613
40% discount for everolimus in the combination			-£81,251
50% discount for everolimus in the combination			-£101,890
60% discount for everolimus in the combination			-£122,529
70% discount for everolimus in the combination			-£143,167
PFS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£1,400
10% discount for everolimus in the combination			-£18,163
20% discount for everolimus in the combination			-£37,726
30% discount for everolimus in the combination			-£57,289
40% discount for everolimus in the combination			-£76,852
50% discount for everolimus in the combination			-£96,415
60% discount for everolimus in the combination			-£115,977
70% discount for everolimus in the combination			-£135,540
PFS Extrapolation model	Piecewise - Weibull	Parametric - Weibull	£2,452
10% discount for everolimus in the combination			-£16,536
20% discount for everolimus in the combination			-£35,524
30% discount for everolimus in the combination			-£54,511
40% discount for everolimus in the combination			-£73,499
50% discount for everolimus in the combination			-£92,487
60% discount for everolimus in the combination			-£111,475
70% discount for everolimus in the combination			-£130,463
PFS Extrapolation model	Piecewise - Weibull	Individual - Gompertz	£1,112
10% discount for everolimus in the combination			-£18,593
20% discount for everolimus in the combination			-£38,297
30% discount for everolimus in the combination			-£58,002
40% discount for everolimus in the combination			-£77,707
50% discount for everolimus in the combination			-£97,412
60% discount for everolimus in the combination			-£117,117
70% discount for everolimus in the combination			-£136,822
Utility values	Axis Study	Vignette Study	£1,390
10% discount for everolimus in the combination			-£14,651
20% discount for everolimus in the combination			-£30,692
30% discount for everolimus in the combination			-£46,733
40% discount for everolimus in the combination			-£62,774

Parameter	Base case	Scenario	ICER
50% discount for everolimus in the combination			-£78,815
60% discount for everolimus in the combination			-£94,856
70% discount for everolimus in the combination			-£110,897
Everolimus Price	List Price	Generic (capecitabine as proxy)	-£163,376
10% discount for everolimus in the combination			-£166,289
20% discount for everolimus in the combination			-£169,202
30% discount for everolimus in the combination			-£172,115
40% discount for everolimus in the combination			-£175,028
50% discount for everolimus in the combination			-£177,940
60% discount for everolimus in the combination			-£180,853
70% discount for everolimus in the combination			-£183,766

Figure 116 LEN+EVE vs Nivolumab

Parameter	Base case	Scenario	ICER
Treatment Duration	Clinical trial data	Switch at progression	£66,757
10% discount for everolimus in the combination			£53,597
20% discount for everolimus in the combination			£40,437
30% discount for everolimus in the combination			£27,277
40% discount for everolimus in the combination			£14,116
50% discount for everolimus in the combination			£956
60% discount for everolimus in the combination			-£12,204
70% discount for everolimus in the combination			-£25,364
Discount rate	3.5%	0%	£17,907
10% discount for everolimus in the combination			£7,506
20% discount for everolimus in the combination			-£2,895
30% discount for everolimus in the combination			-£13,297
40% discount for everolimus in the combination			-£23,698
50% discount for everolimus in the combination			-£34,100
60% discount for everolimus in the combination			-£44,501
70% discount for everolimus in the combination			-£54,902
Discount rate	3.5%	5%	£16,787
10% discount for everolimus in the combination			£5,145
20% discount for everolimus in the combination			-£6,496
30% discount for everolimus in the combination			-£18,138

Parameter	Base case	Scenario	ICER
40% discount for everolimus in the combination			-£29,779
50% discount for everolimus in the combination			-£41,421
60% discount for everolimus in the combination			-£53,062
70% discount for everolimus in the combination			-£64,704
OS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£19,379
10% discount for everolimus in the combination			£5,440
20% discount for everolimus in the combination			-£8,500
30% discount for everolimus in the combination			-£22,440
40% discount for everolimus in the combination			-£36,380
50% discount for everolimus in the combination			-£50,320
60% discount for everolimus in the combination			-£64,259
70% discount for everolimus in the combination			-£78,199
OS Extrapolation model	Piecewise - Weibull	Parametric - Gompertz	£19,906
10% discount for everolimus in the combination			£5,336
20% discount for everolimus in the combination			-£9,234
30% discount for everolimus in the combination			-£23,804
40% discount for everolimus in the combination			-£38,374
50% discount for everolimus in the combination			-£52,944
60% discount for everolimus in the combination			-£67,515
70% discount for everolimus in the combination			-£82,085
OS Extrapolation model	Piecewise - Weibull	Individual - Weibull	£17,755
10% discount for everolimus in the combination			£5,758
20% discount for everolimus in the combination			-£6,239
30% discount for everolimus in the combination			-£18,236
40% discount for everolimus in the combination			-£30,233
50% discount for everolimus in the combination			-£42,231
60% discount for everolimus in the combination			-£54,228
70% discount for everolimus in the combination			-£66,225
PFS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£17,034
10% discount for everolimus in the combination			£5,706
20% discount for everolimus in the combination			-£5,621
30% discount for everolimus in the combination			-£16,949
40% discount for everolimus in the combination			-£28,277
50% discount for everolimus in the combination			-£39,604

Parameter	Base case	Scenario	ICER
60% discount for everolimus in the combination			-£50,932
70% discount for everolimus in the combination			-£62,260
PFS Extrapolation model	Piecewise - Weibull	Parametric - Weibull	£17,012
10% discount for everolimus in the combination			£5,959
20% discount for everolimus in the combination			-£5,094
30% discount for everolimus in the combination			-£16,147
40% discount for everolimus in the combination			-£27,200
50% discount for everolimus in the combination			-£38,252
60% discount for everolimus in the combination			-£49,305
70% discount for everolimus in the combination			-£60,358
PFS Extrapolation model	Piecewise - Weibull	Individual - Gompertz	£16,976
10% discount for everolimus in the combination			£5,568
20% discount for everolimus in the combination			-£5,841
30% discount for everolimus in the combination			-£17,249
40% discount for everolimus in the combination			-£28,657
50% discount for everolimus in the combination			-£40,066
60% discount for everolimus in the combination			-£51,474
70% discount for everolimus in the combination			-£62,883
Utility values	Axis Study	Vignette Study	£13,464
10% discount for everolimus in the combination			£4,615
20% discount for everolimus in the combination			-£4,234
30% discount for everolimus in the combination			-£13,083
40% discount for everolimus in the combination			-£21,932
50% discount for everolimus in the combination			-£30,781
60% discount for everolimus in the combination			-£39,629
70% discount for everolimus in the combination			-£48,478
Everolimus Price	List Price	Generic (capecitabine as proxy)	-£78,638
10% discount for everolimus in the combination			-£80,329
20% discount for everolimus in the combination			-£82,019
30% discount for everolimus in the combination			-£83,709
40% discount for everolimus in the combination			-£85,400
50% discount for everolimus in the combination			-£87,090
60% discount for everolimus in the combination			-£88,780

Parameter	Base case	Scenario	ICER
70% discount for everolimus in the combination			-£90,471

Figure 117 LEN+EVE vs Everolimus

Parameter	Base case	Scenario	ICER
Treatment Duration	Clinical trial data	Switch at progression	£99,272
10% discount for everolimus in the combination			£91,806
20% discount for everolimus in the combination			£84,340
30% discount for everolimus in the combination			£76,874
40% discount for everolimus in the combination			£69,408
50% discount for everolimus in the combination			£61,941
60% discount for everolimus in the combination			£54,475
70% discount for everolimus in the combination			£47,009
Discount rate	3.5%	0%	£91,680
10% discount for everolimus in the combination			£85,666
20% discount for everolimus in the combination			£79,651
30% discount for everolimus in the combination			£73,636
40% discount for everolimus in the combination			£67,621
50% discount for everolimus in the combination			£61,606
60% discount for everolimus in the combination			£55,592
70% discount for everolimus in the combination			£49,577
Discount rate	3.5%	5%	£98,393
10% discount for everolimus in the combination			£91,796
20% discount for everolimus in the combination			£85,198
30% discount for everolimus in the combination			£78,601
40% discount for everolimus in the combination			£72,004
50% discount for everolimus in the combination			£65,407
60% discount for everolimus in the combination			£58,810
70% discount for everolimus in the combination			£52,213
OS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£111,672
10% discount for everolimus in the combination			£104,142
20% discount for everolimus in the combination			£96,612
30% discount for everolimus in the combination			£89,083
40% discount for everolimus in the combination			£81,553
50% discount for everolimus in the combination			£74,023
60% discount for everolimus in the combination			£66,494

Parameter	Base case	Scenario	ICER
70% discount for everolimus in the combination			£58,964
OS Extrapolation model	Piecewise - Weibull	Parametric - Gompertz	£105,146
10% discount for everolimus in the combination			£98,089
20% discount for everolimus in the combination			£91,032
30% discount for everolimus in the combination			£83,975
40% discount for everolimus in the combination			£76,918
50% discount for everolimus in the combination			£69,861
60% discount for everolimus in the combination			£62,804
70% discount for everolimus in the combination			£55,747
OS Extrapolation model	Piecewise - Weibull	Individual - Weibull	£81,569
10% discount for everolimus in the combination			£76,220
20% discount for everolimus in the combination			£70,871
30% discount for everolimus in the combination			£65,522
40% discount for everolimus in the combination			£60,172
50% discount for everolimus in the combination			£54,823
60% discount for everolimus in the combination			£49,474
70% discount for everolimus in the combination			£44,125
PFS Extrapolation model	Piecewise - Weibull	Piecewise - Gompertz	£96,579
10% discount for everolimus in the combination			£90,136
20% discount for everolimus in the combination			£83,693
30% discount for everolimus in the combination			£77,250
40% discount for everolimus in the combination			£70,807
50% discount for everolimus in the combination			£64,364
60% discount for everolimus in the combination			£57,921
70% discount for everolimus in the combination			£51,478
PFS Extrapolation model	Piecewise - Weibull	Parametric - Weibull	£96,485
10% discount for everolimus in the combination			£90,076
20% discount for everolimus in the combination			£83,667
30% discount for everolimus in the combination			£77,258
40% discount for everolimus in the combination			£70,849
50% discount for everolimus in the combination			£64,440
60% discount for everolimus in the combination			£58,031
70% discount for everolimus in the combination			£51,622
PFS Extrapolation model	Piecewise - Weibull	Individual - Gompertz	£97,277

Parameter	Base case	Scenario	ICER
10% discount for everolimus in the combination			£90,784
20% discount for everolimus in the combination			£84,291
30% discount for everolimus in the combination			£77,798
40% discount for everolimus in the combination			£71,305
50% discount for everolimus in the combination			£64,813
60% discount for everolimus in the combination			£58,320
70% discount for everolimus in the combination			£51,827
Utility values	Axis Study	Vignette Study	£98,199
10% discount for everolimus in the combination			£91,656
20% discount for everolimus in the combination			£85,113
30% discount for everolimus in the combination			£78,569
40% discount for everolimus in the combination			£72,026
50% discount for everolimus in the combination			£65,483
60% discount for everolimus in the combination			£58,939
70% discount for everolimus in the combination			£52,396
Everolimus Price	List Price	Generic (capecitabine as proxy)	£101,559
10% discount for everolimus in the combination			£100,596
20% discount for everolimus in the combination			£99,632
30% discount for everolimus in the combination			£98,669
40% discount for everolimus in the combination			£97,705
50% discount for everolimus in the combination			£96,741
60% discount for everolimus in the combination			£95,778
70% discount for everolimus in the combination			£94,814

5.9 Subgroup analysis

No subgroup analyses were performed

5.10 Validation

Validation of de novo cost-effectiveness analysis

Validation of the extrapolation: For the extrapolation, the Tremblay et al (Tremblay, 2015) decision making criteria have been used, which led to the selection of piecewise models for and PFS. As described in Section 5.3, the Tremblay et al, 2015 decision making criteria are based on the NICE DSU 14 on survival extrapolations (Latimer, 2011). An external validation was not performed.

Validation of the costs: As described in Section 5.5, in order to reflect recent NICE guidance in this patient population, the costs inputs were predominantly based on the previous NICE STA submission for axitinib, TA333 (National Institute for Health and Care Excellence, NICE, 2015), in line with feedback received during the NICE submissions for nivolumab (National Institute for Health and Care Excellence, NICE, 2016) and cabozantinib (National Institute for Health and Care Excellence, NICE, 2017). The most recent 2015-2016 NHS reference costs are utilised. In addition, the costs were validated by 8 NHS England and Wales practising clinical experts.

External validation of the utility and disutility: As described in Section 5.4, the utility values used in the basecase were in line with recent draft NICE committee recommendations during the review of cabonzatinib (GID-TA10075) and were the same as those used in the axitinib NICE submission from the AXIS study. The utility and disutility values were also validated by 8 NHS England and Wales practising clinical experts.

External validation of the Adverse events prevalence and costs: The AE costs were based on a HRG/DRG approach. The HRG approach is in line with the NICE guidelines. The AEs with validated by 8 NHS England and Wales practising clinical experts.

Quality control: The quality control was performed both by Eisai internal HEOR experts and an external health economist.

5.11 Interpretation and conclusions of economic evidence

Overall, the economic evaluation of lenvatinib in combination with everolimus was conducted according to all the NICE technical and clinical guidelines. The methods and data used to analyse the cost effectiveness of the combination for previously treated, advanced RCC patients are believed to be the best available and are predominantly based on recent NICE assessments in this same indication.

The main weakness of the evaluation is the uncertainty around the relative treatment effects in the absence of direct head to head comparisons. In addition, it is not possible to provide true estimations of the cost effectiveness of LEN+EVE in the absence of information on the PAS price of everolimus.

6 Assessment of factors relevant to the NHS and other parties

The number of cases of kidney cancer was estimated by applying an annual incidence rate (CancerResearchUK, 2017c) to the population of England and Wales estimating the incidence of kidney cancer to be 11,713. The incidence for the following years was assumed to increase in line with population annual growth rates ((ONS, 2017)) of 0.71%.

Of these 11,713 patients with kidney cancer, it is estimated that 86% (10,074 patients) will have renal cell carcinoma (CancerResearchUK, 2017d)) and 25% (2,519 patients) of these patients will have metastatic or advanced disease (CancerResearcUK, 2017e).

Further estimations of number of metastatic RCC patients who would receive second-line treatment are taken from the the RCC treatment architecture report developed by Kantar Health (CancerMPact, 2015), giving a total

A summary of the total eligible patients for each year of the budget impact model is given in Figure 118.

Figure 118 Total eligible patients

Patient Flow	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Selected population	57,415,704	57,823,355	58,233,901	58,647,362	59,063,758	59,483,111
Incidence of kidney cancer	11,713	11,797	11,881	11,966	12,051	12,137
Renal Cell Carcinoma (RCC) patients	10,074	10,146	10,219	10,292	10,366	10,440
Metastatic RCC (mRCC) patients	2,519	2,537	2,556	2,575	2,594	2,613
First line - Patients Systemically treated for mRCC	2,003	2,018	2,033	2,048	2,063	2,078
Second line - Patients Systematically treatment for mRCC	990	998	1,006	1,014	1,022	1,030

The split of comparator treatments received by each patient is taken from an updated RCC treatment architecture report developed by Kantar Health (CancerMPact, 2016) and is given in Figure 119.

Figure 119 Baseline Market share estimates

Drug	Baseline market share
Axitinib	[redacted]
Cabozantinib	[redacted]
Everolimus	[redacted]
Nivolumab	[redacted]

If the lenvatinib and everolimus combination becomes available, it is anticipated that [redacted]% of eligible patients will be treated with the combination in year 1. This is based on internal market share assumptions. This is predicted to increase to [redacted]% in year 2, followed by [redacted]% in year 3, [redacted]% in year 4 and [redacted]% in year 5. The market share for 'Other' treatment was redistributed amongst other treatments proportional to the size of their baseline market share.

Figure 120 Estimated Patient numbers

Drug	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Patient number estimates of current care						
Axitinib	379	382	385	388	391	394
Cabozantinib	13	14	14	14	14	14
Everolimus	446	449	453	457	460	464
Nivolumab	152	154	155	156	157	158
Total	**990**	**998**	**1006**	**1014**	**1022**	**1030**
Patient number estimates if lenvatinib and everolimus combination becomes available						
Lenvatinib and everolimus combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[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]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The drug costs (acquisition and administration costs of treatment), medical costs (ie resource utilisation costs) and adverse event costs were added together to give the total treatment cost for patients. Units are described in more detail in Section 5.5.

Treatment duration for each therapy, as described in Section 5.2 is also incorporated into the budget impact calculations.

Figure 121 shows the expected incremental budget impact of the lenvatinib and everolimus combination at list price. In year 1 the budget impact is expected to be 1.33 million pounds rising to 4.11 in year 5

Figure 121 Incremental budget impact (in million pounds)

Drug	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical costs	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events costs	0.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Incremental costs	**0.00**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Incremental budget	**0.0%**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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8 Appendices

8.1 Summary of product characteristics

8.2 European Medicines Agency. Kisplyx Assessment Report. Procedure Nº EMEA/H/C/004224/0000

8.3 Systematic literature Review

8.4 Study 205 protocol

8.5 Indirect treatment comparison report

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Level 1A
City Tower
Manchester
M1 4BT
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Single Technology Appraisal

Lenvatinib in combination with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Dear Easai Ltd,

The Evidence Review Group, the BMJ Technology Assessment Group, and the technical team at NICE have looked at the submission received on 31 March 2017 from Eisai. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on Thursday 11 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk)

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

A1. **Priority question**. Please test and provide results for the proportional hazards assumption for PFS and OS between lenvatinib + everolimus and everolimus monotherapy in HOPE 205.

A2. **Priority question**. Please justify the choice of indirect treatment comparison (ITC) method used in the company submission (CS) in light of the proportional hazards assumption not holding within all trials in the network, as indicated in the assessment of proportional hazards in the CS for the cabozantinib STA (GID-TA10075 committee papers ACD1, CS pages 89-90, Table 32, and Appendix 10).

A3. **Priority question**. As the proportional hazards assumption does not seem to hold within all trials in the network please re-assess PFS and OS in the ITC using alternative methods which do not rely on proportional hazards, e.g. as described by Ouwens et al. 2010 or Jansen et al. 2011 in GID-TA10075 (AC1 committee papers, CS Section 4.10.4, pages 91-93, and AC2 committee papers, company response Section 1, pages 6-8.1, 2).

- Based on the uncertainty within the network connecting axitinib to lenvatinib + everolimus, please consider assuming that axitinib has a similar efficacy to everolimus monotherapy for all outcomes when re-analysing the ITC; an assumption that has been accepted by the assessment committee for both the nivolumab (TA417, ACD1) and cabozantinib (GID-TA10075, ACD1) STAs.
- Please use independently assessed data for all trials where this is available (all trials except CheckMate 025) irrespective of main analysis reported in trial. For CheckMate 025 please use the investigator assessed outcome data.
- Please also use the full trial population rather than the subgroup of patients with one prior TKI from METEOR, and CheckMate 025 (and from RECORD-1 if using full network), as was done in the CS.
- If you decide not to assume similar efficacy of axitinib and everolimus, and therefore the network will still include RECORD-1, TARGET and AXIS, please use:
    - the subgroup of AXIS who have had prior sunitinib and
    - RPSFT crossover adjusted data for RECORD-1 and placebo-censored data for TARGET, as was done in the CS.

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A4. Please provide additional information regarding the FDA's request for re-stratification in the OS and PFS cox model calculation. What changes did the FDA request in the calculation of stratification variables and how did this affect the outcome data? Please also provide references in support of the information in addition to the Full Prescribing Information - Reference ID: 3931091, FDA 2015 mentioned in the CS.

A5. Please add information to the baseline demographic characteristics on country for each treatment group in HOPE 205.

A6. Please provide baseline demographic and disease characteristics of the subgroup of participants from UK sites in HOPE 205.

A7. Please provide outcome data for the subgroup of participants from UK sites in HOPE 205 for PFS, OS, and tumour response.

A8. Please provide results for each step in the multi-step ITC for PFS, OS, and ORR.

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. **Priority question.** Please provide the individual patient data (time, event and treatment arm) used to generate Kaplan-Meier (KM) plots, for overall survival (OS), progression-free survival (PFS), and time to treatment discontinuation (TTD) as a comma-separated file for the third EMA data cut (31st July 2015) of the HOPE 205 trial.

B2. **Priority question.** Please provide the KM data along with the number of patients at risk for OS, PFS and TTD as a comma-separated file for the third EMA data cut (31st July 2015) of the HOPE 205 trial.

B3. **Priority question.** Please fit dependent and independent parametric survival curves for TTD for the relevant arms of the HOPE 205 trial, using the same selection of distributions as for PFS and OS, and determine which the best fitting model is.

B4. **Priority question.** Please estimate TTD curves for axitinib, cabozantinib and nivolumab by using digitised KM data from relevant publications to fit independent parametric survival curves. Refer to the cabozantinib TA (GID -TA10075) committee papers below for reference to the relevant KM plots.

- Nivolumab TTD KM plot: ACD1 (6th March 2017), Figure 27, page 34.
- Cabozantinib TTD KM plot: Committee papers (6th March 2017), Figure 32, page 68.

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- Note that axitinib TTD plots were not identified by the Company in TA10075 so treatment until progression was assumed.

B5. **Priority question.** Please provide a scenario analysis where time on treatment is based on the curves derived from the response to questions B3 and B4.

B6. **Priority question.** Please provide individual plots for each type of parametric model considered in Section 5.3 of the CS (both dependent and independent), showing the fitted curves for the two relevant treatment groups of the HOPE 205 trial, superimposed onto Kaplan-Meier plots for OS, PFS and TTD.

B7. **Priority question.** When using the Weibull model to fit curves to the HOPE 205 trial groups for PFS (either dependently or independently fitted), the resulting everolimus curve has a lower hazard than the nivolumab curve derived from applying the ITC HR to the lenvatinib combination group curve. This contradicts the results of the ITC. Please use a consistent approach to derive each of the comparator survival curves to ensure relative treatment effects are not estimated using different underlying survival models, as this can cause inaccuracies.

B8. The log-cumulative hazard plots in Figures 66, 67, 73 and 74 show one arm labelled as placebo. Please clarify the treatment arms shown in these plots. Also, please clarify the treatment arms used in the plot in Figures 65 and 72.

PSA parameters

B9. Please justify the use of the log-normal distribution in the PSA for the PFS HR, when the HR for OS uses the normal distribution.

B10. Please clarify why the random number used to make the PFS HR probabilistic is dependent on the random number used for the OS HR. Please explain the value of 0.4579 used to weight the OS value.

B11. Please justify why some parameters, in particular utilities, are not varied in the economic model.

Model corrections

B12. The treatment duration of LEN+EVE in the PSA is multiplied by an unconstrained sampled ratio and therefore results in proportions of patients on treatment greater than 1 in some cases. Please correct this error.

B13. The treatment duration for the comparator treatments is not varied in the PSA. Please correct this error.

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B14. The acquisition cost for everolimus in the monotherapy arm is estimated in the economic model by multiplying the cost of a 5 mg tablet by 2 instead of applying the cost of 10 mg tablet, which has a lower cost. Please apply the cost of the 10 mg tablet for the everolimus monotherapy in the economic model.

B15. The calculation used for QALYs implies that all patients who are on treatment have a utility associated with pre-progression. Please amend the calculation to account for a decreased utility for patients who remain on treatment but with progressed disease.

B16. A half-cycle correction appears to have been applied to life-years twice in the 'Appendix Transition'! sheet of the model. The first time in cells K22:M261 and then again in cells AA21:AC261. Please correct this for all the comparators.

Additional analyses

B17. Please carry out a scenario analysis including the costs of subsequent therapies currently available on the NHS as treatments for RCC at any line. Please do this for all the comparators based on what patients received in their respective trials.

B18. Please carry out a scenario analysis similar to that used in TA417 (see committee papers – slide 25) where it was assumed that 50% of patients on nivolumab had a mortality rate equal to the general population after year 5.

B19. Please carry out a scenario analysis similar to that used in TA417 (see committee papers – slide 22) where it was assumed that nivolumab had a utility benefit over everolimus.

Literature searching

B20. Four studies reporting economic evaluations were identified and excluded in the systematic literature review for randomised clinical trials, but were not identified in the search for economic evaluations. This refers to study numbers 527,764, 765 and 766 in Table 6.1.1 of Appendix 8.3. Please clarify why these studies were not identified in the economic search.

B21. Please clarify why the systematic literature search for cost-effectiveness studies was restricted to studies published from 2005 onwards?

Other

B22. The dose reductions used in Figure 94 on page 160 for cabozantinib, axitinib and nivolumab do not match the values reported in their respective technology appraisals (i.e. TA333, TA417, and GID-TA10075). Please clarify how the dose reductions were estimated for each comparator treatment.

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B23. Please clarify why an administration cost associated with oral therapies has been assumed, given that oral therapies are self-administered at home by the patient (lenvatinib, everolimus, axitinib and cabozantinib).

B24. Please clarify the inclusion criteria for adverse events in the economic model, as they are only a subset of those presented in Figure 49 of the CS.

Section C: Textual clarifications and additional points

C1. Please confirm which data cut-off was used for subsequent therapies received in each treatment group in HOPE 205. If these data are from an earlier data cut-off, then please provide these data for the July 2015 data cut.

C2. Please confirm the numbers for the inclusion/exclusion of citations at each stage in the systematic literature review of clinical studies as there are several discrepancies within and between the PRISMA diagram in the main CS (Figure 13) and in Appendix 8.3 (Figure 3.1.1) including assessments based on title and abstract and full text appraisal.

C3. Please explain the contradictory result for the updated OS analysis (data cut 31 Jul 2015) for which the 95% confidence interval indicates a statistically significant difference (HR: 0.59; 95% CI 0.36-0.97) whereas the p-value does not (P=0.065).

C4. Please confirm the data cut-off date for the PFS results presented in the CS.

C5. Please confirm the PFS completion rate at the July 2015 data cut-off in Figure 29 which seems to be lower than at the earlier data cut-off of December 2014.

C6. Please confirm the number of patients who discontinued treatment for disease progression, adverse events or patient's choice in each treatment group in Figure 19 as these don't add up to the total number of patients discontinuing treatment in each arm.

C7. Please provide a reference for the proportion of m/aRCC expected to receive first line therapy (CS, Section 6).

C8. Please confirm if duration of prior VEGF-targeted therapy in Figure 21 are reported as mean or median.

C9. The economic model labels the "third data cut" as 2016. Please clarify if this is the 31 July 2015 data cut as specified in the CS.

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C10. The results of the probabilistic sensitivity analysis in the model are very different to those results reported on page 174 of the CS. Please clarify whether the results given in the CS are correct.

C11. The utility values measured in the AXIS trial are not provided in the reference stated (Rini *et al.* 2011). Please clarify the reference for these utility values.

C12. Please clarify whether Table 30 in the Clinical Study Report (E7080-G000-205) gives the numbers of treatment-emergent adverse events or treatment-related adverse events. The table header uses both terms.

References

1. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1(3-4):258-71.
2. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.

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The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on Thursday 11 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk)

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

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Section A: Clarification on effectiveness data

A1. **Priority question**. Please test and provide results for the proportional hazards assumption for PFS and OS between lenvatinib + everolimus and everolimus monotherapy in HOPE 205.

The results of the proportional hazard assumption testing for both PFS and OS between lenvatinib + everolimus and everolimus monotherapy in HOPE 205 were provided in the company submission (CS). This was conducted on the ITT population from the study.

For OS, this information is provided on pages 117-118, where treatment 0 refers to everolimus monotherapy and treatment 1 refers to lenvatinib + everolimus. For PFS, the information can be found on page 127, where treatment 0 refers to everolimus monotherapy and treatment 1 refers to lenvatinib + everolimus.

A2. **Priority question**. Please justify the choice of indirect treatment comparison (ITC) method used in the company submission (CS) in light of the proportional hazards assumption not holding within all trials in the network, as indicated in the assessment of proportional hazards in the CS for the cabozantinib STA (GID-TA10075 committee papers ACD1, CS pages 89-90, Table 32, and Appendix 10).

As stated on page 11 of Appendix 8.5 (ITC report), consistency across the trials included in the analysis was assessed by examining median PFS in patients treated with everolimus across the trials. Median PFS was higher in the primary analysis of HOPE 205 (5.5 months) than in the other three studies (3.8 to 4.4 months) which appears contrary to the larger proportion of patients with poorer risk and worse performance status in HOPE 205. This may be explained, at least in part, by the extent of prior therapy, with median PFS of 5.5 months in HOPE 205 being similar to that of the subgroup with one prior VEGF in RECORD-1 (5.4 months). Estimates of median PFS did not vary substantially by method of response assessment (HOPE 205: investigator 5.5 vs IRR 5.6 months; RECORD-1: investigator 4.6 vs IRR 4.0 months). Extent of prior therapy and method of response assessment did not substantially modify the hazard ratio estimates within the everolimus trials; and therefore indirect comparisons were conducted despite these potential differences in baseline risk.

Section 4.2 of the ITC report on page 19 describes the limitations to the interpretation of the analysis. It highlights that the assumption of constancy of the relative effect is violated which limits the validity of the ITC estimates.

The proportional hazards assumption was not formally tested as part of the submitted ITC analysis and this will be provided as part of the response to A3.

A3. **Priority question**. As the proportional hazards assumption does not seem to hold within all trials in the network please re-assess PFS and OS in the ITC using

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alternative methods which do not rely on proportional hazards, e.g. as described by Ouwens et al. 2010 or Jansen et al. 2011 in GID-TA10075 (AC1 committee papers, CS Section 4.10.4, pages 91-93, and AC2 committee papers, company response Section 1, pages 6-8.1, 2).

- Based on the uncertainty within the network connecting axitinib to lenvatinib + everolimus, please consider assuming that axitinib has a similar efficacy to everolimus monotherapy for all outcomes when re-analysing the ITC; an assumption that has been accepted by the assessment committee for both the nivolumab (TA417, ACD1) and cabozantinib (GID-TA10075, ACD1) STAs.
- Please use independently assessed data for all trials where this is available (all trials except CheckMate 025) irrespective of main analysis reported in trial. For CheckMate 025 please use the investigator assessed outcome data.
- Please also use the full trial population rather than the subgroup of patients with one prior TKI from METEOR, and CheckMate 025 (and from RECORD-1 if using full network), as was done in the CS.
- If you decide not to assume similar efficacy of axitinib and everolimus, and therefore the network will still include RECORD-1, TARGET and AXIS, please use:
    - the subgroup of AXIS who have had prior sunitinib and
    - RPSFT crossover adjusted data for RECORD-1 and placebo-censored data for TARGET, as was done in the CS.

Response to be provided separately by 5pm 22nd May, as agreed.

A4. Please provide additional information regarding the FDA's request for re-stratification in the OS and PFS cox model calculation. What changes did the FDA request in the calculation of stratification variables and how did this affect the outcome data? Please also provide references in support of the information in addition to the Full Prescribing Information - Reference ID: 3931091, FDA 2015 mentioned in the CS.

As stated on page 57 of the CS, the difference between the EMA and FDA data lies in the use of different stratification variables: the third cut IVRS (interactive voice recording system) dataset was used for the FDA while the third cut CRF (case report form) data was used for the EMA.

During the FDA's review of the regulatory dossier, they requested an alternative analysis of the efficacy results of the third datacut (31st July 2015). The FDA requested that, for the calculation of the HRs (hazard ratios) of PFS and OS, the stratification factors were based

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on the value in the IVRS system, instead of the actual CRF values as used in the original CSR (clinical study report) analysis. The FDA reasoned that the primary analysis of a registration trial had to follow the intent-to-treat principle and the IVRS stratification factor is considered to be ITT, regardless of what was pre-specified in the statistical analysis plan.

The table below provides information on the outcomes of the EMA and FDA analyses.

OS and PFS results from third datacut (31 July 2015): EMA and FDA analyses

	Lenvatinib + everolimus (n=51)	**Single-arm lenvatinib (n=52)**	**Single-arm everolimus (n=50)**
Progression-Free Survival[a]			
Events (n)	26 (51%)	38 (73%)	37 (74%9
PFS (months) Median (95% CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
Stratified Hazard Ratio (95% CI)			
EMA analysis vs single arm everolimus	0.40 (0.24, 0.68)		
FDA analysis vs single arm everolimus	0.37 (0.22, 0.62)		
Overall Survival[b]			
Deaths (n)	32 (62.7%)	34 (65.4%)	37 (74.0%)
OS (months) Median (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
Stratified Hazard Ratio (95% CI)			
EMA analysis vs single arm everolimus	0.59 (0.36, 0.96)		
FDA analysis vs single arm everolimus	0.67 (0.42, 1.08)		

Abbreviations: CI, Confidence interval; OS, Overall Survival; PFS, Progression-free survival
[a] Investigator assessment
[b] Data cutoff date: 31 July 2015
Source: CS and Lenvatinib Prescribing information Reference ID 3931091

As requested, a copy of the lenvatinib full Prescribing Information - Reference ID: 3931091 has been provided as a separate attachment.

A5. Please add information to the baseline demographic characteristics on country for each treatment group in HOPE 205.

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Please see the updated table on baseline demographic characteristics provided in the response to question A6 which now includes information on country for each treatment group in HOPE 205.

A6. Please provide baseline demographic and disease characteristics of the subgroup of participants from UK sites in HOPE 205.

Please find overleaf an amended version of Figure 20 from the CS, which includes baseline demographic and disease characteristics of the ITT population and the UK participants from the HOPE 205 study, as requested. The characteristics for the UK patients do not differ greatly from those of the ITT population.

The table also includes information on country for each treatment group in HOPE 205, as per question A5.

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Baseline demographic and disease characteristics of ITT population and UK participants in study E7080-G000-205

Baseline characteristic	ITT Population			UK Patients		
	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)	Lenvatinib + everolimus (n=17)	Single-arm lenvatinib (n=15)	Single-arm everolimus (n=18)
Country UK Czech Republic Poland Spain United States	 17 (33.3%) 13 (25.5%) 8 (15.7%) 8 (15.7%) 5 (9.8%)	 15 (28.8%) 5 (9.6%) 9 (17.3%) 6 (11.5%) 17 (32.7%)	 18 (36.0%) 5 (10.0%) 9 (18.0%) 4 (8.0%) 14 (28%)	N/A	N/A	N/A
Age (years)	61 (44–79)	64 (41–79)	59 (37–77)	66 (54- 74)	61 (41-76)	60 (39, 75)
Sex						
Men	35 (69%)	39 (75%)	38 (76%)	11 (65%)	10 (67%)	12 (67%)
Women	16 (31%)	13 (25%)	12 (24%)	6 (35%)	5 (33%)	6 (33%)
ECOG Performance status						
0	27 (53%)	29 (56%)	28 (56%)	10 (59%)	7 (47%)	10 (56%)
1	24 (47%)	23 (44%)	22 (44%)	7 (41%)	8 (53%)	8 (44%)
MSKCC risk group						
Favourable	12 (24%)	11 (21%)	12 (24%)	3 (18%)	1 (7%)	3 (17%)
Intermediate	19 (37%)	18 (35%)	19 (38%)	7 (41%)	4 (27%)	8 (44%)
Poor	20 (39%)	23 (44%)	19 (38%)	7 (41%)	10 (67%)	7 (39%)
Heng risk group*						
Favourable	8 (16%)	7 (14%)	9 (18%)	2 (12%)	1 (7%)	1 (6%)
Intermediate	32 (64%)	33 (64%)	29 (58%)	12 (71%)	10 (67%)	13 (72%)
Poor	10 (20%)	12 (23%)	12 (24%)	3 (18%)	4 (27%)	4 (22%)
Haemoglobin, n (%)						
≤130 g/L (men) or ≤115 g/L (women)	33 (65%)	36 (69%)	31 (62%)	13 (77%)	13 (87%)	11 (61%)

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Baseline characteristic	ITT Population			UK Patients		
>130 g/L (men) or >115 g/L (women)	18 (35%)	16 (31%)	19 (38%)	4 (24%)	2 (13%)	7 (39%)
Corrected serum calcium, n (%)						
≥2・5 mmol/L	6 (12%)	8 (15%)	8 (16%)	2 (12%)	5 (33%)	4 (22%)
<2・5 mmol/L	45 (88%)	44 (85%)	42 (84%)	15 (88%)	10 (67%)	14 (78%)
Number of metastases						
1	18 (35%)	9 (17%)	5 (10%)	8 (47%)	4 (27%)	2 (11%)
2	15 (29%)	15 (29%)	15 (30%)	5 (29%)	5 (33%)	7 (39%)
≥3	18 (35%)	28 (54%)	30 (60%)	4 (24%)	6 (40%)	9 (50%)
Sites of metastasis						
Bone	12 (24%)	13 (25%)	16 (32%)	4 (24%)	4 (27%)	7 (39%)
Liver	10 (20%)	14 (27%)	13 (26%)	5 (29%)	2 (13%)	4 (22%)
Lung	27 (53%)	35 (67%)	35 (70%)	8 (47%)	9 (60%)	11 (61%)
Lymph nodes	25 (49%)	31 (60%)	33 (66%)	7 (41%)	9 (60%)	9 (50%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Centre

Data are number of patients (%), or median (range). * One patient in the lenvatinib plus everolimus group was excluded because of missing baseline laboratory values.

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A7. Please provide outcome data for the subgroup of participants from UK sites in HOPE 205 for PFS, OS, and tumour response.

In HOPE 205, a third of the patients were from the UK which is more than any other country, as indicated in the table provided above in response to A6. In addition, as also indicated above, the baseline characteristics of the UK population do not differ greatly from those of the ITT population. Therefore, it would be expected that the outcome data for the ITT population is reflective of UK patients.

A8. Please provide results for each step in the multi-step ITC for PFS, OS, and ORR.

Please find the results for each step in the multi-step ITC for PFS and OS below. The results for each step in the multi-step ITC for ORR can be found in Table 3.4.2 on page 15 of Appendix 8.5 (ITC report).

PFS (Main analysis as reported by trial)
Lenvatinib+ Everolimus vs Everolimus: HR (95% CI) = 0.40 (0.24-0.68) (HOPE 205)
Everolimus vs Placebo: HR (95% CI) = 0.30 (0.22-0.4) (RECORD-1)
Placebo versus Sorafenib: HR (95% CI) = 2.27 (1.82-2.86) (TARGET)
Sorafenib versus Axitinib: HR (95% CI) = 1.50 (1.23-1.84) (AXIS)
Lenvatinib + Everolimus vs Axitinib: HR (95% CI) = [redacted]

OS (Latest data cut adjusting for cross-over)
Lenvatinib+ Everolimus vs Everolimus: HR (95% CI) = 0.59 (0.36-0.97) (HOPE 205)
Everolimus vs Placebo: HR (95% CI) = 0.60 (0.22-1.65) (RECORD-1)
Placebo versus Sorafenib: HR (95% CI) = 1.28 (1.03-1.61) (TARGET)
Sorafenib versus Axitinib: HR (95% CI) = 1.03 (0.85-1.25) (AXIS)
Lenvatinib + Everolimus vs Axitinib: HR (95% CI) = [redacted])

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Section B: Clarification on cost-effectiveness data

Survival analysis

B1. **Priority question.** Please provide the individual patient data (time, event and treatment arm) used to generate Kaplan-Meier (KM) plots, for overall survival (OS), progression-free survival (PFS), and time to treatment discontinuation (TTD) as a comma-separated file for the third EMA data cut (31st July 2015) of the HOPE 205 trial.

Please find attached the individual patient data (time, event and treatment arm) used to generate Kaplan-Meier (KM) plots, for overall survival (OS), progression-free survival (PFS), and time to treatment discontinuation (TTD) for the third EMA data cut (31st July 2015) of the HOPE 205 trial which have been provided as three separate comma-separated files.

B2. **Priority question.** Please provide the KM data along with the number of patients at risk for OS, PFS and TTD as a comma-separated file for the third EMA data cut (31st July 2015) of the HOPE 205 trial.

Please find attached the KM data along with the number of patients at risk for OS, PFS and TTD for the third EMA data cut (31st July 2015) of the HOPE 205 trial which have been provided as three separate comma-separated files.

B3. **Priority question.** Please fit dependent and independent parametric survival curves for TTD for the relevant arms of the HOPE 205 trial, using the same selection of distributions as for PFS and OS, and determine which the best fitting model is.

When the treatment duration data are incomplete, it is common to offer extrapolation options to generate the curve tail. In the case of this trial, a total of 4 patients were still on treatment at the end of the trial (only 2 of which were in the LEN+EVE arm). As the data are complete, it can be assumed that the Kaplan-Meier estimator would generate an appropriate estimate of treatment duration.

The limitation with applying standard extrapolation techniques when the data are complete is that there is a risk of creating a long tail that significantly overestimates the treatment duration. An option has been included in the revised model, presented as an additional scenario, in which the whole curve is extrapolated using a proportional hazard Weibull parametric model. The exponential curve offered the best AIC/BIC fit, in addition to a conservative estimate of the area under the curve.

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Model	Obs	ll(null)	ll(model)	df	AIC	BIC
LN	101	-154.8179	-151.5843	3	309.1686	317.014
LL	101	-157.3873	-154.0225	3	314.0451	321.8904
EXP	101	-156.0846	-152.0718	2	308.1436	313.3738
Gamma	101	-154.1357	-150.4137	4	308.8274	319.2879
Gompertz	101	-156.0794	-151.9535	3	309.9071	317.7524
Weibull	101	-156.0824	-151.8747	3	309.7494	317.5948

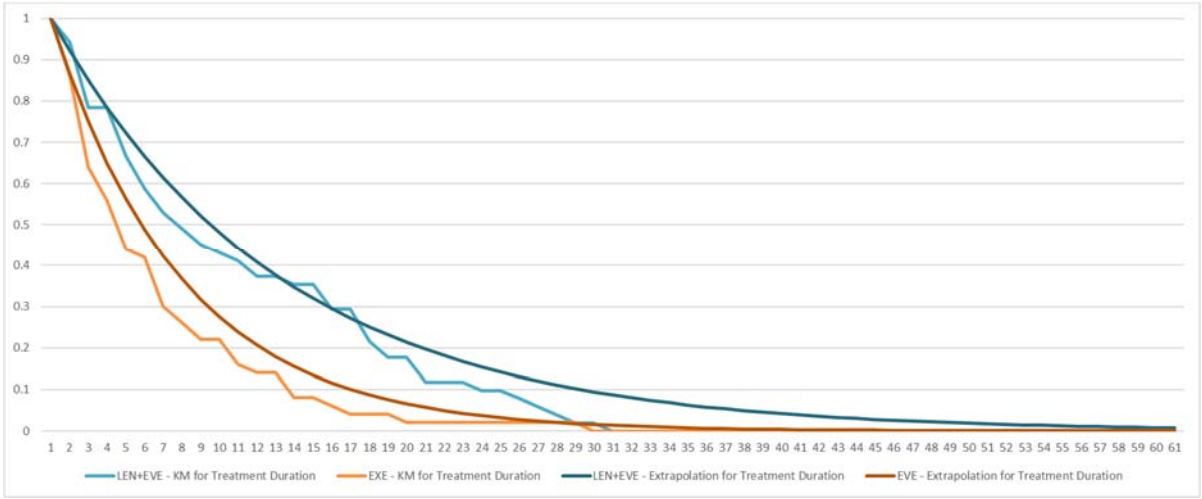
Note: N=Obs used in calculating BIC; see **[R] BIC note**.

The results of this scenario are presented in the following table

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	52,929	103,016	65,388	143,891

**Note: Includes modifications to EVE prices and removal of oral administration costs*

The following graph presents the fit of the extrapolation (exponential i.e. best fitting curve) to the actual Kaplan-Meier, showing the important overestimation of the extrapolated tail.



B4. **Priority question.** Please estimate TTD curves for axitinib, cabozantinib and nivolumab by using digitised KM data from relevant publications to fit independent parametric survival curves. Refer to the cabozantinib TA (GID -TA10075) committee papers below for reference to the relevant KM plots.

- Nivolumab TTD KM plot: ACD1 (6th March 2017), Figure 27, page 34.

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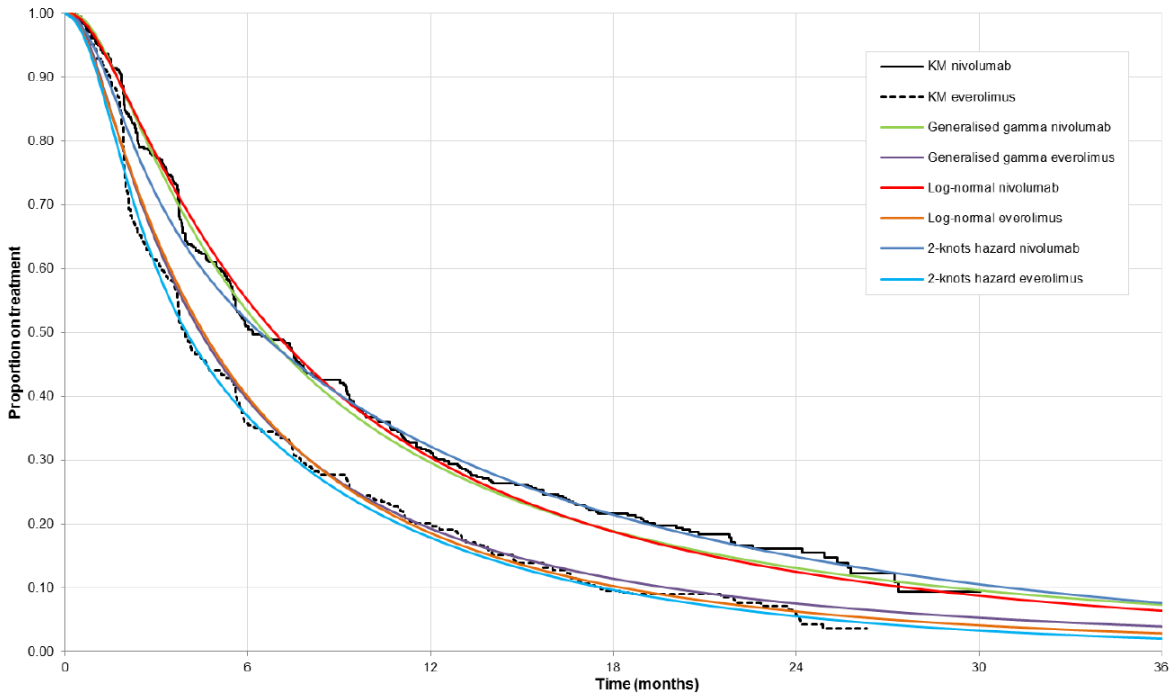
- Cabozantinib TTD KM plot: Committee papers (6th March 2017), Figure 32, page 68.
- Note that axitinib TTD plots were not identified by the Company in TA10075 so treatment until progression was assumed.

The treatment duration for cabozantinib and nivolumab was directly based on the digitisation of the respective Kaplan-Meier curves. To avoid having to generate more assumptions for the extrapolation of these curves, the extrapolation was also digitised. For axitinib, PFS was used as a proxy for treatment duration in the absence of TTD data.

Nivolumab TTD – ERG extrapolation: The generalised gamma curve was used. For data after month 36, an exponential tail was applied.

Figure 44. Model fits to CheckMate 025 TTD data



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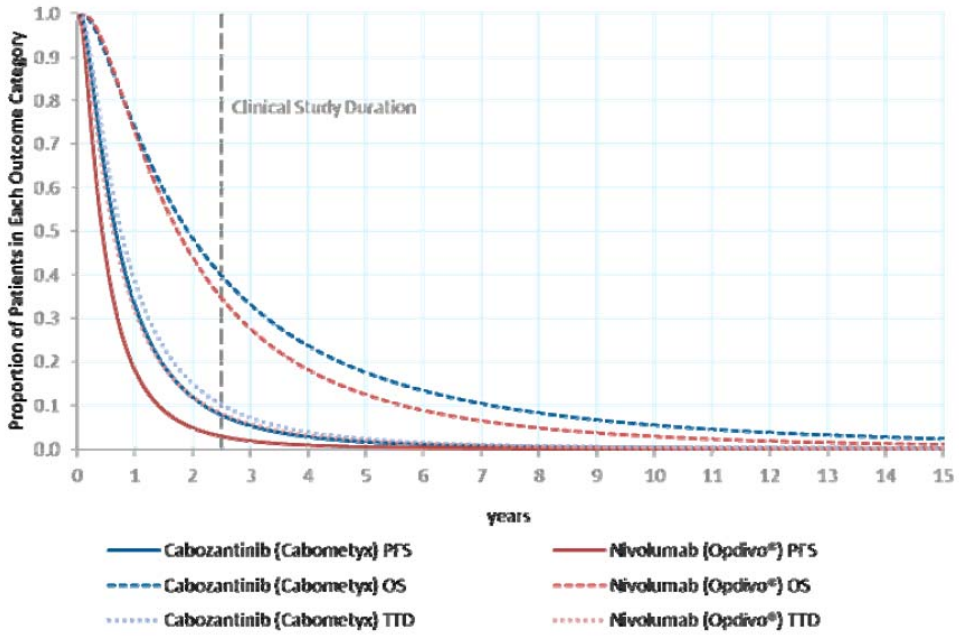
Cabozantinib TTD extrapolation



B5. **Priority question.** Please provide a scenario analysis where time on treatment is based on the curves derived from the response to questions B3 and B4.

An additional scenario was added to the revised model incorporating the time on treatment curves derived in B3 and B4 (cell G28 in model parameters).

The results of this scenario are presented in the following table

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	55,782	-113,160	-199,216	122,404

**Note: Includes modifications to EVE prices and removal of oral administration costs*

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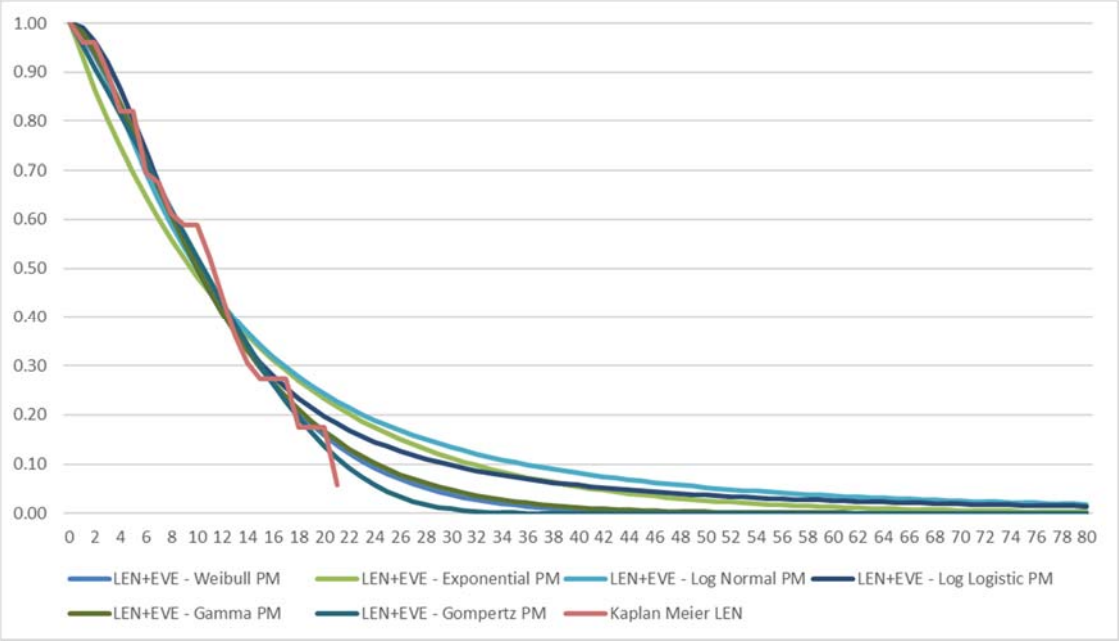
B6. **Priority question.** Please provide individual plots for each type of parametric model considered in Section 5.3 of the CS (both dependent and independent), showing the fitted curves for the two relevant treatment groups of the HOPE 205 trial, superimposed onto Kaplan-Meier plots for OS, PFS and TTD.

This option was added to the "Outcomes and Costs" sheet in the revised model, below line 88. The base-case is presented below.

LEN+EVE

PARAMETRIC PFS



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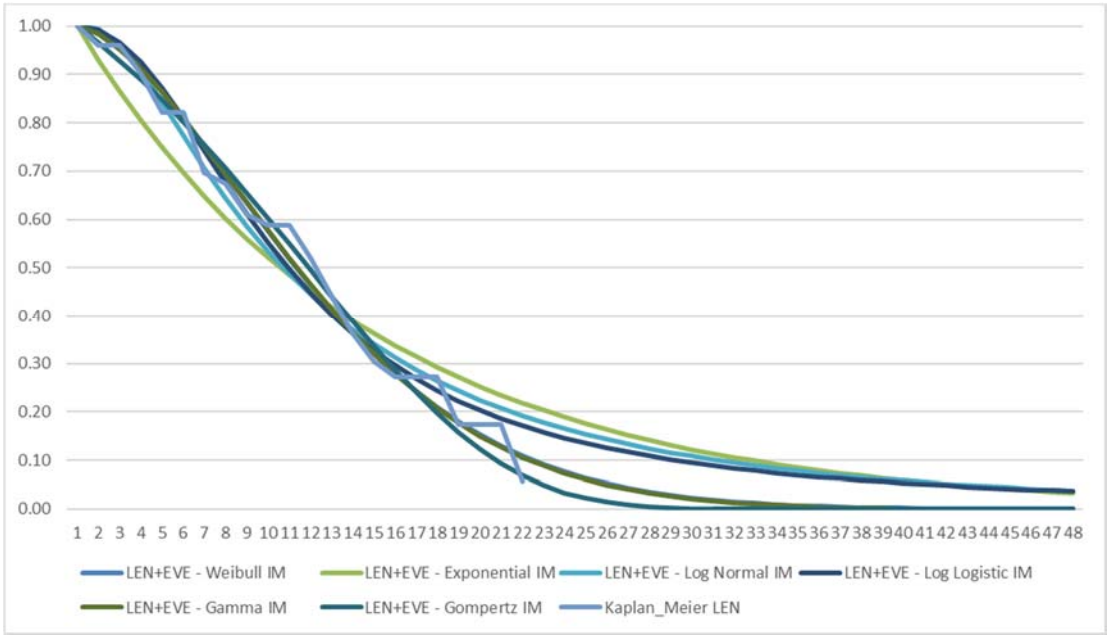
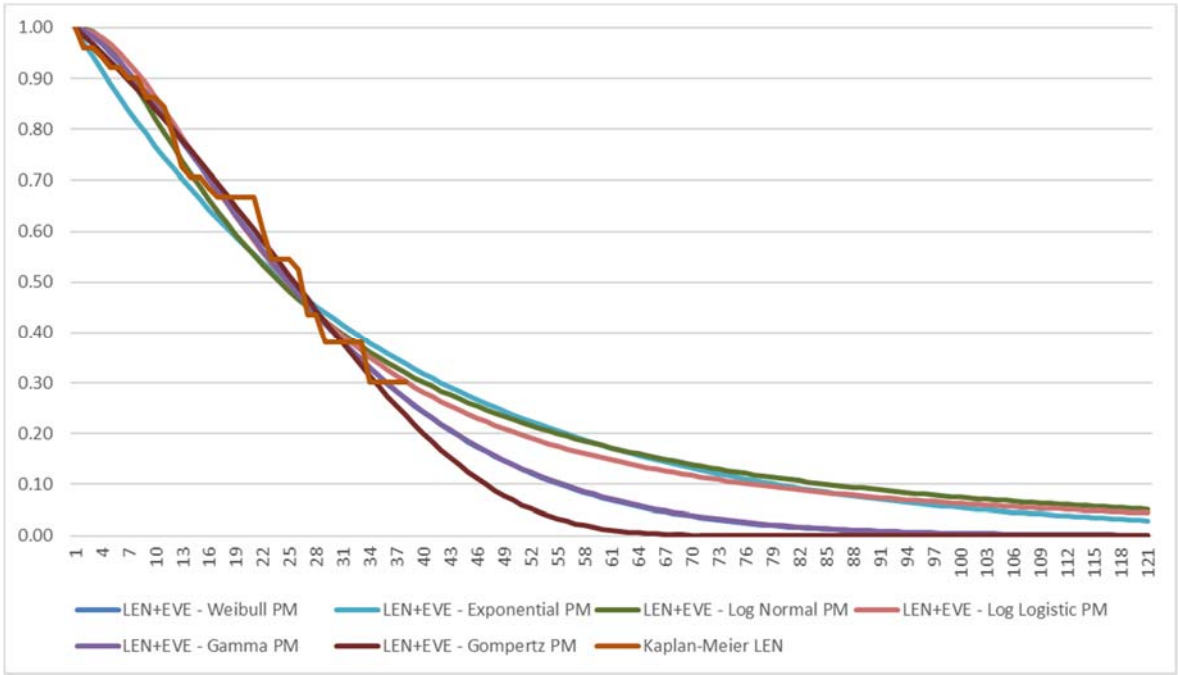
INDIVIDUAL PFS



PARAMETRIC OS



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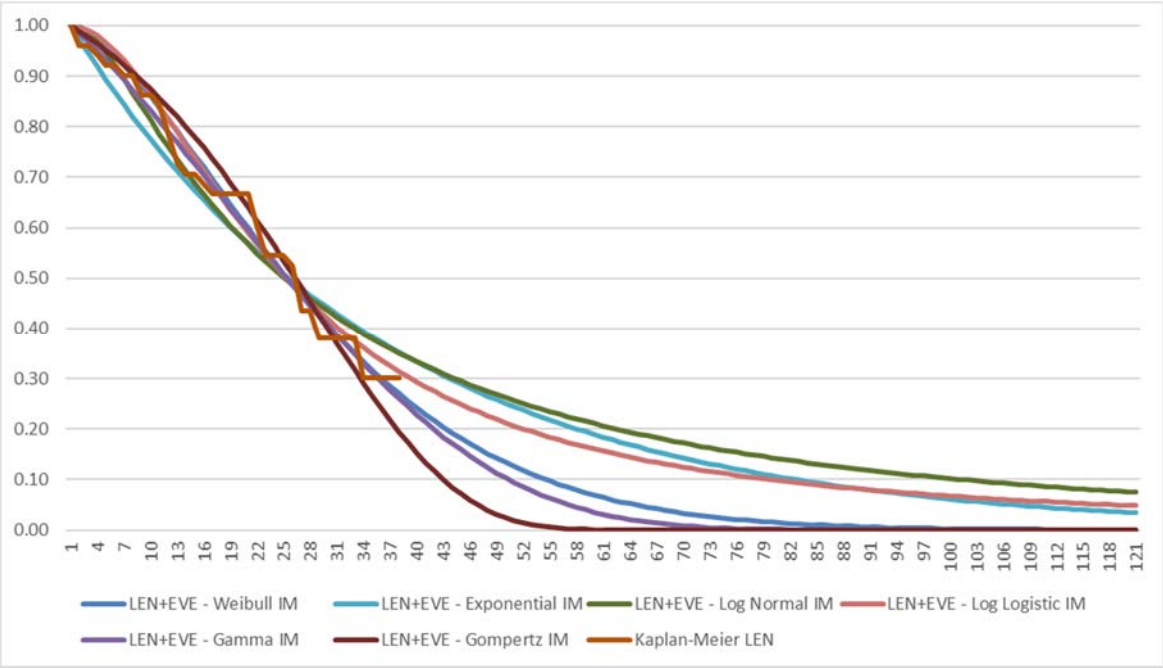
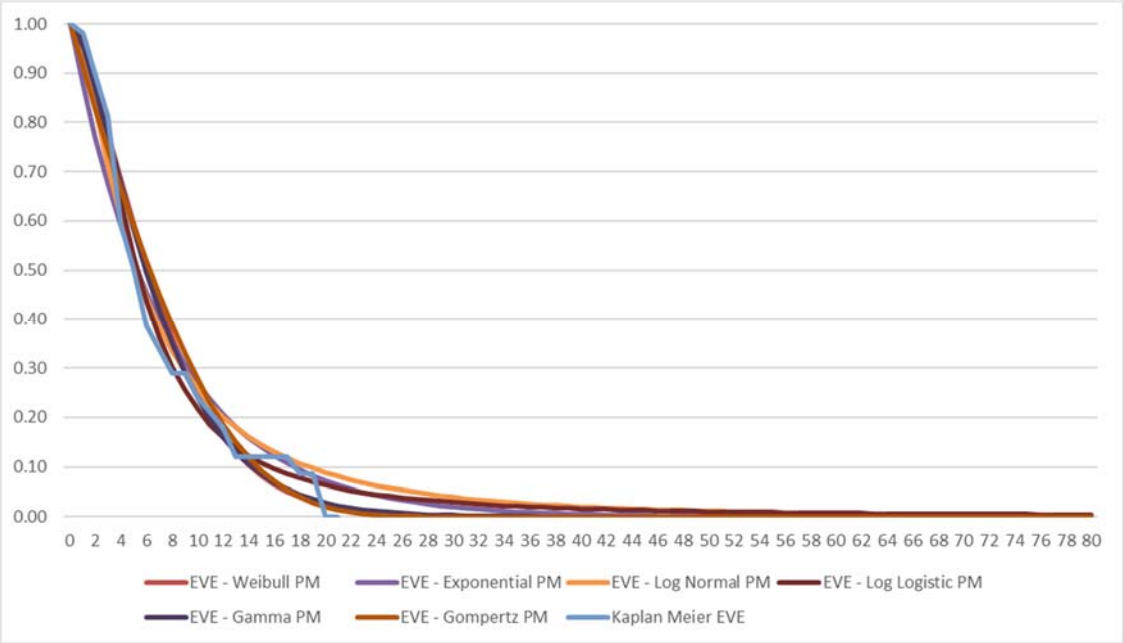
INDIVIDUAL OS



EVE

PARAMETRIC PFS



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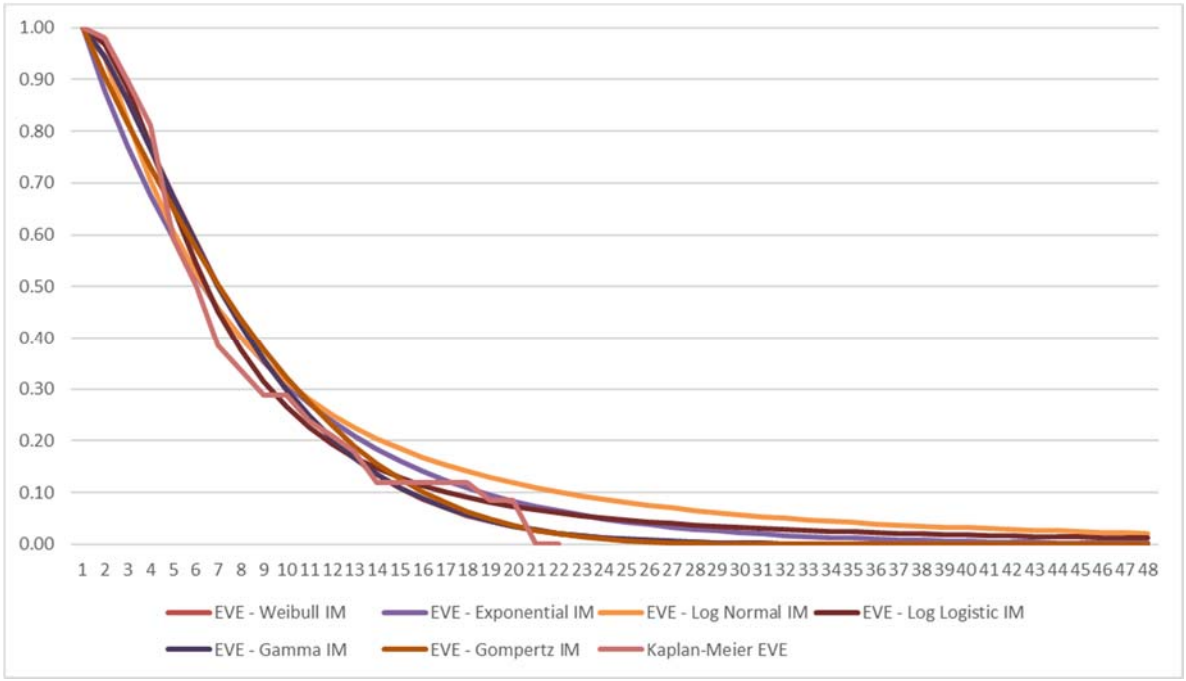
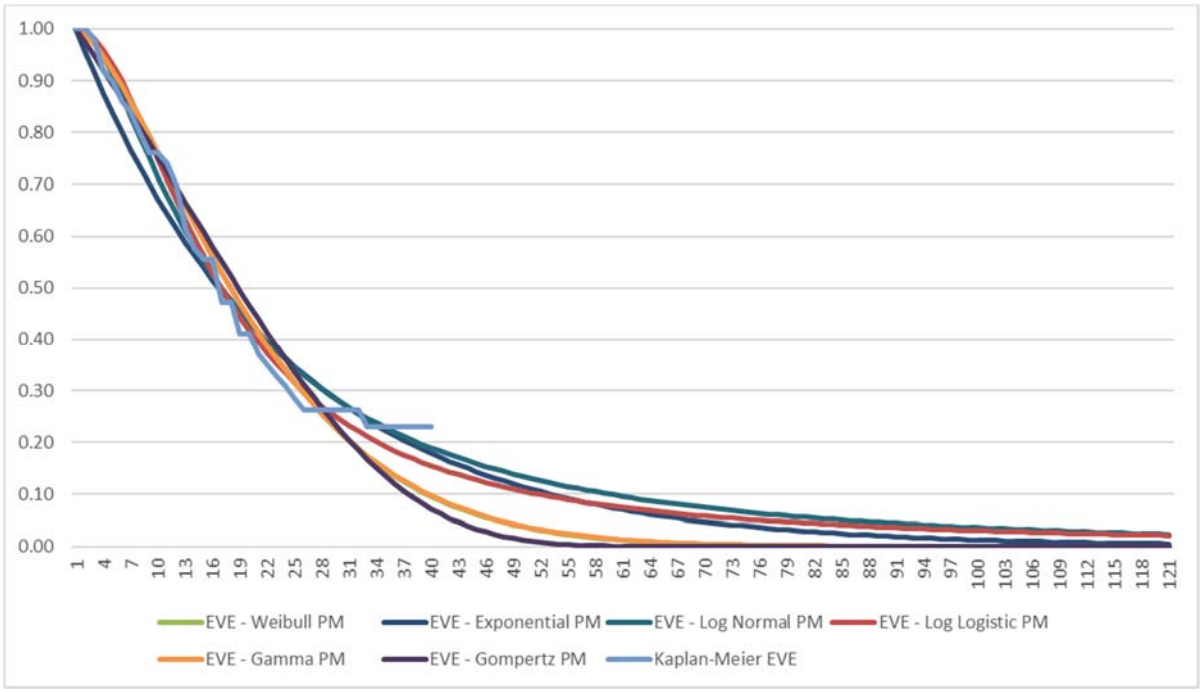
INDIVIDUAL PFS



PARAMETRIC OS



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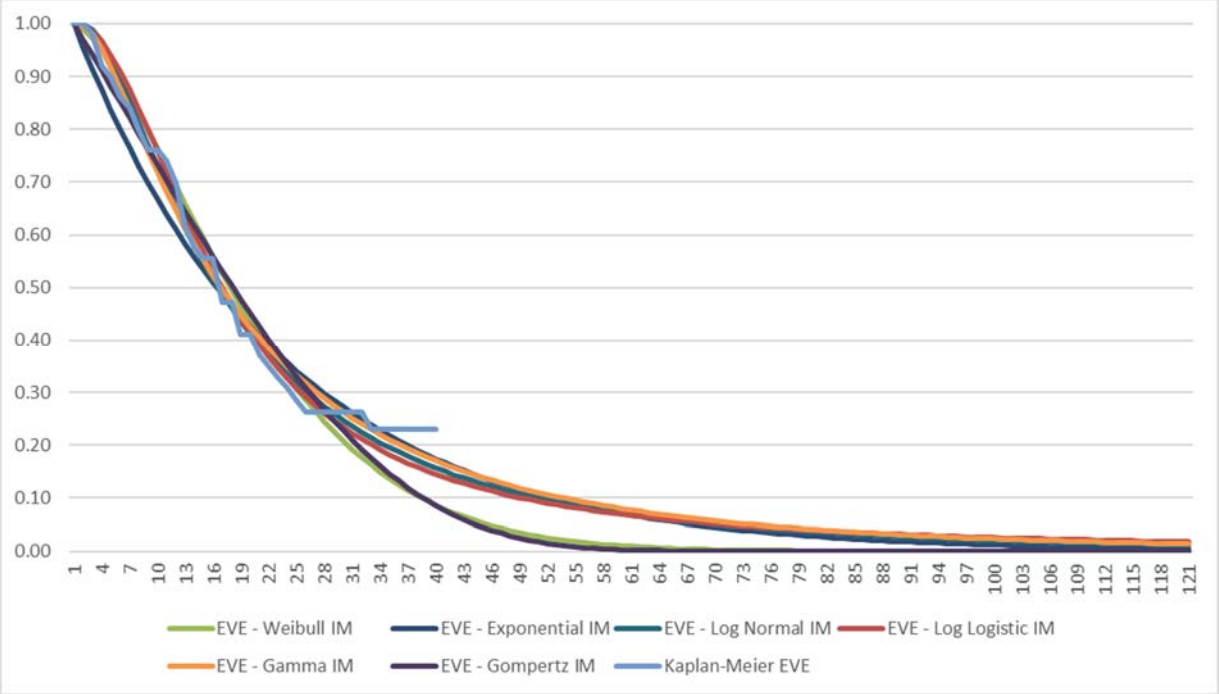
INDIVIDUAL OS



B7. **Priority question.** When using the Weibull model to fit curves to the HOPE 205 trial groups for PFS (either dependently or independently fitted), the resulting everolimus curve has a lower hazard than the nivolumab curve derived from applying the ITC HR to the lenvatinib combination group curve. This contradicts the results of the ITC. Please use a consistent approach to derive each of the comparator survival curves to ensure relative treatment effects are not estimated using different underlying survival models, as this can cause inaccuracies.

In the base-case model, the Kaplan-Meier model for EVE crosses the NIV hazard mapping for PFS only. The ITC specified the HR of LEN+EVE versus EVE to be 0.40 and LEN+EVE versus NIV to be [redacted]. While it may appear as though the ITC is not respected, the area under the curve is 6.48 months for EVE and 6.53 months for NIV: the trend follows the ITC and it could be said that the difference is small. All piecewise models will create this crossing when a traditional hazard mapping technique based on the treatment arm is used. While the piecewise approach shows a crossing, other extrapolation techniques seem to amplify this effect.

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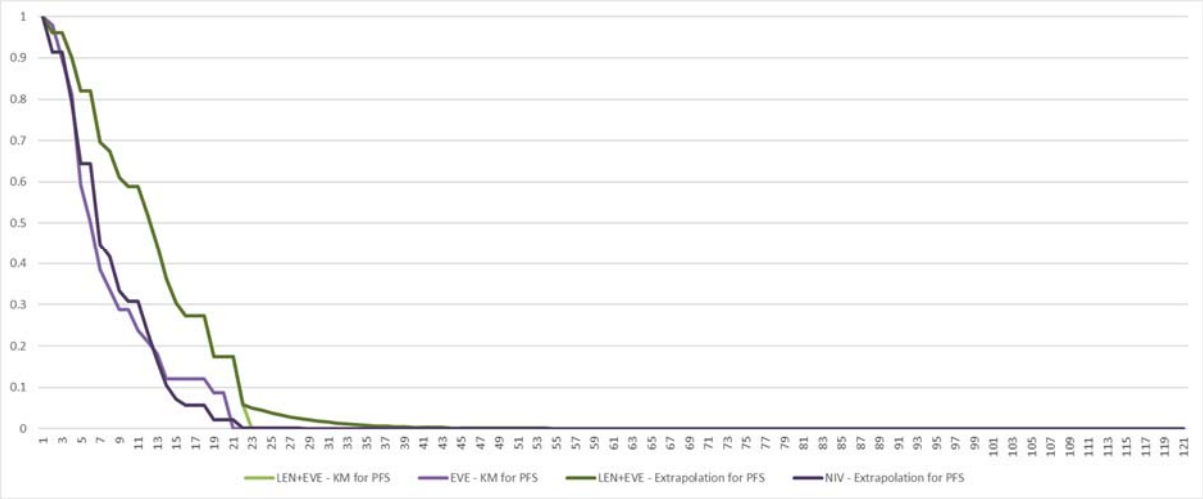
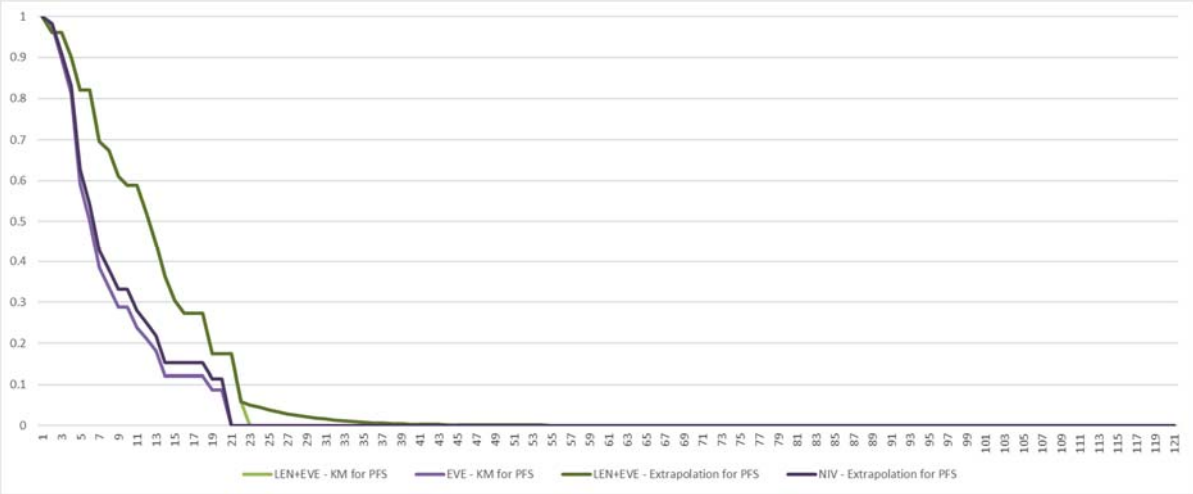


As this effect mostly affects NIV, an option (cell AB36 in the “Model Parameters” sheet) to map NIV on placebo instead of the treatment has been included in the revised model. This has very little impact on the ICER vs NIV (see below).



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The results of this scenario are presented in the following table

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	32,971	2,167	7,881	122,404

**Note: Includes modifications to EVE prices and removal of oral administration costs*

B8. The log-cumulative hazard plots in Figures 66, 67, 73 and 74 show one arm labelled as placebo. Please clarify the treatment arms shown in these plots. Also, please clarify the treatment arms used in the plot in Figures 65 and 72.

The term placebo was used interchangeably with EVE in some of the coding, as EVE is the control arm in the HOPE 205 clinical trial. Therefore, the term placebo is used for EVE when analysing the within-trial study i.e. not to be confounded with standard of care in the economic model. These data are based on the within-trial extrapolation analysis, where standard of care is not a treatment option.

To clarify, in Figures 66, 67, 74 and 74, Lenvima refers to LEN+EVE and placebo refers to EVE. As described in the response to question A1, in Figures 65 and 72, treatment 0 refers to EVE and treatment 1 refers to LEN+EVE.

PSA parameters

B9. Please justify the use of the log-normal distribution in the PSA for the PFS HR, when the HR for OS uses the normal distribution.

Below are some data and justifications for the distributions used in the PSA. A normal distribution was used for OS as the data were closer to a normal distribution, while the PFS values were clearly right skewed. In addition, applying an unrealistic right-skewed distribution created inconsistency where the PFS and OS were crossing i.e. where PFS became larger than OS, which is not possible.

Application of the variability in the model

OS and PFS: OS and PFS are partitions in this model. Often in a partition survival model, the parameters of the (shape, scale) parametric function will become stochastic. As this model is built on an ITC for most of the comparators, the HR from the ITC was varied

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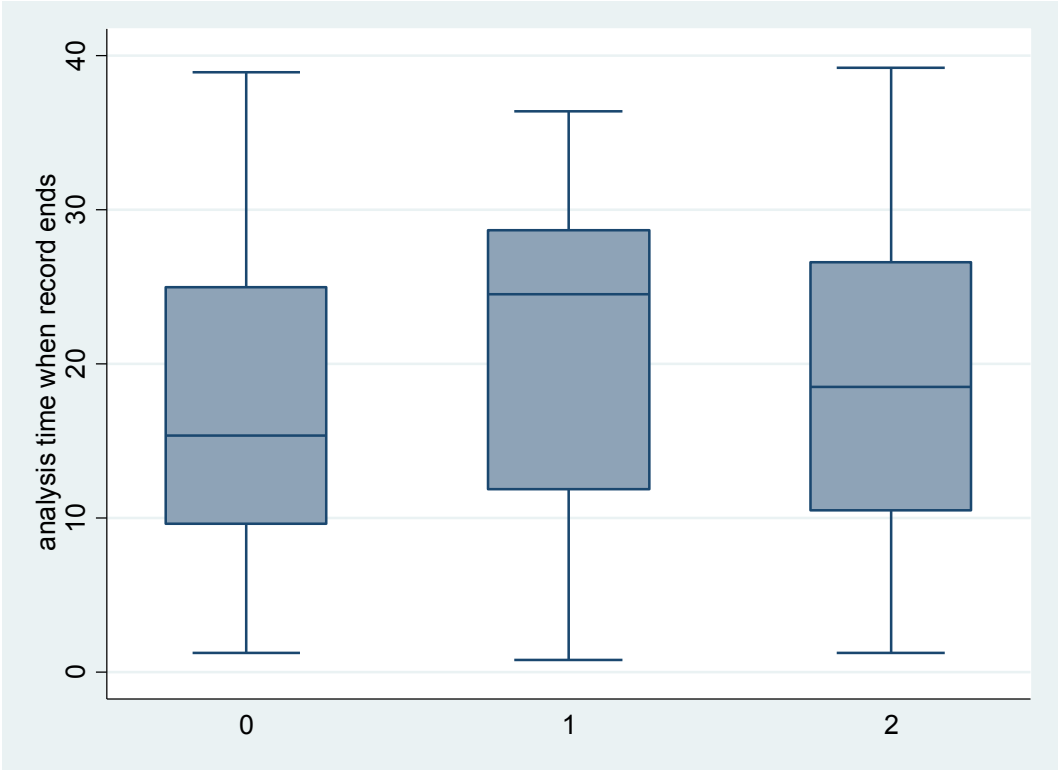
instead of the extrapolation coefficients. In this model, we used the hazard ratio for PFS and OS from the model and applied stochasticity in the hazard mapping of the LEN+EVE arm. For OS, the HR is 0.59 (0.36 – 0.97), and therefore the efficacy of LEN+EVE in relation to EVE will vary accordingly in the PSA following a log-normal law. In summary, we applied the uncertainty to the LEN+EVE arm in comparison to the EVE, but we also applied the uncertainty to the other comparators in their hazard mapping versus LEN+EVE (CAB, NIV, AXI). As per recommendations in Claxton et al. (2008), the hazard ratio is a result of the Cox survival model (after exp() transformation).

LEN+EVE OS distribution versus EVE



Note: 0 – EXE, 1 – LEN; 2 – LEN+EVE

Distributions were selected for the PSA as follows:

- It is recommended that specifying the distribution and defining the interval for uncertainty analysis follow standard statistical methods (e.g. beta distributions are a natural match for binomial data; gamma or log normal for right skew parameters; log normal for relative risks or hazard ratios; logistic for odds ratios). These principals were applied in distribution selection for this analysis.
- Little information is available regarding the distribution of cost, so we assumed a right-skewed distribution. Therefore, a log-normal distribution was applied for all the cost variables.

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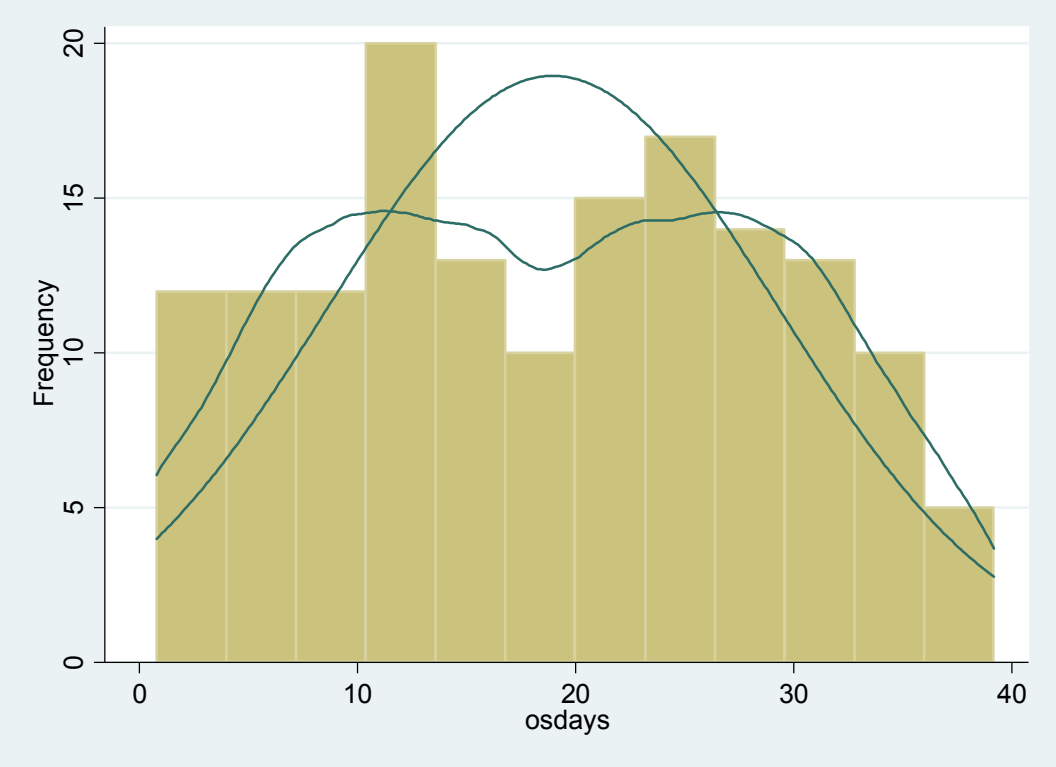
- OS seemed to follow a normal distribution. PFS was right-skewed in this data set and log-normal was therefore applied for this parameter. Log-normal is also recommended for hazard ratios.

Distribution of OS



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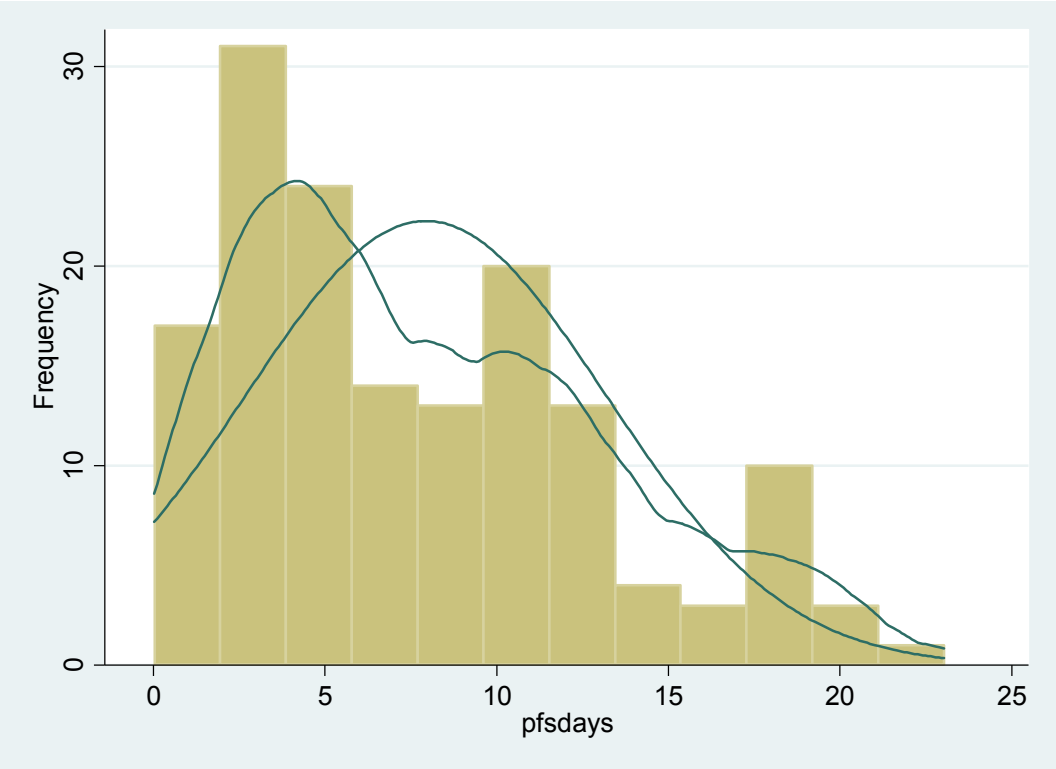
Distribution of PFS



Dosing variables (e.g. treatment duration below) seemed right skewed, as discontinuation and PFS had higher hazards at the beginning of the trial. As treatment duration is a partition and was also right-skewed, like PFS, log-normal distribution was applied. The use of a beta distribution seemed a good fit for the dose intensity of LEN+EVE and the comparators as they are proportions. The standard error was generated using the traditional formula for proportions: sqrt((p*(1-p)/n))).

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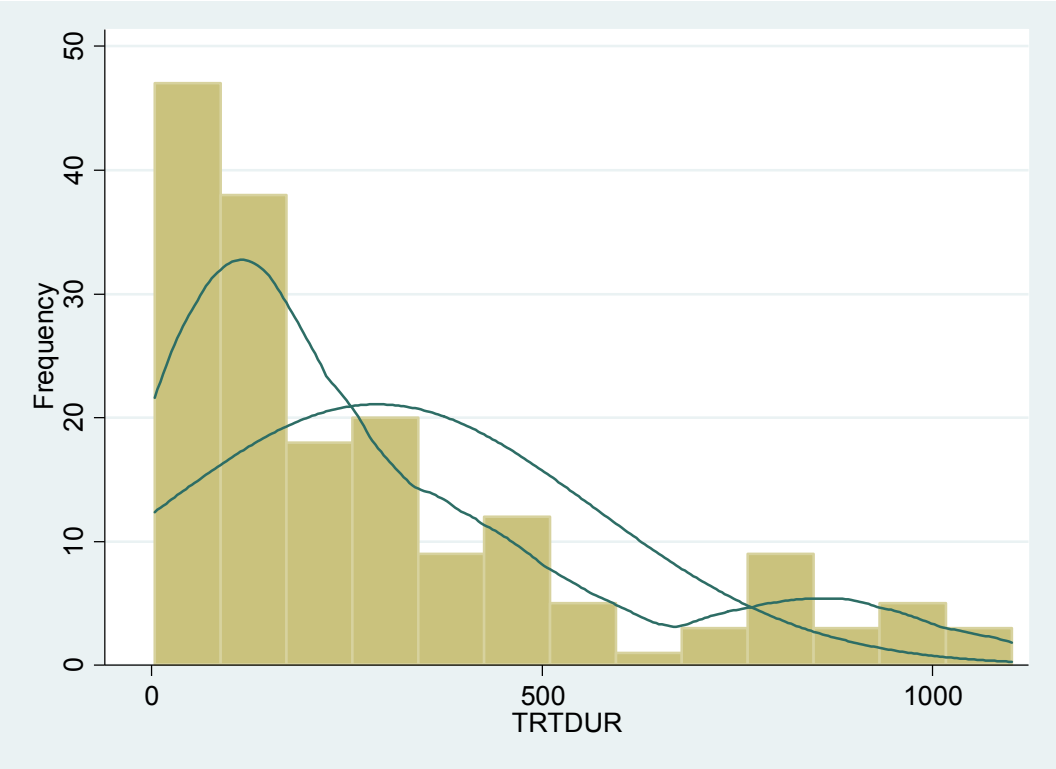
Distribution of treatment duration



Beta distribution was applied to the utility variables to allow a flexible fit to the theoretical 0-1 boundary of utility values. As standard errors were not available for the literature values, a standard error of 5% was applied.

B10. Please clarify why the random number used to make the PFS HR probabilistic is dependent on the random number used for the OS HR. Please explain the value of 0.4579 used to weight the OS value.

The correlation between OS and PFS in the LEN+EVE clinical trial was 0.4579 (based on within-trial data). This correlation was used to generate a link between PFS and OS and to prevent the PFS partition from increasing above the OS partition. The random value of the PFS distribution for each drug was built upon the random value of its OS distribution for 45.79% of its value and an independent random value was applied to the remaining value (100% - 45.79%).

This dependency between OS and PFS was added to the model, considering the proximity of some OS and PFS HR. With several treatments in close HR proximity, unconstrained OS and PFS random values would sometimes lead to inconsistent incremental costs and QALYS, resulting in many large values in the PSA. To avoid restricting the OS or PFS

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random value too much, the added dependency between PFS and OS ensures the results have a higher face validity in comparison to the base-case.

B11. Please justify why some parameters, in particular utilities, are not varied in the economic model.

The utility was varied when the vignette-based study data were used in the model (scenario analysis), but it was not varied in the base-case when the AXIS utility values were used. The revised model has been modified to include the AXIS utility values in the PSA.

In the vignette study, pre-progression utility (PE: 0.795; SE: 0.040) is varied using a beta distribution. Post-progression utility (PE: 0.355; SE: 0.018) is also varied using a beta distribution.

In the AXIS study, the pre-progression utility (PE: 0.692; SE: 0.035) is varied using a beta distribution. Post-progression utility (PE: 0.61; SE: 0.031) is also varied using a beta distribution.

Some variables, such as BSA or KG, were not varied but these variables are less important in this model as most of the drugs are orally administered.

Model corrections –

B12. The treatment duration of LEN+EVE in the PSA is multiplied by an unconstrained sampled ratio and therefore results in proportions of patients on treatment greater than 1 in some cases. Please correct this error.

A constraint was applied to treatment duration to lock it at <=1.

B13. The treatment duration for the comparator treatments is not varied in the PSA. Please correct this error.

Information on treatment duration variability for the comparators was difficult to find in the literature and so the comparator treatment duration was not applied in the model. In th amended version of the model, the PSA includes independent variation of treatment duration per arm. Standard error is assumed to be proportional to LEN+EVE i.e. 12.58% of the area under the curve.

B14. The acquisition cost for everolimus in the monotherapy arm is estimated in the economic model by multiplying the cost of a 5 mg tablet by 2 instead of applying the cost of 10 mg tablet, which has a lower cost. Please apply the cost of the 10 mg tablet for the everolimus monotherapy in the economic model.

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The 10mg cost is now applied in the revised model. After applying this change (but before considering other changes), the ICER was 96,403 compared to 124,946, as initially submitted (LEN versus EVE). See additional scenarios as well.

B15. The calculation used for QALYs implies that all patients who are on treatment have a utility associated with pre-progression. Please amend the calculation to account for a decreased utility for patients who remain on treatment but with progressed disease.

In the HOPE 205 trial, no patients were allowed to stay on treatment after progression. Some patients were kept on their primary therapy in the SOR and EVE trial, but the proportion of patients who were allowed to use the drug post-progression was small. Continued use of the same drug was probably more realistic when no other treatments were available i.e. when SOR trial was performed. As many options are now available, physicians are very unlikely to keep the patients on their primary therapy and much more likely to switch patients to a secondary therapy. This has been shown in recent trials i.e. NIV and LEN+EVE, in which patients were switched to secondary therapy after progression.

B16. A half-cycle correction appears to have been applied to life-years twice in the 'Appendix Transition'! sheet of the model. The first time in cells K22:M261 and then again in cells AA21:AC261. Please correct this for all the comparators.

This change has been applied to the revised model. As the transition page used columns K and L directly, this correction did not affect the result to our knowledge.

Additional analyses –

B17. Please carry out a scenario analysis including the costs of subsequent therapies currently available on the NHS as treatments for RCC at any line. Please do this for all the comparators based on what patients received in their respective trials.

We included secondary therapy in the model based on the answer to Question C1. The market shares used are based on clinical trial data i.e. patients in each secondary therapy for both the LEN+EVE and EVE arms (pooled data). The data used are identical for each model arm. The data were not based on respective clinical trial data for the comparators for the following reasons: (1) data are not available for all drugs, including LEN+EVE in the respective clinical trials, and (2) the difference in cost could be related to an expensive secondary therapy and would bias the ICER, (3) the secondary therapy would be significantly biased by the availability of drugs at the end of the trial, and not based on clinical practice. Using real world evidence is more robust than using trial data, mainly because the trials were not performed at the same time, and many comparators were not available when these trials were performed. Therefore, a more realistic approach is to use a similar secondary therapy for each model arm.

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The results of this scenario are presented in the following table.

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	32,651	1,417	6,452	121,914

**Note: Includes modifications to EVE prices and removal of oral administration costs*

B18. Please carry out a scenario analysis similar to that used in TA417 (see committee papers – slide 25) where it was assumed that 50% of patients on nivolumab had a mortality rate equal to the general population after year 5.

The survival rate at 5 years is 4% in the partition approach, so this assumption only affects a small proportion of patients. The natural mortality approach is applied to 50% of patients, while the other 50% follow the basecase course (i.e. partition approach). See additional scenarios (LEN versus NIV). See option in cell AB29 of "Model Parameters" sheet in the revised model

The results of this scenario are presented in the following table.

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	32,971	2,167	7,670	122,404

**Note: Includes modifications to EVE prices and removal of oral administration costs*

B19. Please carry out a scenario analysis similar to that used in TA417 (see committee papers – slide 22) where it was assumed that nivolumab had a utility benefit over everolimus.

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A scenario using the axitinib utility values from Table 51 below was added to the revised model, as per the scenario conducted by the ERG in TA147.

The results of this scenario are presented in the following table.

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	32,971	2,167	-55,957	204,579

**Note: Includes modifications to EVE prices and removal of oral administration costs*

Table 51. Health state utility values by treatment

Treatment	PFS	PPS	Treatment-specific disutility due to disease progression
Nivolumab	0.7975	0.7281	-0.0694 (-8.7%)
Everolimus	0.7618	0.6970	-0.0649 (-8.5%)
Axitinib	0.6920	0.6100	-0.0820 (-11.9%)
BSC	0.6920	0.6100	-0.0820 (-11.9%)
Abbreviations used in the table: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival.			

SUMMARY OF THE CHANGES

The only changes directly implemented in the amended base-case that modified the ICER are question B14 and question B23. The other questions were addressed by adding additional scenarios. The PSA was also modified to include more parameters.

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The following table presents the results of the amended base-case versus AXI

Additional scenarios Lenvima + Everolimus (LEN+EVE) versus Axitinib (AXI)

		Cost LEN+EVE	Cost Axitinib (AXI)	LYs LEN+EVE	LYs Axitinib (AXI)	QALYs LEN+EVE	QALYs Axitinib (AXI)	Incremental Lys	Incremental QALY	Incremental cost	Cost per QALY
Basecase		***71,333***	***52,495***	***2.22***	***1.34***	***1.42***	***0.85***	***0.89***	***0.57***	***18,838***	***32,971***
Treatment duration - switching at progression		*79,319*	*39,611*	*2.22*	*1.34*	*1.42*	*0.86*	*0.89*	*0.57*	*39,708*	*70,023*
Treatment duration - extrapolation		*82,616*	*52,495*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*30,122*	*52,929*
Treatment duration - Digitalization		*71,333*	*39,611*	*2.22*	*1.34*	*1.42*	*0.86*	*0.89*	*0.57*	*31,722*	*55,782*
Extreme discounting values (0% Ben and costs)		*73,886*	*54,037*	*2.37*	*1.39*	*1.51*	*0.88*	*0.98*	*0.63*	*19,850*	*31,674*
Extreme discounting values (5% Ben and costs)		*70,319*	*51,873*	*2.17*	*1.32*	*1.39*	*0.84*	*0.85*	*0.55*	*18,447*	*33,530*
LEN+EVE OS CI+ (based on trial HR CI's)		*75,236*	*55,018*	*3.05*	*1.87*	*1.93*	*1.18*	*1.18*	*0.75*	*20,218*	*26,959*
LEN+EVE OS CI- (based on trial HR CI's)		*68,375*	*50,603*	*1.60*	*0.94*	*1.04*	*0.61*	*0.66*	*0.43*	*17,772*	*41,088*
LEN+EVE PFS CI+ (based on trial HR CI's)		*72,363*	*52,826*	*2.22*	*1.34*	*1.45*	*0.87*	*0.89*	*0.58*	*19,537*	*33,557*
LEN+EVE PFS CI- (based on trial HR CI's)		*70,546*	*52,226*	*2.22*	*1.34*	*1.40*	*0.84*	*0.89*	*0.56*	*18,320*	*32,492*
Overall survival	Piecewise - Gompertz (second best)	*70,588*	*52,406*	*2.07*	*1.32*	*1.33*	*0.84*	*0.75*	*0.49*	*18,182*	*37,382*
	Parametric - Gompertz (Best fitting)	*70,351*	*52,357*	*2.02*	*1.31*	*1.30*	*0.84*	*0.71*	*0.46*	*17,994*	*38,940*
	Parametric - Weibull (second best)	*71,135*	*52,477*	*2.18*	*1.33*	*1.40*	*0.85*	*0.85*	*0.55*	*18,657*	*34,051*
	Individual - Weibull (Best fitting)	*71,193*	*52,644*	*2.20*	*1.37*	*1.41*	*0.87*	*0.83*	*0.53*	*18,549*	*34,744*
	Individual - Gompertz (second best)	*70,267*	*52,729*	*2.00*	*1.39*	*1.29*	*0.88*	*0.61*	*0.40*	*17,539*	*43,506*
Progression free survival	Piecewise - Gompertz (second best)	*71,294*	*52,495*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*18,799*	*32,962*
	Parametric - Weibull (Best fitting)	*71,415*	*52,456*	*2.22*	*1.34*	*1.43*	*0.85*	*0.89*	*0.58*	*18,959*	*32,946*
	Individual - Gompertz (Best fitting)	*71,252*	*52,501*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*18,751*	*32,960*
	Individual - Weibull (second best)	*71,347*	*52,500*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*18,847*	*32,980*
Additional set of utility (vignette study)		*71,333*	*52,495*	*2.22*	*1.34*	*1.19*	*0.71*	*0.89*	*0.49*	*18,838*	*38,811*
Additional set of utility (TA417) option		*71,333*	*52,495*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*18,838*	*32,971*
Evorolimus Generic price (capecitabine price as a proxy)		*84,920*	*66,272*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*18,648*	*32,638*
Secondary therapy included		*84,734*	*51,599*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*33,135*	*95,972*
Natural mortality for NIV after 60 months		*71,333*	*52,495*	*2.22*	*1.34*	*1.42*	*0.85*	*0.89*	*0.57*	*18,838*	*32,971*

The following table presents the results of the additional scenarios versus CAB

Additional scenarios Lenvima + Everolimus (LEN+EVE) versus Cabozantinib (CAB)

		Cost LEN+EVE	Cost Cabozantinib (CAB)	LYs LEN+EVE	LYs Cabozantinib (CAB)	QALYs LEN+EVE	QALYs Cabozantinib (CAB)	Incremental Lys	Incremental QALY	Incremental cost	Cost per QALY
Basecase		***71,333***	***71,086***	***2.22***	***2.06***	***1.42***	***1.31***	***0.16***	***0.11***	***247***	***2,167***
Treatment duration - switching at progression		*79,319*	*66,099*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*13,220*	*118,341*
Treatment duration - extrapolation		*82,616*	*71,086*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*11,531*	*103,016*
Treatment duration - Digitalization		*71,333*	*84,527*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.12*	*-13,194*	*-113,160*
Extreme discounting values (0% Ben and costs)		*73,886*	*73,529*	*2.37*	*2.18*	*1.51*	*1.38*	*0.18*	*0.13*	*357*	*2,811*
Extreme discounting values (5% Ben and costs)		*70,319*	*70,112*	*2.17*	*2.01*	*1.39*	*1.28*	*0.16*	*0.11*	*208*	*1,901*
LEN+EVE OS CI+ (based on trial HR CI's)		*75,236*	*74,741*	*3.05*	*2.84*	*1.93*	*1.78*	*0.22*	*0.15*	*494*	*3,382*
LEN+EVE OS CI- (based on trial HR CI's)		*68,375*	*68,317*	*1.60*	*1.47*	*1.04*	*0.95*	*0.12*	*0.09*	*58*	*649*
LEN+EVE PFS CI+ (based on trial HR CI's)		*72,363*	*71,713*	*2.22*	*2.06*	*1.45*	*1.33*	*0.16*	*0.12*	*651*	*5,426*
LEN+EVE PFS CI- (based on trial HR CI's)		*70,546*	*70,579*	*2.22*	*2.06*	*1.40*	*1.29*	*0.16*	*0.11*	*-33*	*-300*
Overall survival	Piecewise - Gompertz (second best)	*70,588*	*70,515*	*2.07*	*1.94*	*1.33*	*1.24*	*0.13*	*0.09*	*73*	*798*
	Parametric - Gompertz (Best fitting)	*70,351*	*70,307*	*2.02*	*1.90*	*1.30*	*1.21*	*0.12*	*0.09*	*44*	*502*
	Parametric - Weibull (second best)	*71,135*	*70,914*	*2.18*	*2.02*	*1.40*	*1.29*	*0.16*	*0.11*	*221*	*1,994*
	Individual - Weibull (Best fitting)	*71,193*	*70,997*	*2.20*	*2.04*	*1.41*	*1.30*	*0.15*	*0.11*	*195*	*1,817*
	Individual - Gompertz (second best)	*70,267*	*70,316*	*2.00*	*1.90*	*1.29*	*1.21*	*0.10*	*0.08*	*-48*	*-636*
Progression free survival	Piecewise - Gompertz (second best)	*71,294*	*71,080*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*214*	*1,887*
	Parametric - Weibull (Best fitting)	*71,415*	*71,072*	*2.22*	*2.06*	*1.43*	*1.31*	*0.16*	*0.12*	*343*	*2,937*
	Individual - Gompertz (Best fitting)	*71,252*	*71,071*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*180*	*1,604*
	Individual - Weibull (second best)	*71,347*	*71,084*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*263*	*2,292*
Additional set of utility (vignette study)		*71,333*	*71,086*	*2.22*	*2.06*	*1.19*	*1.05*	*0.16*	*0.14*	*247*	*1,790*
Additional set of utility (TA417) option		*71,333*	*71,086*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*247*	*2,167*
Evorolimus Generic price (capecitabine price as a proxy)		*84,920*	*84,762*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*158*	*1,386*
Secondary therapy included		*84,734*	*51,599*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*33,135*	*95,972*
Natural mortality for NIV after 60 months		*71,333*	*71,086*	*2.22*	*2.06*	*1.42*	*1.31*	*0.16*	*0.11*	*247*	*2,167*

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The following table presents the results of the additional scenarios versus NIV

Additional scenarios Lenvima + Everolimus (LEN+EVE) versus Nivolumab (NIV)

		Cost LEN+EVE	Cost Nivolumab (NIV)	LYs LEN+EVE	LYs Nivolumab (NIV)	QALYs LEN+EVE	QALYs Nivolumab (NIV)	Incremental Lys	Incremental QALY	Incremental cost	Cost per QALY
Basecase		***71,333***	***69,896***	***2.22***	***1.94***	***1.42***	***1.23***	***0.29***	***0.20***	***1,437***	***7,299***
Treatment duration - switching at progression		*79,319*	*68,534*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.20*	*10,785*	*55,258*
Treatment duration - extrapolation		*82,616*	*69,896*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.19*	*12,720*	*65,388*
Treatment duration - Digitalization		*71,333*	*110,708*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.20*	*-39,375*	*-199,216*
Extreme discounting values (0% Ben and costs)		*73,886*	*71,960*	*2.37*	*2.04*	*1.51*	*1.29*	*0.32*	*0.22*	*1,926*	*8,819*
Extreme discounting values (5% Ben and costs)		*70,319*	*69,072*	*2.17*	*1.89*	*1.39*	*1.20*	*0.28*	*0.19*	*1,248*	*6,614*
LEN+EVE OS CI+ (based on trial HR CI's)		*75,236*	*73,362*	*3.05*	*2.67*	*1.93*	*1.68*	*0.38*	*0.25*	*1,874*	*7,394*
LEN+EVE OS CI- (based on trial HR CI's)		*68,375*	*67,284*	*1.60*	*1.38*	*1.04*	*0.89*	*0.22*	*0.15*	*1,091*	*7,174*
LEN+EVE PFS CI+ (based on trial HR CI's)		*72,363*	*69,452*	*2.22*	*1.94*	*1.45*	*1.25*	*0.29*	*0.21*	*2,911*	*14,095*
LEN+EVE PFS CI- (based on trial HR CI's)		*70,546*	*70,251*	*2.22*	*1.94*	*1.40*	*1.21*	*0.29*	*0.19*	*295*	*1,551*
Overall survival	**Piecewise - Gompertz (second best)**	*70,588*	*69,443*	*2.07*	*1.84*	*1.33*	*1.17*	*0.23*	*0.16*	*1,145*	*7,199*
	Parametric - Gompertz (Best fitting)	*70,351*	*69,259*	*2.02*	*1.80*	*1.30*	*1.15*	*0.22*	*0.15*	*1,092*	*7,175*
	Parametric - Weibull (second best)	*71,135*	*69,747*	*2.18*	*1.90*	*1.40*	*1.21*	*0.28*	*0.19*	*1,388*	*7,285*
	Individual - Weibull (Best fitting)	*71,193*	*69,848*	*2.20*	*1.93*	*1.41*	*1.22*	*0.27*	*0.18*	*1,344*	*7,272*
	Individual - Gompertz (second best)	*70,267*	*69,337*	*2.00*	*1.82*	*1.29*	*1.16*	*0.18*	*0.13*	*931*	*7,088*
Progression free survival	**Piecewise - Gompertz (second best)**	*71,294*	*69,897*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.20*	*1,397*	*7,136*
	Parametric - Weibull (Best fitting)	*71,415*	*69,939*	*2.22*	*1.94*	*1.43*	*1.23*	*0.29*	*0.20*	*1,476*	*7,354*
	Individual - Gompertz (Best fitting)	*71,252*	*69,890*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.19*	*1,362*	*7,007*
	Individual - Weibull (second best)	*71,347*	*69,888*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.20*	*1,459*	*7,410*
Additional set of utility (vignette study)		*71,333*	*69,896*	*2.22*	*1.94*	*1.19*	*0.94*	*0.29*	*0.25*	*1,437*	*5,732*
Additional set of utility (TA417) option		*71,333*	*69,896*	*2.22*	*1.94*	*1.42*	*1.45*	*0.29*	*-0.03*	*1,437*	*-55,957*
Evorolimus Generic price (capecitabine price as a proxy)		*84,920*	*83,657*	*2.22*	*1.94*	*1.42*	*1.23*	*0.29*	*0.20*	*1,263*	*6,416*
Secondary therapy included		*84,734*	*51,599*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*33,135*	*95,972*
Natural mortality for NIV after 60 months		*71,333*	*70,725*	*2.22*	*2.13*	*1.42*	*1.35*	*0.10*	*0.08*	*608*	*7,670*

The following table presents the results of the additional scenarios versus EVE

Additional scenarios Lenvima + Everolimus (LEN+EVE) versus Everolimus (EVE)

		Cost LEN+EVE	Cost Everolimus (EVE)	LYs LEN+EVE	LYs Everolimus (EVE)	QALYs LEN+EVE	QALYs Everolimus (EVE)	Incremental Lys	Incremental QALY	Incremental cost	Cost per QALY
Basecase		***71,333***	***29,073***	***2.22***	***1.69***	***1.42***	***1.08***	***0.53***	***0.35***	***42,260***	***122,404***
Treatment duration - switching at progression		*79,319*	*33,298*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.34*	*46,021*	*133,776*
Treatment duration - extrapolation		*82,616*	*33,213*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.34*	*49,403*	*143,891*
Treatment duration - Digitalization		*71,333*	*29,073*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*42,260*	*122,404*
Extreme discounting values (0% Ben and costs)		*73,886*	*30,160*	*2.37*	*1.78*	*1.51*	*1.13*	*0.58*	*0.38*	*43,726*	*115,781*
Extreme discounting values (5% Ben and costs)		*70,319*	*28,643*	*2.17*	*1.66*	*1.39*	*1.06*	*0.51*	*0.33*	*41,676*	*125,209*
LEN+EVE OS CI+ (based on trial HR CI's)		*75,236*	*29,073*	*3.05*	*1.69*	*1.93*	*1.08*	*1.36*	*0.85*	*46,163*	*54,276*
LEN+EVE OS CI- (based on trial HR CI's)		*68,375*	*29,073*	*1.60*	*1.69*	*1.04*	*1.08*	*-0.10*	*-0.04*	*39,302*	*-1,043,235*
LEN+EVE PFS CI+ (based on trial HR CI's)		*72,363*	*28,772*	*2.22*	*1.69*	*1.45*	*1.10*	*0.53*	*0.35*	*43,591*	*123,108*
LEN+EVE PFS CI- (based on trial HR CI's)		*70,546*	*29,321*	*2.22*	*1.69*	*1.40*	*1.06*	*0.53*	*0.34*	*41,225*	*121,378*
Overall survival	**Piecewise - Gompertz (second best)**	*70,588*	*28,719*	*2.07*	*1.62*	*1.33*	*1.03*	*0.45*	*0.29*	*41,869*	*142,150*
	Parametric - Gompertz (Best fitting)	*70,351*	*28,330*	*2.02*	*1.54*	*1.30*	*0.98*	*0.48*	*0.31*	*42,021*	*133,712*
	Parametric - Weibull (second best)	*71,135*	*28,518*	*2.18*	*1.58*	*1.40*	*1.01*	*0.61*	*0.39*	*42,617*	*108,868*
	Individual - Weibull (Best fitting)	*71,193*	*28,397*	*2.20*	*1.55*	*1.41*	*0.99*	*0.64*	*0.41*	*42,796*	*103,221*
	Individual - Gompertz (second best)	*70,267*	*28,286*	*2.00*	*1.53*	*1.29*	*0.98*	*0.47*	*0.31*	*41,981*	*135,817*
Progression free survival	**Piecewise - Gompertz (second best)**	*71,294*	*29,073*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.34*	*42,221*	*122,659*
	Parametric - Weibull (Best fitting)	*71,415*	*29,050*	*2.22*	*1.69*	*1.43*	*1.08*	*0.53*	*0.35*	*42,364*	*122,428*
	Individual - Gompertz (Best fitting)	*71,252*	*29,048*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.34*	*42,204*	*123,558*
	Individual - Weibull (second best)	*71,347*	*29,050*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.34*	*42,297*	*122,882*
Additional set of utility (vignette study)		*71,333*	*29,073*	*2.22*	*1.69*	*1.19*	*0.85*	*0.53*	*0.34*	*42,260*	*124,685*
Additional set of utility (TA417) option		*71,333*	*29,073*	*2.22*	*1.69*	*1.42*	*1.22*	*0.53*	*0.21*	*42,260*	*204,579*
Evorolimus Generic price (capecitabine price as a proxy)		*84,920*	*42,836*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*42,084*	*121,894*
Secondary therapy included		*84,734*	*51,599*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*33,135*	*95,972*
Natural mortality for NIV after 60 months		*71,333*	*29,073*	*2.22*	*1.69*	*1.42*	*1.08*	*0.53*	*0.35*	*42,260*	*122,404*

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NEW PSA RESULTS

PSA results

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Mean ICER	47,343	279,561	29,567	154,941
Median ICER	38,119	18,498	22,149	133,132
% under 25,000	23.8%	54.8%	51.4%	0.1%
% under 50,000	67.1%	66.6%	65.8%	0.5%

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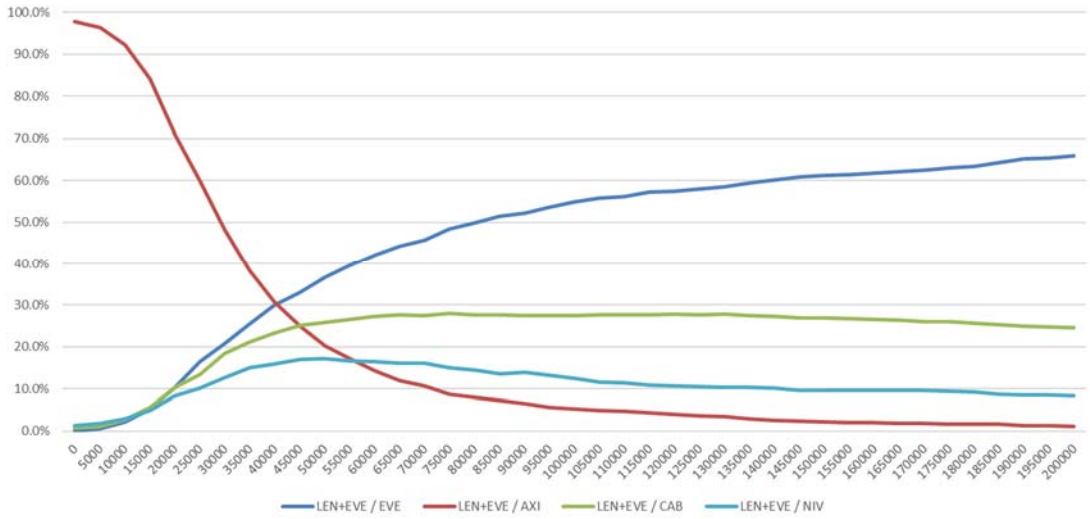

Literature searching

B20. Four studies reporting economic evaluations were identified and excluded in the systematic literature review for randomised clinical trials, but were not identified in the search for economic evaluations. This refers to study numbers 527,764, 765 and 766 in Table 6.1.1 of Appendix 8.3. Please clarify why these studies were not identified in the economic search.

Please find attached Appendix 3 from the SLR report, which was not included originally in error. This Appendix lists all of the excluded economic studies, including study numbers 527, 764, 765 and 766, which were identified in the search for economic evaluations and are listed as numbers 430, 514, 513 and 512 respectively.

B21. Please clarify why the systematic literature search for cost-effectiveness studies was restricted to studies published from 2005 onwards?

As the first TKIs in this indication were only approved by the European Medicines Agency in July 2006, this restriction was considered appropriate and sufficient to capture all the relevant cost-effectiveness studies within this patient population.

Other

B22. The dose reductions used in Figure 94 on page 160 for cabozantinib, axitinib and nivolumab do not match the values reported in their respective technology appraisals (i.e. TA333, TA417, and GID-TA10075). Please clarify how the dose reductions were estimated for each comparator treatment.

As stated in the CS on pages 159 - 160, dose reduction assumptions in the model are based on the data from the corresponding clinical trials. Wastage was included in the drug costs,

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meaning that the within-trial doses were rounded up to the nearest possible whole pill or vial amount.

In Figure 94, the dose reduction percentages reported for lenvatinib and everolimus were taken directly from the mean doses reported in the HOPE 205 study ie 13.3mg/18mg = 73.9% for lenvatinib and 4.4mg/5mg = 88% for everolimus 5mg.

To ensure that all dosing costs were applied consistently to cabozantinib, axitinib and nivolumab and in the absence of patient level data, a similar approach was taken to calculate the dose reductions required for these comparators.

In the cabozantinib Phase III trial (Choueiri 2016), only the median daily dose of 43mg was reported which is 71.7% of the required dose of 60mg, as reported in the dose reduction column of Figure 94. In the axitinib phase III trial (Rini 2011), the mean relative dose intensity (defined as the actual total dose / intended total dose × 100) was 99% in the axitinib group, as reported in the dose reduction column of Figure 94. In the nivolumab phase III trial (Motzer 2015), dose reductions were not allowed and therefore equal to 100% of the required dose, as reported in the dose reduction column of Figure 94.

B23. Please clarify why an administration cost associated with oral therapies has been assumed, given that oral therapies are self-administered at home by the patient (lenvatinib, everolimus, axitinib and cabozantinib).

Upon further reflection and review of previous NICE submissions, Eisai have amended this in our base-case to assume no administration cost for oral therapies ie lenvatinib, everolimus, axitinib and cabozantinib. The results of the revised base-case can be found below:

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404

**Note: Includes modifications to EVE prices*

B24. Please clarify the inclusion criteria for adverse events in the economic model, as they are only a subset of those presented in Figure 49 of the CS.

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The adverse events included in the economic model were those Grade 3/4 treatment emergent adverse events which were identified as impacting on quality of life. These adverse events were validated by 8 practising NHS clinicians from England and Wales who provided input at an advisory board.

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Section C: Textual clarifications and additional points

C1. Please confirm which data cut-off was used for subsequent therapies received in each treatment group in HOPE 205. If these data are from an earlier data cut-off, then please provide these data for the July 2015 data cut.

The data provided on post-treatment anti-cancer therapy in Table 14.2.3.1.3 of the CSR is from the 13 June 2014 datacut. Please find below the data for the July 2015 datacut.

Table 14.2.3.1.3a Summary of Post-Treatment Anti-Cancer Therapy
Full Analysis Set

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Any Subjects Who Took Anti-cancer Therapy after Treatment Discontinuation	18 (35.3)	16 (30.8)	18 (36.0)
Vascular Endothelial Growth Factor (VEGF) Inhibitor	9 (17.6)	5 (9.6)	13 (26.0)
Axitinib	6 (11.8)	2 (3.8)	12 (24.0)
Pazopanib	1 (2.0)	0	1 (2.0)
Sorafenib	1 (2.0)	0	0
Sunitinib	1 (2.0)	0	2 (4.0)
Bevacizumab	0	1 (1.9)	1 (2.0)
Cabozantinib	0	2 (3.8)	0
Mammalian Target of Rapamycin (mTOR) Inhibitor	5 (9.8)	9 (17.3)	2 (4.0)
Everolimus	5 (9.8)	7 (13.5)	2 (4.0)
Temsirolimus	0	2 (3.8)	0
OTHER ANTICANCER THERAPY	2 (3.9)	0	0
Various Therapeutic Radio	1 (2.0)	0	0
Zoledronic Acid	1 (2.0)	0	0
Monoclonal Antibody (mAb)	1 (2.0)	2 (3.8)	0
Monoclonal Antibodies	1 (2.0)	2 (3.8)	0
Cytokine	0	0	2 (4.0)
Interferon	0	0	2 (4.0)

Data Cut-off Date: 31JUL2015
Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.

C2. Please confirm the numbers for the inclusion/exclusion of citations at each stage in the systematic literature review of clinical studies as there are several discrepancies

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within and between the PRISMA diagram in the main CS (Figure 13) and in Appendix 8.3 (Figure 3.1.1) including assessments based on title and abstract and full text appraisal.

Please find overleaf an updated PRISMA diagram confirming the numbers for the inclusion/exclusion of citations at each stage.

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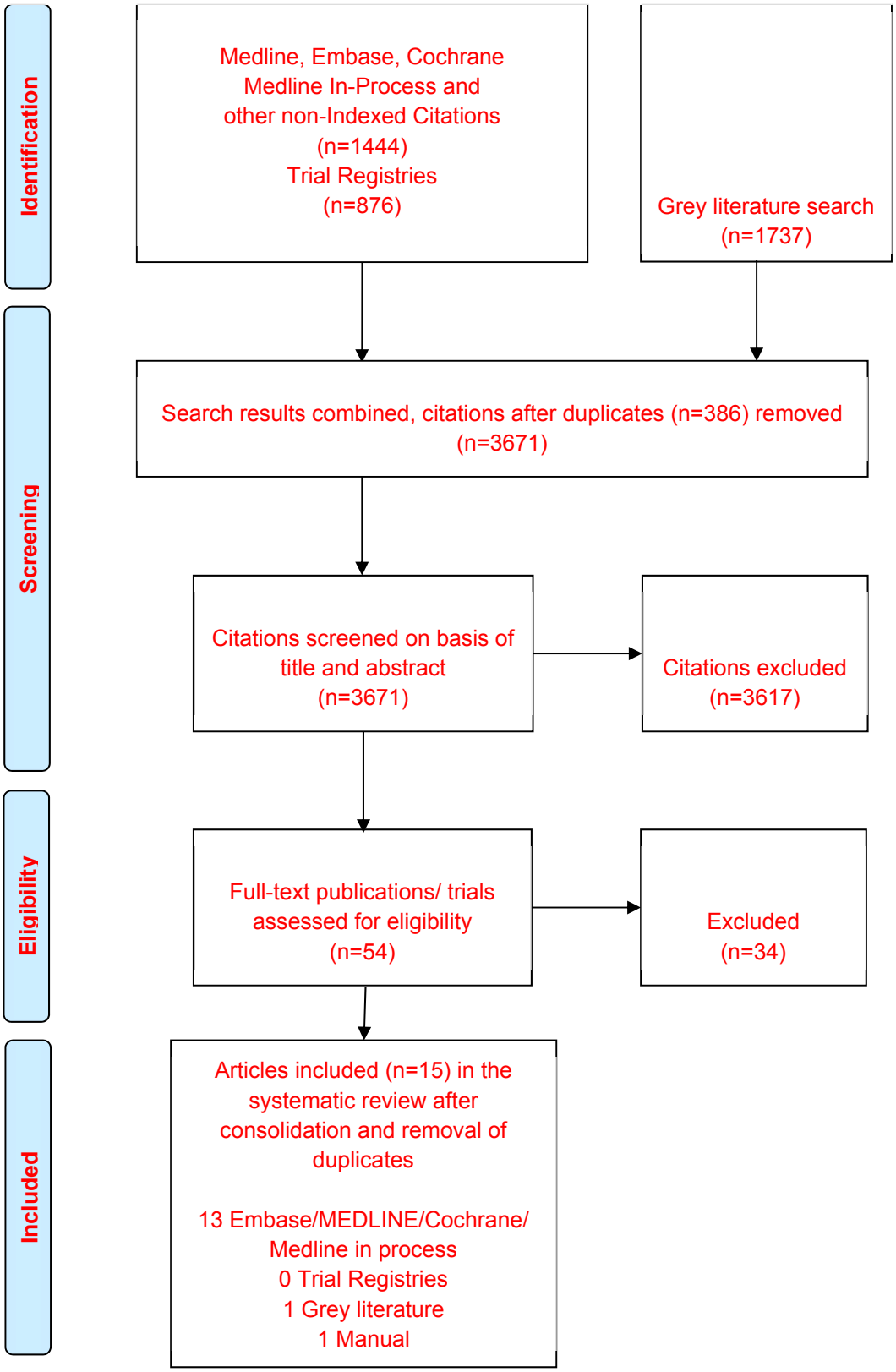
PRISMA Study Attrition Diagram for Systematic Literature Review of a/mRCC



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C3. Please explain the contradictory result for the updated OS analysis (data cut 31 Jul 2015) for which the 95% confidence interval indicates a statistically significant difference (HR: 0.59; 95% CI 0.36-0.97) whereas the p-value does not (P=0.065).

As a standard approach with OS analysis (including this updated OS analysis), the HR and its confidence interval were estimated by a cox model with proportional hazard assumption between the two treatment groups. The p-value was from a log rank test which is a non-parametric test.

These are two different methods to obtain relevant inferential information and this may not result in the same conclusion depending on how the significance level was set. In this updated OS analysis, the fact that the upper limit of 95% CI was just below 1 (0.97) and the p-value was just above 0.05 suggest that there is a marginal statistically significant benefit with lenvatinib + everolimus over everolimus monotherapy in OS.

C4. Please confirm the data cut-off date for the PFS results presented in the CS.

Pages 52 – 55 of the CS presents the PFS results of the primary analysis ie June 2014 data cut off.

C5. Please confirm the PFS completion rate at the July 2015 data cut-off in Figure 29 which seems to be lower than at the earlier data cut-off of December 2014.

Please note that there is an error in Figure 29. The PFS completion rate for the data cut-off of December 2014 should have read “51%”.

C6. Please confirm the number of patients who discontinued treatment for disease progression, adverse events or patient’s choice in each treatment group in Figure 19 as these don’t add up to the total number of patients discontinuing treatment in each arm.

Please find overleaf a corrected CONSORT diagram.

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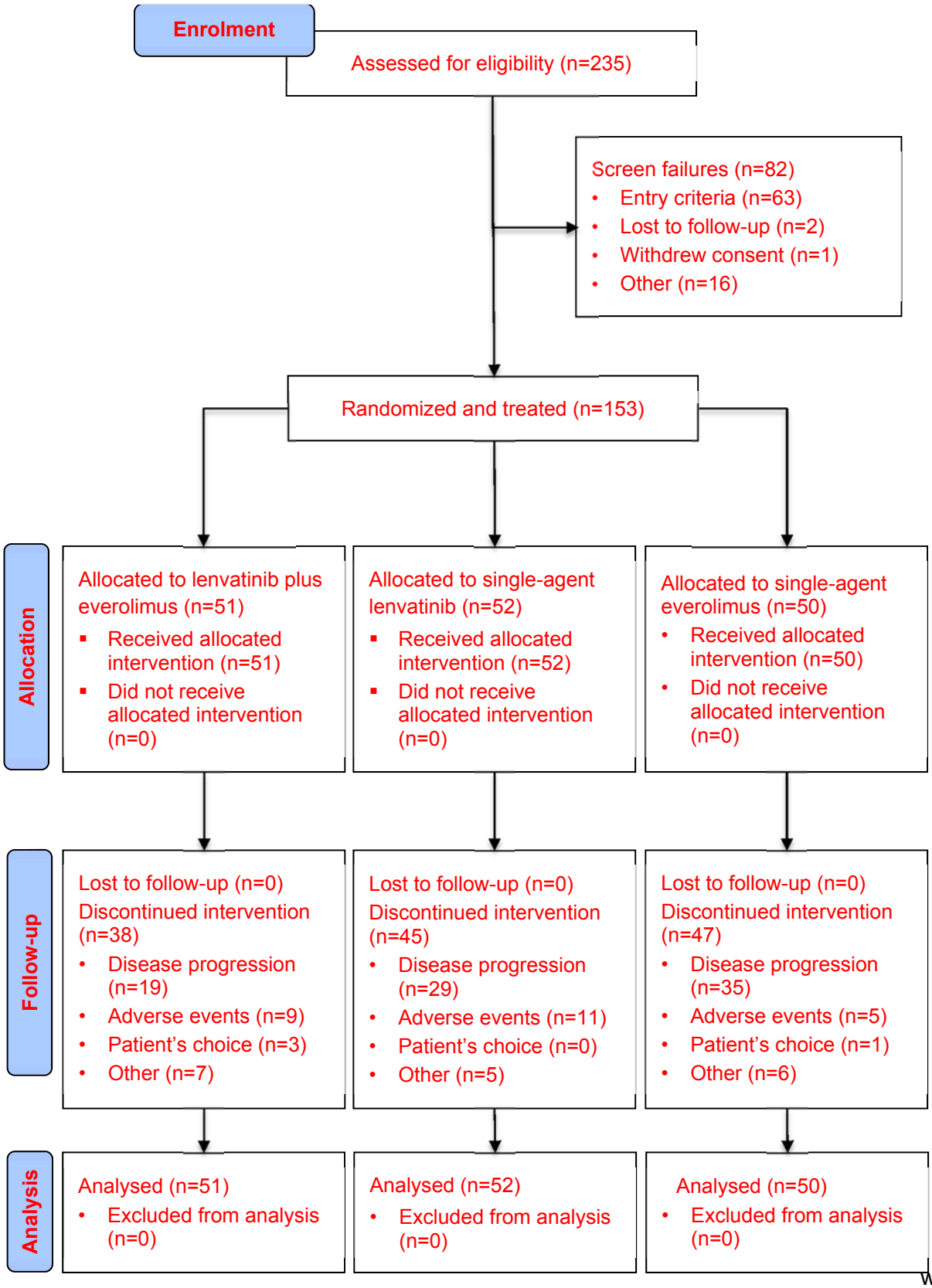
CONSORT 2010 Flow diagram E7080-G000-205 study



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C7. Please provide a reference for the proportion of m/aRCC expected to receive first line therapy (CS, Section 6).

The proportion of m/aRCC expected to receive first line systemic therapy is provided in Table 9 of the RCC treatment architecture report developed by Kantar Health (2015).

C8. Please confirm if duration of prior VEGF-targeted therapy in Figure 21 are reported as mean or median.

The duration of prior VEGF-targeted therapy in Figure 21 are reported as median.

C9. The economic model labels the "third data cut" as 2016. Please clarify if this is the 31 July 2015 data cut as specified in the CS.

Yes this is the 31 July 2015 data cut as specified in the CS. The model labels it as 2016 as this was when the data was submitted to the EMA. Eisai apologises for the lack of consistency.

C10. The results of the probabilistic sensitivity analysis in the model are very different to those results reported on page 174 of the CS. Please clarify whether the results given in the CS are correct.

Eisai believe that the PSA results presented in the CS were correct, but we identified some errors in the functionality of the PSA in the model originally submitted as part of the CS. These have been corrected in the revised model and updated PSA results are presented after Question B19 in this response.

C11. The utility values measured in the AXIS trial are not provided in the reference stated (Rini *et al.* 2011). Please clarify the reference for these utility values.

The utility values measured in the AXIS trial which were referred to in the CS on page 149 and used in the base case were taken from the axitinib NICE company submission – Table 42 on page 158.

C12. Please clarify whether Table 30 in the Clinical Study Report (E7080-G000-205) gives the numbers of treatment-emergent adverse events or treatment-related adverse events. The table header uses both terms.

Table 30 in the Clinical Study Report gives the numbers of treatment-related adverse events which includes treatment-emergent adverse events (TEAEs) that were considered by the investigator to be possibly or probably related to study treatment or TEAEs with a missing causality.

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References

1. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1(3-4):258-71.
2. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.
3. Claxton, K., Sculpher, M., McCabe, C., Briggs, A., Akehurst, R., Buxton, M., ... & O'Hagan, T. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health economics 2005*; *14*(4):339-347.

Single Technology Appraisal

Lenvatinib in combination with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Dear Eisai Ltd,

The Evidence Review Group, the BMJ Technology Assessment Group, and the technical team at NICE have looked at the submission received on 31 March 2017 from Eisai. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on Thursday 11 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk)

Yours sincerely

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A3. **Priority question**. As the proportional hazards assumption does not seem to hold within all trials in the network please re-assess PFS and OS in the ITC using alternative methods which do not rely on proportional hazards, e.g. as described by Ouwens et al. 2010 or Jansen et al. 2011 in GID-TA10075 (AC1 committee papers, CS Section 4.10.4, pages 91-93, and AC2 committee papers, company response Section 1, pages 6-8.1, 2).

- Based on the uncertainty within the network connecting axitinib to lenvatinib + everolimus, please consider assuming that axitinib has a similar efficacy to everolimus monotherapy for all outcomes when re-analysing the ITC; an assumption that has been accepted by the assessment committee for both the nivolumab (TA417, ACD1) and cabozantinib (GID-TA10075, ACD1) STAs.

- Please use independently assessed data for all trials where this is available (all trials except CheckMate 025) irrespective of main analysis reported in trial. For CheckMate 025 please use the investigator assessed outcome data.

- Please also use the full trial population rather than the subgroup of patients with one prior TKI from METEOR, and CheckMate 025 (and from RECORD-1 if using full network), as was done in the CS.

- If you decide not to assume similar efficacy of axitinib and everolimus, and therefore the network will still include RECORD-1, TARGET and AXIS, please use:

    - the subgroup of AXIS who have had prior sunitinib and

    - RPSFT crossover adjusted data for RECORD-1 and placebo-censored data for TARGET, as was done in the CS.

Eisai have re-assessed PFS and OS in a Bayesian network meta-analysis (NMA) using fractional polynomials as described by Jansen et al. 2011. The full report of this analysis is provided separately in an Appendix and the methodology and results are summarised below.

As requested, Eisai have assumed that axitinib and everolimus monotherapy have similar efficacy, in accordance with advice received from clinical experts and the NICE assessment committee for cabozantinib (GID-TA10075) and nivolumab (TA417).

Eisai maintains that the investigator assessed PFS for HOPE 205 is the most appropriate to use for this analysis. It is consistent with the data used in the cost effectiveness model and provided previously in response to B1 and B2 of the clarification questions. As stated in the Company Submission (CS) in Section 4.6, the study protocol specified that tumour response data were obtained from investigator's assessment of the imaging scans and no independent tumour assessments were performed.

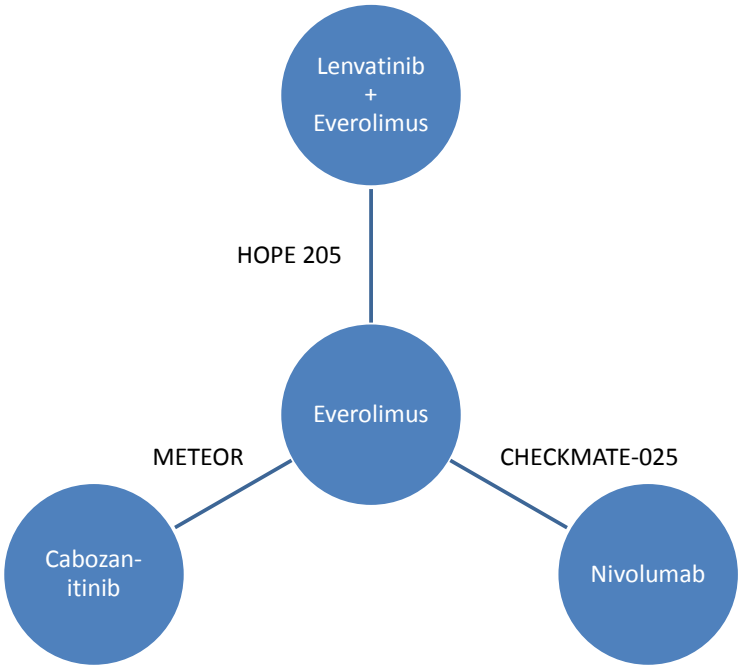
An ad hoc analysis of efficacy using independent radiological review for response assessment was later undertaken upon request of the EMA. Therefore, the protocol

specified progression would be ascertained based on investigator assessment which resulted in some patients being classified with progressive disease before the ad hoc analysis by the IRR committee. These patients may have then switched to subsequent therapy and had no further scans available for IRR, introducing potential bias in the IRR results.

Therefore, the analysis is based on investigator assessment of PFS for HOPE 205 and CHECKMATE-025, and independently assessed data for METEOR.

As requested above, the analysis includes the full populations for all trials, as was done in the CS. The latest data cut (31 Jul 2015) is used for PFS and OS in HOPE 205.

Network of trials included in the ITC for a/mRCC



a/mRCC, advanced/metastatic renal cell carcinoma; ITC, indirect treatment comparison.

ITC Methods

Survival data was digitally extracted from the relevant KM curves for CHECKMATE-025 and METEOR to prepare data for the fractional polynomial NMA and to assess the proportional hazards assumption.

The proportional hazards assumption was violated for PFS in CHECKMATE-025 and METEOR studies. The test for proportional hazards for PFS was not statistically significant for HOPE 205; however, the test was underpowered due to the sample size and the diagnostic plots were similar to the other studies. The proportional hazard assumptions held for OS within the HOPE 205 and METEOR trials, but not for CHECKMATE-025.

Details of the digitisation and assessment of the proportional hazards assumption are provided in the Appendix.

The efficacy of lenvatinib plus everolimus was compared with cabozantinib and nivolumab using a NMA with parametric fractional polynomial survival functions which do not rely on the proportional hazard assumption. This method, described by Jansen 2011, allows a wide family of survival functions to be modelled including Weibull and Gompertz. Only fixed effects models were considered as there was limited time available for these new analyses. It is anticipated that random effects models may be less stable due to only three trials being available across the four treatments of interest. The ERG accepted only fixed effects results for the cabozantinib submission (ERG review of Company response to ACD, p2).

First order fractional polynomial for hazard function:

$$\ln(h_{jkt}) = \beta_{0jk} + \beta_{1jk} t^{P1}$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} & if\ k = b \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} + \begin{pmatrix} \delta_{0jk} \\ \delta_{1jk} \end{pmatrix} & if\ k \neq b \end{cases}$$

$$\text{where } \begin{pmatrix} \delta_{0jk} \\ \delta_{1jk} \end{pmatrix} = \begin{pmatrix} d_{0k} \\ d_{1k} \end{pmatrix} - \begin{pmatrix} d_{0b} \\ d_{1b} \end{pmatrix}$$

Second order fractional polynomial for hazard function:

$$\ln(h_{jkt}) = \begin{cases} \beta_{0jk} + \beta_{1jk} t^{P1} + \beta_{2jk} t^{P2}\ if\ P1 \neq P2 \\ \beta_{0jk} + \beta_{1jk} t^{P1} + \beta_{2jk} t^{P1} \ln(t)\ if\ P1 = P2 \end{cases} \quad with\ t^0 = \ln(t)$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \\ \beta_{2jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} & if\ k = b \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} + \begin{pmatrix} \delta_{0jk} \\ \delta_{1jk} \\ \delta_{2jk} \end{pmatrix} & if\ k \neq b \end{cases}$$

$$\text{where } \begin{pmatrix} \delta_{0jk} \\ \delta_{1jk} \\ \delta_{2jk} \end{pmatrix} = \begin{pmatrix} d_{0k} \\ d_{1k} \\ d_{2k} \end{pmatrix} - \begin{pmatrix} d_{0b} \\ d_{1b} \\ d_{2b} \end{pmatrix}$$

where *j* denotes study (1 to 3), *k* denotes treatment (1 to 4), *b* denotes 'baseline' treatment (everolimus) and *t* denotes time.

Thus, h_{jkt} is the hazard rate for intervention *k* in trial *j* at time *t* with parameters β which comprises the vectors μ for the 'baseline' treatment (everolimus) and δ for the difference in log hazard curves for treatment *k* relative to 'baseline' (everolimus). Under the proportional hazards assumption d_1 is zero and thus non zero estimates of d_1 reflect the change in the log hazard ratio over time.

Model parameters were estimated using Markov Chain Monte Carlo (MCMC) method in WinBugs. Two chains were run for 50,000 iterations and discarded as 'burn-in, and then the

model was run for a further 50,000 iterations for inference. Non-informative priors were used for μ and *d*. Diagnostic plots were examined for convergence including the Gelman-Rubin statistic. The powers for the fractional polynomials were chosen from the set: -2, -1, -0.5, 0, 0.5, 1, and 2, although due to time constraints not all possible second order models were considered. The Deviance Information Criterion (DIC) was used to compare the goodness of fit. The model with the lowest DIC provides the 'best' fit to the data.

WinBugs code and data for the fractional polynomial NMA are available in the Appendix.

ITC Results

Progression-free survival

The model fit statistics for PFS are provided below. The 'best' model fit for PFS was a second order fractional polynomial model (P1=-2, P2=-2). This model provided a better fit (DIC=777.2) than the second order model used in the cabozantinib submission (P1=-1, P2=-1) when fitted to the three trials here (DIC=831.6). Visual inspection of the best fitting model overlaid on the KM data demonstrates a good fit for all treatments (See Figure overleaf.)

Alternate models, including the "best" fitting first order fractional polynomial model are available in the Appendix.

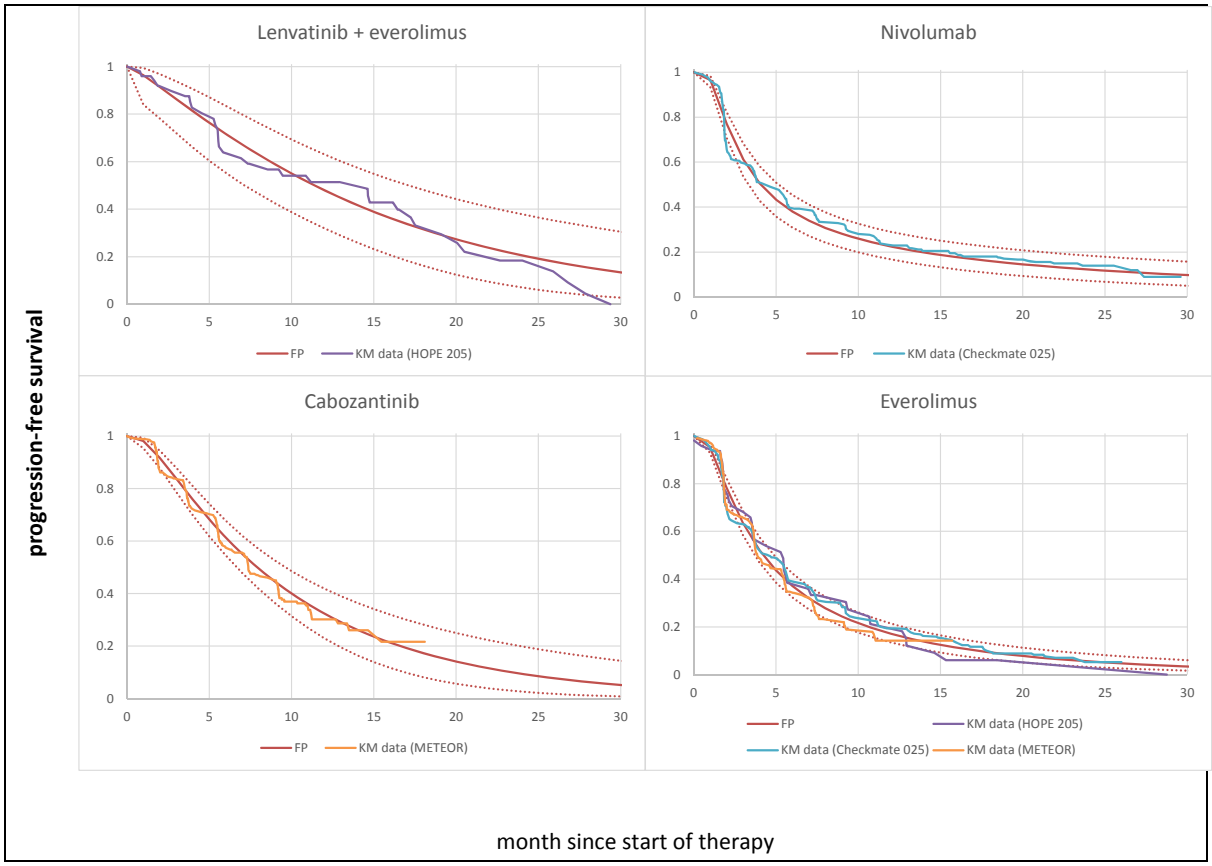
Model fit statistics from the fractional polynomial models: PFS

	Power P1	Power P2	Posterior mean residual deviance (Dbar)	Deviance posterior mean of parameters (Dhat)	Effective number of parameters (pD)	Deviance Information Criteria (DIC)
First order	-2	-	994.692	982.88	11.812	1006.50
	-1	-	1033.78	1021.85	11.929	1045.71
	-0.5	-	1044.51	1032.60	11.912	1056.42
	0[a]	-	1039.69	1027.75	11.937	1051.63
	0.5	-	1041.43	1029.55	11.883	1053.32
	1[b]	-	1039.69	1027.75	11.937	1051.63
Second order	**-2**	**-2**	**759.534**	**741.872**	**17.662**	**777.195**
	-2	-1	779.985	762.174	17.811	797.796
	-2	-0.5	797.518	779.546	17.971	815.489
	-2	0	819.970	802.04	17.93	837.901
	-1	-1	813.642	795.713	17.929	831.572
	-1	-0.5	837.816	820.079	17.738	855.554
	-1	0	866.012	848.061	17.951	883.963
	-1	0.5	894.846	877.211	17.634	912.480
	-0.5	-0.5	922.695	905.491	17.204	939.899
	-0.5	0	893.703	876.932	16.770	910.473
	-0.5	0.5	922.829	905.494	17.335	940.165
	0	0	923.591	905.952	17.639	941.230
	0	0.5	951.466	934.04	17.426	968.892

PFS, progression-free survival

Notes: a corresponds to Weibull distribution for hazard function; b corresponds to Gompertz distribution for hazard function.

Fitted PFS based on the best fitting fixed-effects second-order fractional polynomial model (P1=-2, P2=-2) overlaid on extracted KM data



FP, fractional polynomial; KM, Kaplan-Meier; PFS, progression-free survival.
Notes: dotted lines represent 95% credible intervals.

The hazard ratios over time for PFS resulting from this model are presented in the Appendix and show that lenvatinib plus everolimus is superior (hazard ratio less than 1) to everolimus monotherapy, cabozantinib and nivolumab from about two months; however the 95% credible intervals cross 1 indicating these differences are not statistically significant. The survival curves further illustrate PFS is higher for lenvatinib plus everolimus than the other treatments after the first two months although the credible intervals overlap.

Overall survival

The model fit statistics for OS are provided below. The 'best' model fit for OS was a first order fractional polynomial model (P1=-1). This model has the same powers as the model with the 'best' fit in the cabozantinib submission for two trials only (CHECKMATE-025 and METEOR). Visual inspection of the best fitting model overlaid on the KM data demonstrates a reasonable fit (see Figure overleaf); however, survival was consistently underestimated for nivolumab. The model fit statistics are based on the average fit across the network; that is, the fractional polynomial may not fit any individual treatment well but, on average, the family of curves is the best fit for the network.

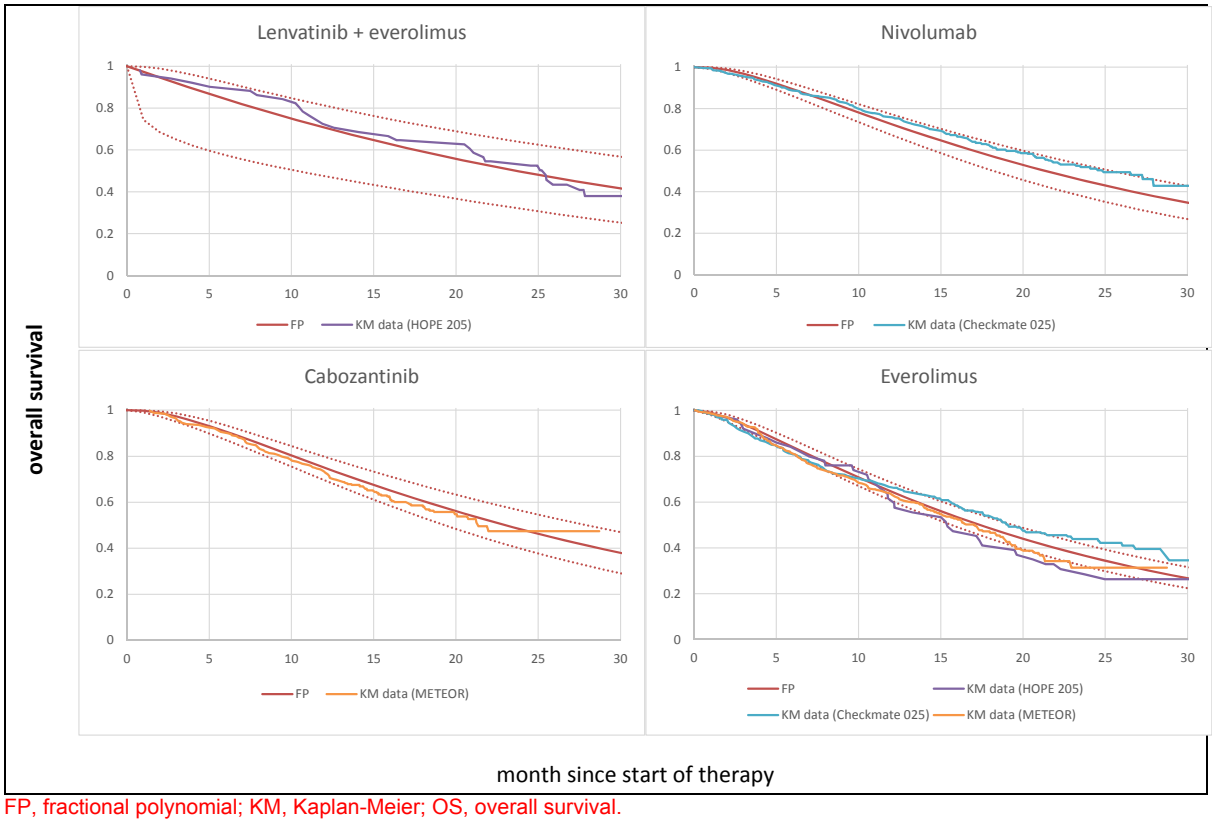
Model fit statistics from the fractional polynomial models: OS

	Power P1	Power P2	Posterior mean residual deviance (Dbar)	Deviance posterior mean of parameters (Dhat)	Effective number of parameters (pD)	Deviance Information Criteria (DIC)
First order	-2	-	630.175	618.724	11.451	641.626
	-1	**-**	**628.476**	**616.68**	**11.796**	**640.272**
	-0.5	-	632.259	620.47	11.789	644.048
	0	-	639.797	628.004	11.793	651.589
	0.5	-	649.446	637.466	11.979	661.425
	1	-	658.530	646.507	12.024	670.554
Second order	-2	-2	627.884	611.093	16.791	644.676
	-2	-1	625.923	609.044	16.878	642.801
	-2	-0.5	625.482	608.276	17.207	642.689
	-2	0	624.455	607.389	17.066	641.521
	-2	0.5	624.521	607.274	17.247	641.768
	-2	1	624.615	607.341	17.274	641.889
	-1	-1	626.519	609.207	17.312	643.830
	-1	-0.5	627.051	609.43	17.621	644.672
	-1	0	627.233	609.908	17.325	644.558
	-1	0.5	628.234	610.518	17.716	645.950
	-1	1	628.295	610.958	17.337	645.632
	-0.5	-0.5	628.497	611.058	17.439	645.935
	-0.5	0	629.071	612.634	16.437	645.508
	-0.5	0.5	630.831	613.733	17.097	647.928
	-0.5	1	632.44	614.947	17.494	649.934
	0	0	634.317	615.649	18.668	652.985
	0	0.5	634.945	617.718	17.227	652.172
	0	1	636.981	619.517	17.464	654.444
	0.5	0.5	639.018	622.162	16.855	655.873
	0.5	1	642.103	624.325	17.778	659.881

OS, overall survival

Notes: a corresponds to Weibull distribution for hazard function; b corresponds to Gompertz distribution for hazard function.

Fitted OS based on the best fitting fixed-effects first-order fractional polynomial model (P1=-1) overlaid on extracted KM data



FP, fractional polynomial; KM, Kaplan-Meier; OS, overall survival.
Notes: Dotted lines represent 95% credible interval.

The hazard ratios over time for OS resulting from the 'best' fitting model are presented in the Appendix and show that lenvatinib plus everolimus is superior (hazard ratio less than 1) to everolimus monotherapy, cabozantinib and nivolumab from approximately two (everolimus) to eight (cabozantinib) months; however the 95% credible intervals cross 1 indicating these differences are not statistically significant. The survival curves further illustrate OS is higher for lenvatinib plus everolimus than everolimus from around 8 months and higher than cabozantinib and nivolumab from around 20 months although the credible intervals overlap.

Alternate models and further results from the ITC analysis are available in the Appendix.

Revised cost effectiveness model and results

As per the NICE committee's preferred option during the cabozantinib review in GID-TA0075 (Second ACD, page 13), in the revised cost-effectiveness model which has been provided separately, Eisai have included scenario analyses using fractional polynomial modelling across the entire time horizon for both overall and progression-free survival.

Two scenarios have been included in the model for PFS and OS, the "best" fitting first-order and "best" fitting second-order models, respectively. This structure enables the ERG to test for both first and second order models for any parameters. Please note that for OS, the second order model P1=-1, P2=0 has been provided, as the best fitting model according to DIC (P1=-2, P2=0), did not fit LEN+EVE well and significantly underestimated OS. Second

order models with higher powers (P1≥-1) provided better a fit for lenvatinib plus everolimus, but not overall (as indicated by DIC).

As indicated above, for PFS, the 'best' model fit was a second order fractional polynomial model (P1=-2, P2=-2). For OS, the 'best' model fit was a first order fractional polynomial model (P1=-1).

Scenario analysis: Best model fit for both: PFS (P1=-2, P2=-2) and OS (P1=-1)

The results of this scenario are presented in the following table

	LEN+EVE / AXI	LEN+EVE / CAB	LEN+EVE / NIV	LEN+EVE / EVE
Submitted Basecase	32,906	1,683	17,146	96,403
Amended Basecase*	32,971	2,167	7,299	122,404
Current option*	28,743	16,083	10,730	160,142

**Note: Includes modifications to EVE prices and removal of oral administration costs*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it 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.

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.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Kidney Cancer Support Network

Your position in the organisation: [redacted]

Brief description of the organisation:

(For example: who funds the organisation? How many members does the organisation have?)

Kidney Cancer Support Network (KCSN) was founded in 2006 by cancer patients/survivors Rose Woodward and Julia Black, who started by offering 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, more generally, 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 900 kidney cancer patients and carers, and a further 600+ active and committed patients and carers on its confidential social networking sites. KCSN is unique; until recently it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Although KCSN remains patient-led, the group is now a registered charity, which enables it raise the funds to better meet the growing needs of the kidney cancer community it represents.

KCSN is funded by grants from trusts/foundations/grant-making organisations and the pharmaceutical industry, in addition to donation from patients and fundraising events/activities carried out by the kidney cancer community in the UK.

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: None

2. 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?

Kidney Cancer Support Network (KCSN) is a patient-led kidney cancer charity with the largest and most active patient and carer membership across the UK. As such, we feel we are in the strongest position to feedback how metastatic renal cell carcinoma (mRCC) affects the day-to-day lives of people living with this disease.

In 2014, there were more than 12,500 new cases of kidney cancer diagnosed in the UK (34 cases diagnosed every day) and kidney cancer is the seventh most common cancer affecting British people (2014). Kidney cancer accounts for 3% of all new UK cancer cases (2014). In 2014, nearly 4,500 people died from the disease and about 40% of kidney cancer patients will

be diagnosed with late stage disease. In these cases, it is estimated that around only 10% of people will survive for five years or more (Cancer Research UK). It is difficult to remain positive in the face of figures like this.

Metastatic RCC is a devastating disease and is currently incurable. The majority of mRCC patients are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings with it 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 more rare 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, while spread of the cancer to the brain can lead to severe and debilitating headaches, confusion and, in some cases, paralysis. Kidney function is often compromised and patients find daily living difficult, often needing periods of rest during the day. Patients diagnosed with hereditary kidney cancer or rare RCC subtypes currently have very limited treatment options.

Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period of time. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Clinicians in the UK should have the ability to choose the most effective treatments for individual patients from those available. Without a choice of treatment alternatives in the second- and third-line, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second- and third-line therapy to continue managing their disease, and to maintain quality of life.

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. Kidney cancer cases are rising year-on-year and there is a strong unmet need for second- or third-line treatment with better overall survival rates than currently exist, especially for difficult-to-treat rare subtypes of RCC. The impact of a terminal diagnosis on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one has come to the end of their available treatment options.

3. 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 most patients, the most important treatment outcome would be no evidence of disease, i.e., a potential cure for their kidney cancer. The hope of achieving this outcome spurs patients on to continue to take current medication, despite significant toxicity, and to search for alternative, more effective treatments that can extend overall survival. Failing no evidence of disease, tumour shrinkage or disease stability would be the next best outcome for patients.

In addition to treatment outcomes, quality of life is also an important consideration for many patients. Most patients would prefer a treatment that allows them to continue to lead as normal a life as possible, and to contribute both socially and economically to their communities:

> *"The extra years, which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various ……. enterprises which I manage……..I'm making a hugely positive contribution to society, and the wider economy, and I wish to be able to carry*

on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities".

"……has enabled me to enjoy every day, do 3 or 4 days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths……".

Although less serious than some of the side effect to current treatment, some patients find the changes to their appearance caused by current first-line treatments distressing: white, thinning hair, and pale skin make them feel nearer to death and also singles people out as cancer patients. Some of the current treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The current treatment pathway for mRCC is for surgery (either radical or partial nephrectomy), followed by either sunitinib or pazopanib in the first-line setting, and axitinib or everolimus in the second-line setting, all of which are oral medicines and have similar modes of action. Recently, nivolumab was recommended for use within NHS England for second- or third-line treatment of mRCC, and is the first third-line treatment in use by the NHS. Nivolumab is an immunotherapy (anti-PD-1), which is administered as a biweekly intravenous infusion, requiring outpatient hospital treatment (chemotherapy chair resources), and the associated travel time and expense for the patient and carer.

We have extracted the following details from statements submitted to the KCSN by patients living with mRCC. Using currently available drugs, many patients suffer with:

• Extreme fatigue

• 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

All the above side effects require additional medicines to help patients manage the drugs and/or tumour pain, which requires opioid prescriptions. Costs for additional medicines to mitigate the side effects of these targeted therapies should be taken into account.

Other less serious side effects, which still affect the patient's quality of life, are loss of taste, loss of and change of hair colour, depression, loss of libido, and inability to drive. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment as a result of severe side effects. Patients are aware that these treatments are life-extending drugs, but they continue to look for drugs with different modes of action, which can give improved overall survival with better quality of life.

The following statements from mRCC patients on axitinib and everolimus highlight the impact of these drugs on quality of life:

"….. my husband started on Axitinib. We had hoped this drug would work well but the treatment was stopped …. when my husband developed severe sepsis. ……. Axitinib caused severe side effects for my husband and at times he was unable to eat or walk. Axitinib caused diarrhoea, severe blistering to feet and mouth and we had to

seek help from a chiropodist to try and enable him to walk but even she couldn't help him. In all my husband lost 5 stone in weight during his time on TKIs."

"I was on pazopanib when my oncologist determined that it was starting to fail. At that point I was advised that everolimus was to be made available to me. Initially side effects were minimal, however about a month [sic] I started to get very bad mouth ulcers, which took a few weeks to clear up, fatigue and tiredness. Also experienced anaemia and had 2 blood transfusions. I suffered from nosebleeds, mainly when blowing my nose! Lung condition didn't help and was experiencing dry cough and breathlessness as well. Experienced lots of indigestion also had mild doses of feeling shaky and shivery. Ct scan showed that everolimus was struggling ……".

4. What do patients or carers consider to be the advantages of the treatment 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 being appraised.

Clinicians in the UK should have the ability to choose the most effective treatments for individual patients from those available. 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, selection of the most effective treatment for individual patients is accomplished by trial and error. Without the lenvatinib/everolimus combination, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the second-line, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second-line therapy to continue managing their disease, and to maintain quality of life.

The current second-line treatment options are not effective for everyone, and can be difficult to access. Axitinib, everolimus and nivolumab are the only second-line treatments available to patients in England on the NHS. Undue restrictions in accessing the lenvatinib/everolimus combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Choice in the second-line, and access to new innovative treatments remains paramount to managing the progression of this disease. Having a choice in second-line treatment 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.

Please explain any advantages that patients or carers think this

treatment has over other NHS treatments in England.

The lenvatinib/everolimus combination is the second drug combination for the treatment of advanced RCC to undergo NICE appraisal (the first being the bevacizumab/interferon combination). Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However, the lenvatinib/everolimus combination seems to be well tolerated, as well as proven to be more effective at extending overall survival compared to single agent therapy with lenvatinib and everolimus. In addition, a number of drug combinations have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the lenvatinib/everolimus combination could, therefore, be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment 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.

Patients/carers have the following main concerns regarding current NHS treatments for mRCC in England:

- Current treatments do not cure mRCC: the disease can be controlled for, on average, 2 years with current first-line treatments, after which second-line treatments can extend life for another year or more. Patients need more choice in the second-line to effectively manage their disease and give them good quality life
- There are no biomarkers of response to treatment with current NHS treatments, and clinicians are unable to predict which patients will respond to which drug. This results in patients being unnecessarily exposed to the side effects of current treatment without the benefits of the drug if they are found to be non-responders. Selection of the most effective treatment for individual patients is accomplished by trial-and-error.

- The toxicity of current treatments is a concern for patients, as described in section 3 above.
- Some of the side effects of current treatments, such as depression, loss of libido, inability to drive, hair and skin changes all have an impact on the psychological well-being and quality of life of patients, which negatively impacts family/social life and work life. Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental health
- The impact of a terminal diagnosis on the family, as well as the patient, is also a major concern, both in terms of the psychological wellbeing of family members and the financial situation of the family if the patient is unable to return to work.

Please list any concerns patients or carers have about the treatment being appraised.

The lenvatinib/everolimus combination is currently not available to patients anywhere in the UK, via the Early Access to Medicines Scheme (EAMS), clinical trials or managed access programmes. Since the completion of study 205, the most recent clinical trial for lenvatinib/everolimus in mRCC, in June 2014, most of the UK patients have sadly died. We have, therefore, been unable to determine any concerns patients or carers have about the lenvatinib/everolimus combination.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

See comment above

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

A number of drug combinations have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the lenvatinib/everolimus combination could, therefore, be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

None

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ 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 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 how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects 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.

8. 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.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Patients who have conditions that make it difficult to swallow tablets or gastrointestinal conditions that interfere with the absorption of the drug, for example ulcerative colitis.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The lenvatinib/everolimus combination is the second drug combination for the treatment of mRCC to undergo NICE appraisal (the first being the bevacizumab/interferon combination). Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However, the lenvatinib/everolimus combination seems to be well tolerated, as well as proven to be more effective at extending overall survival compared to single agent therapy with lenvatinib and everolimus.

This has led to the lenvatinib/everolimus combination designated a breakthrough therapy by the FDA as a treatment for advanced or metastatic RCC. As a breakthrough therapy, the lenvatinib/everolimus combination has been fast tracked for approval in a number of countries, including the US and Europe, based on the phase 3 clinical trial data.

Are there any other issues that you would like the Appraisal Committee to consider?

Lenvatinib is a multiple kinase inhibitor against VEGF kinases, in addition to other tyrosine kinases implicated in pathogenic angiogenesis, tumour growth and cancer progression. It is the first multiple kinase inhibitor to gain marketing authorisation in North America and Europe for advanced RCC, and has proven to be effective in the treatment of certain kinds of thyroid cancer. 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 patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs 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 the rest of Europe and North America.

A number of clinical trials have been conducted in previously treated advanced/metastatic RCC patients with the lenvatinib/everolimus combination in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of lenvatinib/everolimus on the NHS, we would have to question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drug is rejection by NICE.

We appreciate that the lenvatinib/everolimus combination is expensive, and we urge NICE and the manufacturer to negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as professional inadequacy. NICE and the manufacturer need to think outside the box to negotiate an alternative funding scheme, for example, the government could pay for those cases where

lenvatinib/everolimus is effective, and the manufacturer reimburse the NHS for those cases who do not respond to treatment. This will require more collaborative working with the manufacturer to negotiate an acceptable patient access scheme.

Current treatments have proven to shrink tumours and delay disease progression in some patients, but adding the lenvatinib/everolimus combination as a choice in the second-line (and beyond) enables patients and clinicians to have individualised treatment plans to better control this disease and maintain a high quality of life. It could also address the massive unmet need for treatment options in the third-line.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Lenvatinib is the first multiple kinase inhibitor to be granted marketing authorisation for mRCC in North America and Europe. The lenvatinib/everolimus combination has been designated a breakthrough therapy by the FDA
- The lenvatinib/everolimus combination seems to be well tolerated, as well as proven to be more effective at extending overall survival compared to single agent therapy with lenvatinib and everolimus
- The lenvatinib/everolimus combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC
- Adding the lenvatinib/everolimus combination as a choice in the second-line (and beyond) enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life
- The lenvatinib/everolimus combination addresses the massive unmet need for treatment options in the third-line.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it 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.

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.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: [redacted]

Your position in the organisation: Medical writer

Brief description of the organisation: We provide support to patients and families of people with kidney cancer, raise awareness, run campaigns, provide information and fund research into kidney cancer. The organisation is funded by donations and each year we communicate with 3640 new patients.

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: None

2. 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?

Different people will react to living with kidney cancer differently 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.

3. 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.

Treatment outcomes would most certainly include 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.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

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. 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 recent introduction of nivolumab (immunotherapy) as a NICE recommended 2nd line drug is very good news. We are awaiting reports back on how effective this drug is for patients and we are hopeful that in the future immunotherapies and combinations of treatments may give alternate options and even better results.

Giving alternate options for patients can be invaluable especially in an era where personalised medicine may be introduced. It may be found that tivozanib works for a set of patients where other treatments fail. A multitude of treatment options is always desirable.

4. What do patients or carers consider to be the advantages of the treatment 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 being appraised.

The use of a combination of lenvatinib and everolimus together doubled the progression free survival and extended the overall survival of patients by 10.1 months, when compared to everolimus alone, in the phase II trial. (Motzer et al, 2015) Any increase in survival is priceless for people with advanced kidney cancer. Enabling them to spend time with their family and share important life events.

The side effects were increased in when the two drugs were used in combination but they were manageable.

Motzer R, Hutson T, Glen H, et al. Randomized phase 2 three-arm trial of lenvatinib (LEN), everolimus (EVE), and LNE+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC). J Clin Oncol. 2015;33 (suppl; abstr 4506). - See more at:

http://www.onclive.com/conference-coverage/asco-2015/lenvatinib-plus-everolimus-improves-survival-in-mrcc#sthash.jUeXA61R.dpuf

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Alternative options for the treatment of kidney cancer are very important. Kidney cancer is a very heterogenous disease and some people with advanced kidney cancer may respond one treatment, others may respond to a different treatment. Having a variety of options is very important.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

I don't know of any difference in opinion.

5. What do patients and/or carers consider to be the disadvantages of the treatment 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.

I think patients and carers are concerned over the lack of options available to them.

Coping with the side effects of TKI's are a worry for patients and can affect their quality of life but I think most people with advanced kidney cancer are

willing to take the treatment for the extension of life that it may bring. Any improvement in side effects is a positive.

Some drugs have a greater efficacy in some people and not others. However having a variety of treatments to try is a significant advantage as a different drug might work better and having more options gives hope and comfort to the patient.

Please list any concerns patients or carers have about the treatment being appraised.

I don't know of any concerns

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I don't know of any difference in opinions

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients with advanced (stage 3 or 4) disease are likely to require targeted therapies to extend their life. People who have failed prior systemic treatment are likely to need another treatment option, which introducing an lenvatinib/everolimus combination will provide.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients with early stage disease are less likely to require targeted therapy.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

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 as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The lenvatinib/everolimus combination is not routinely used as part of NHS care yet.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

I think the lenvatinib/everolimus combination is associated with more adverse effects but most patients we have spoken to are willing to manage side effects if the drug will extend their life. This balance should be clearly explained to patients prior to them starting the drug.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

It is not already available on the NHS

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

If yes, please provide references to the relevant studies.

Our kidney Cancer UK annual survey. However, no one who completed the survey was on the lenvatinib/everolimus combination trial.

8. 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.

None known

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

None known

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Drugs are routinely used and recommended by NICE singularly. Kidney Cancer UK feel that treating kidney cancer using combinations of targeted therapies which inhibit multiple intercellular pathways should be explored and it may provide more promising results. We feel that this trial and appraisal is a step in the right direction.

Are there any other issues that you would like the Appraisal Committee to consider?

I think that the number of different options available to people with advanced kidney cancer is very important. Having a variety of options provides hope and comfort.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- People with advanced kidney cancer have very few treatment options and require a variety of drug choices.
- Using a combination of drugs, which inhibit multiple drug targets and cellular pathways is innovative and looks promising.
- PFS and overall survival are very important to the patient and to most it would be the number one consideration when taking a drug.
- Different drugs work for different people. A particular group of people may respond really well to one targeted therapy, others may respond better to another. Having a variety available is important.

NHS England submission on the NICE appraisal of the combination of lenvatinib plus everolimus in the treatment of advanced/metastatic renal cell adenocarcinoma

1. The first line setting of systemic therapy for renal cell carcinoma (RCC) in NHS England currently has the options of either sunitinib or pazopanib. Further lines of treatment can involve axitinib or nivolumab or cabozantinib or everolimus, all of them given as single agents. These 4 second line options have differing modes of action and hence NHS England considers them also to be potential options beyond 2nd line therapy if it is appropriate for patients to receive further treatment (ie if they remain fit for treatment and do not have clearly refractory disease).
2. NHS England notes the expected marketing authorisation to state that the combination of lenvatinib plus everolimus is for patients with advanced RCC following1 prior VEGF targeted treatment. This is in keeping with this combination being a potential option in the 2nd line therapy place in the RCC treatment pathway as outlined above.
3. The main evidence base for the licensing of the combination of lenvatinib plus everolimus is unusual for a drug which has a marketing authorisation as a 2nd line treatment option in advanced/metastatic RCC in that it is from a 3 arm randomised phase II study which enrolled a total of only 153 patients. However the comparison of lenvatinib plus everolimus versus everolimus reduces to a total of only 101 patients and thus to a very small evidence base.
4. This small evidence base for the comparison of lenvatinib plus everolimus versus everolimus has consequences in that there is an imbalance in randomisation in factors such as previous treatments (previous sunitinib 71% vs 56%, pazopanib 18 vs 26%), previous nephrectomy (86% vs 96%).
5. The trial was also open label with a primary end point of progression free survival (PFS) as assessed by the investigators who were unblinded to the treatment received. There is no doubt that the difference in investigator assessed PFS is impressive (14.6 mo vs 5.5 mo and based on a total of 101 events in the 3 arm 153 patient study). NHS England observes that both the FDA and the EMA requested an ad hoc, retrospective, blinded and independent radiological review which assessed a total of 86 progression events (90 were required by the statistical analysis plan). This independent review showed that median PFS for the comparison of lenvatinib plus everolimus vs everolimus was 12.6 mo vs 5.6 mo, there being 24 and 29 progression events in the two arms, respectively. The evidence base for the combination of lenvatinib plus everolimus is thus very small and far smaller than any of the other 4 NICE-approved options as 2nd line therapies for the treatment of advanced RCC. The blinded independent and investigator assessments agreed in 74% of cases as to whether the disease had progressed or not. In view of the small numbers, the open label design, the unblended response assessment by the investigators and the retrospective blinded independent assessment of response, NHS England therefore

concludes that there is considerable uncertainty as to the degree of benefit of the combination of lenvatinib plus everolimus.

6. There was a difference in observed overall survival (OS) between the lenvatinib plus everolimus and the single agent everolimus arms, 25.5 mo vs 15.4 mo but this was not statistically significant (the study was not powered to demonstrate OS benefit). In addition, NHS England observes that there were very few patients at risk after 27 months.
7. Impressive as the difference in PFS is, there is no doubt that the combination of lenvatinib plus everolimus has much more toxicity than single agent everolimus. Grades 3 or 4 treatment emergent adverse events were 73% vs 54% of which grade 3 or 4 vomiting was 6% vs 0% (such a degree of vomiting is serious for an oral drug administered daily). The side-effects that more related to the lenvatinib plus everolimus were diarrhoea, loss of appetite, fatigue, nausea and vomiting, cough and weight loss. The rates of premature discontinuation of treatment were 42% vs 24%, of dose reductions were 68% vs 16% and of dose interruptions were 76 vs 50%. The average dose of lenvatinib taken by patients in the study was 13mg, a clinically significant reduction from the starting dose of 18mg. NHS England also notes the small size of the safety database in relation to the combination of lenvatinib plus everolimus.
8. NHS England observes that despite a median PFS exceeding 1 year for the combination of lenavitinib plus everolimus, the median duration of treatment for lenvatinib was only 7.6 mo, further evidence of the toxicity of this combination. NHS England notes too that everolimus was often continued in the combination arm after the lenvatinib had been stopped.
9. Given the large difference in PFS but clearly also the increased toxicity of the combination of lenvatinib plus everolimus, the vital importance of quality of life for patients with advanced RCC having such treatment cannot be stressed too highly. There was no quality of life measurement in the randomised phase 2 trial which is a very important consideration as NHS England understands that a phase III trial is not planned to corroborate the results of this randomised phase II study. NHS England would therefore wish to ensure that the treatment-related adverse events are fully translated into the appropriate utility decrements in the economic modelling. In addition, NHS England notes that the utilities used in the company's economic model came from the AXIS trial in which none of the treatment arms contained lenvatinib or everolimus (the AXIS trial compared axitinib with sorafenib).
10. NHS England notes that the trial patients were all of performance status 0 or 1 and states that if the combination of lenvatinib plus everolimus is recommended by NICE that it will only commission use of the combination in this fit group of patients.
11. NHS England agrees with the ERG that the use and cost of subsequent therapies must be incorporated into the economic model. The majority of patients progressing after 2nd line lenvatinib plus everolimus would be considered for active treatment

provided they remained fit enough to do so and did not have clearly refractory disease. Incorporation of the survival benefit of subsequent treatments has to be accompanied by the costs of such therapies.

12. NHS England's conclusion is that a limited evidence base exists which points to an impressive increase in PFS for the combination of lenvatinib plus everolimus at the cost of clinically and significantly increased side-effects but without any evidence of these impacts on quality of life and other patient reported outcome measures. An independent and blinded retrospective review confirms the difference in PFS to be substantial although not as great as when assessed by the unblinded investigators. There does not seem any likelihood of phase III evidence to confirm these results and to address the uncertainties that are generated by the randomised phase II study being the only evidence on which to appraise the clinical and cost effectiveness of an exciting but toxic combination of lenvatinib plus everolimus without directly measured quality of life data from the same patients enrolled in the study.

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

July 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Professor John Wagstaff

Name of your organisation
Swansea University and Abertawe Bro Morgannwg University Health Board

Are you (tick all that apply):

- ✓a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- ✓an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

I have no links with or funding from the tobacco industry

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have 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 technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Renal cell carcinoma (metastatic, treated) – lenvatinib [ID1029]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it 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, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

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 response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Lucy Willingale
Name of your nominating organisation: KCUK
Do you know if your nominating organisation has submitted a statement?

☐X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐X No

- a carer of a patient with the condition?

☐ Yes ☐X No

- a patient organisation employee or volunteer?

☐X Yes ☐ No

Do you have experience of the treatment being appraised?

☐X Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here X☐ (If you tick this box, the rest of this form will be deleted after submission.)

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/108/10

BMJ Technology Assessment Group

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Head of Health Technology Assessment, BMJ-TAG, London Charlotta Karner, Health Technology Assessment Analysis Manager, BMJ-TAG, London Peter Cain, Health Economist, BMJ-TAG, London Natalie Masento, Associate Health Technology Assessment Analyst, BMJ-TAG, London Fatima Salih, Health Economist, BMJ-TAG, London Victoria Wakefield, Senior Health Technology Assessment Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ Evidence Centre, BMJ Group, BMA House, Tavistock Square, London, WC1H 9JP.
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None.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Natalie Masento	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and provided feedback on the clinical sections
Peter Cain	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
AE	Adverse event
a/m RCC	Advanced /metastatic renal cell carcinoma
AJCC	American Joint Committee on Cancer
BOR	Best overall response
BP	Blood pressure
BSC	Best supportive care
CBR	Clinical benefit ratio
CDF	Cancer Drug Fund
CI	Confidence interval
CR	Complete response
CS	Company submission
CSR	Clinical study report
DCR	Disease control rate
DIC	Deviance information criterion
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions questionnaire
ESMO	European Society of Medical Oncology
FGF	Fibroblast growth factor
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health related quality of life
HSUVs	Health state utility values
IL-2	Interleukine-2
IMDC	International Metastatic RCC Database Consortium
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LY	Life year
MRI	Magnetic Resonance Image
MSKCC	Memorial Sloane Kettering Cancer Centre
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PDGFR	Platelet-derived growth factor receptor.
PH	Proportional hazards
PFS	Progression-free Survival
PR	Partial response

PS	Performance Status
QALY	Quality-adjusted life year
QoL	Quality of Life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection tyrosine kinase receptor
RTK	Receptor tyrosine kinase
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SY	Subject Years
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
TRAEs	Treatment-related adverse events
TTD	Time to treatment discontinuation
US	Ultrasound
VEGF(R)	Vascular endothelial growth factor (receptor)

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of lenvatinib (Kisplyx®; Eisai) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of lenvatinib in combination with everolimus (Afinitor®; company Novartis) for the treatment of adults with advanced renal cell carcinoma (RCC) who have had one prior vascular-endothelial growth factor (VEGF)-targeted therapy.

In August 2016, lenvatinib was granted European marketing authorisation for use in combination with everolimus for the treatment of adult patients with advanced RCC following one prior VEGF-targeted therapy. The clinical evidence presented in the company's submission (CS) is derived from HOPE 205, an open label, phase II, multicentre randomised controlled trial comparing lenvatinib in combination with everolimus with everolimus monotherapy in patients diagnosed with unresectable or advanced, predominantly clear cell, RCC whose disease had progressed on or within nine months of stopping prior therapy with a VEGF-targeted therapy. The final scope issued by NICE specified the population of interest to be adults with advanced RCC who have had one prior VEGF-targeted therapy. The Evidence Review Group (ERG) considers the population, intervention and comparator in HOPE 205 to be relevant to the decision problem. All clinically relevant outcomes were reported in the CS, except for health-related quality of life (HRQoL), which was not captured in HOPE 205.

In the final scope issued by NICE, the comparators of interest were identified as axitinib, nivolumab, everolimus, cabozantinib (subject to ongoing NICE appraisal [GID-TA10075]), and best supportive care (BSC). All comparators were considered in the CS, except for BSC, which the company did not consider to be a relevant comparator as there are several active second-line treatment options for patients with advanced RCC. The ERG considers all comparators considered in the CS to be relevant and in keeping with those currently used in UK clinical practice for patients with advanced RCC who has progressed on one prior VEGF-targeted therapy.

1.2 Summary of clinical effectiveness evidence submitted by the company

One trial, HOPE 205 comparing lenvatinib in combination with everolimus and everolimus monotherapy, provides the only direct evidence informing the efficacy and safety of lenvatinib combination therapy.

HOPE 205 is an international, multicentre, open label, phase II randomised controlled trial, with around 50 patients in each treatment group. Patients were randomised 1:1 to 18mg/day of lenvatinib plus

5mg/day of everolimus or 10mg/day of everolimus monotherapy. Patients eligible for entering the study were adults who were diagnosed with unresectable or advanced, predominantly clear cell, RCC whose disease had progressed on or within nine months of stopping prior therapy with one VEGF-targeted therapy. The primary outcome in HOPE 205 was progression free survival (PFS); other outcomes assessed in the trial included overall survival (OS), tumour response, and safety. All outcomes were investigator assessed (IA) although the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the USA requested *post-hoc* independent radiology review (IRR) of PFS and response data. The patients' baseline characteristics appear relatively well balanced between the trial arms in HOPE 205, although some differences between groups potentially indicate a poorer prognosis for those in the everolimus group compared with patients randomised to lenvatinib combination therapy. However, as the number of patients is very small, the potential impact of the differences is unclear. A third of the trial population was recruited from the UK and the baseline characteristics of the UK patients are similar to the full trial population, which the ERG and its clinical experts consider to be representative of patients in UK clinical practice eligible for treatment with lenvatinib combination therapy, although, as in trials in general, they represent the slightly younger and fitter proportion of patients found in clinical practice. Intention-to-treat (ITT) analyses were performed for all efficacy outcomes and adverse events were analysed using the Safety Analysis Set (all patients who received at least one dose of study medication and had at least one post-baseline safety evaluation).

Lenvatinib combination therapy showed a statistically significant improvement in PFS (median PFS 14.6 months) compared with everolimus (median PFS 5.5 months) in the IA analysis (hazard ratio [HR] 0.40, 95% CI: 0.24 to 0.68, p=0.0005). *Post-hoc* assessment of PFS by IRR showed similar results; median PFS was 12.8 months in the combination group and 5.6 months for the everolimus group (HR 0.45, 95% CI: 0.26 to 0.79, p=0.003). Subgroup analyses of PFS based on Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline, age, sex, region, baseline hypertension status, Memorial Sloan Kettering Cancer Center (MSKCC) risk category, corrected serum calcium, and haemoglobin showed consistent improvements in PFS for the combination group compared with the everolimus group.

The OS analysis of the latest data cut, requested by the EMA, shows that OS is statistically significantly longer for patients treated with lenvatinib combination therapy (median survival 25.5 months) compared with patients receiving everolimus monotherapy (median survival 15.4 months) based on the Cox model (HR 0.59, 95% CI: 0.36 to 0.97), however, the p-value for the log rank test did not reach statistical significance (p=0.065).

Based on the IA more patients treated with lenvatinib combination therapy achieved a complete or partial response than patients treated with everolimus monotherapy, the difference being statistically

significant (RR 7.2, 95% CI: 2.3 to 22.5, p<0.0001) in favour of the combination group. The IRR showed similar result to the IA but with slightly lower objective response rate (ORR) for both groups.

All patients in the trial had at least one treatment emergent adverse event (TEAE). Serious AEs occurred at a slightly higher incidence in the combination group (54.9%) than in the everolimus group (42%). The most common grade 3 TEAEs were diarrhoea (19.6% vs 2.0%, lenvatinib combination vs everolimus), hypertension (13.7% vs 2.0%), fatigue (9.8% vs 0%), anaemia (7.8% vs 12.0%), hypertriglyceridemia (7.8% vs 8.0%), and vomiting (7.8% vs 0%).

Indirect comparisons were needed to estimate the relative efficacy of lenvatinib combination therapy versus nivolumab, cabozantinib, axitinib and BSC (placebo). Five trials comparing treatments for patients with advanced RCC who had failed at least one prior VEGF-targeted therapy were identified; AXIS (axitinib versus sorafenib), CheckMate 025 (nivolumab versus everolimus), HOPE 205 (lenvatinib combination versus everolimus), METEOR (cabozantinib versus everolimus), and RECORD-1 (everolimus versus placebo). TARGET (sorafenib versus placebo), which only enrolled patients who had not had prior anti-VEGF targeted therapy, was also included to form a connected network.

Baseline characteristics were generally balanced between trial arms in all studies included in the network, and the trial populations were relatively similar between studies, however, the trials differed in terms of number and type of prior therapies, subsequent therapies, and outcome assessment (IA or IRR).

The relative efficacy of lenvatinib combination therapy versus each comparator was initially estimated using HRs, which are conditional on the proportional hazards (PHs) assumption being fulfilled. However, the PHs assumption does not hold for PFS in CheckMate 025, METEOR and TARGET, and for OS in CheckMate 025 and TARGET, and the results of these analyses are therefore not presented here. As an alternative, the company assessed PFS and OS in a Bayesian network meta-analysis (NMA) using fractional polynomials, which does not rely on the PHs assumption being fulfilled. Based on the difference in prior therapy in TARGET and confounding of OS due to crossover, which couldn't be adequately adjusted for, axitinib and everolimus were assumed to have similar efficacy for the NMA. The company's primary analyses for PFS and OS were based on the full populations and the primary analysis for all trials, that is, irrespective of number of prior therapy, and investigator or independent outcome assessment.

[redacted]

[redacted]

[redacted] The ERG tested how well the model captures the underlying PFS Kaplan–Meier (KM) data, which showed a good fit for both trial arms in CheckMate 025 and the everolimus group in HOPE 205, but potentially an overestimate of PFS in the lenvatinib combination group in the same trial.

[redacted]

[redacted] The ERG tested how well the model captures the underlying OS KM data, which showed a good fit for both trial arms in both CheckMate 025 and HOPE 205.

[redacted]

[redacted]

[redacted] Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy [redacted] and placebo [redacted] in favour of lenvatinib combination. The difference between lenvatinib combination therapy and nivolumab [redacted], cabozantinib [redacted] and axitinib [redacted] also favoured lenvatinib combination therapy, [redacted].

There was [redacted] in the proportion of patients experiencing at least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib based on the ITC [redacted]. A higher proportion of patients experienced at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted]. There was [redacted] in discontinuation due to AEs between lenvatinib combination therapy and cabozantinib ([redacted]), but [redacted] patients discontinuing treatment due to AE with the lenvatinib combination therapy compared with nivolumab ([redacted]) and placebo ([redacted]).

1.3 Summary of cost effectiveness evidence submitted by the company

The company submitted a *de novo* economic model to assess the cost effectiveness of lenvatinib in combination with everolimus compared to everolimus monotherapy, axitinib, cabozantinib and nivolumab in patients with previously treated renal cell carcinoma. The model has a partitioned survival structure with health states for stable disease, progressed disease and death.

For the lenvatinib combination and everolimus monotherapy groups, the company estimated the proportions of patients being in the stable state and death state directly from Kaplan-Meier (KM) data for progression-free survival (PFS) and overall survival (OS), respectively, from the HOPE 205 trial. The proportion of patients in the progressed disease state was obtained by taking the remainder. To extrapolate beyond the trial follow-up period, the company fitted a range of parametric survival curves and used a range of criteria to assess the best fit, the key criteria being the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, and visual assessment of the curve fits to the data, which the company did using log-cumulative hazard plots against log time. The company assessed both dependent and independent models and chose to use a dependently fitted Weibull model to inform the extrapolation. The extrapolation was determined by calculating the hazard ratio (HR) from cycle-to-cycle in each treatment group and applied these HRs from the last survival probability from the KM data. This ensured a continuous survival function, and was done for both PFS and OS. For the remaining comparators, HRs estimated from the company's indirect treatment comparison (ITC) were applied directly to the lenvatinib combination curves for both PFS and OS. The company also performed scenario analyses using parametric survival curves for the entire time horizon rather than the piecewise modelling approach.

In addition to this, in response to clarification questions, the company also performed an analysis using an NMA to estimate the treatment effects on parameters of log-hazard functions defined by fractional polynomials. A range of different fractional polynomials were tested and the best fitting curves were used in a scenario analysis.

Treatment discontinuation KM data from the HOPE 205 trial were used to estimate primary treatment costs for lenvatinib combination therapy and everolimus monotherapy, while for the remaining comparators, treatment discontinuation was estimated by applying relative ratios of median treatment duration to the lenvatinib combination KM data as if they were HRs. A scenario analysis was provided that used fitted exponential curves to the KM data in the HOPE 205 trial. Subsequent treatments were not included in the base case analysis as all patients were assumed to receive best supportive care, justified by the company as standard care as there are no NICE recommended treatments at third line.

The HOPE 205 trial did not collect EQ-5D data so the company used data from the AXIS trial, which had a population of patients with previously treated renal cell carcinoma, to inform the health state

utility values for stable disease and progressed disease. The impact of adverse events on quality of life was captured using adverse event disutilities obtained from a range of studies identified through the company's systematic literature review.

The results of the company's corrected base case and the ERG's preferred base case are given in Table A, with an incremental analysis of the ERG preferred base case given in Table B.

Table A. Results of the ERG preferred base case (Pairwise)

Results per patient	Lenvatinib comb. (1)	Axitinib (2)	Cabozantinib (3)	Everolimus (4)	Nivolumab (5)	Incremental values			
						(1-2)	(1-3)	(1-4)	(1-5)
Company's corrected base case									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER						32,974	2,166	120,775	7,096
ERG's preferred survival curves: Best fitting fractional polynomials for OS and PFS, and 2-knot spline for TTD									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**63,001**	**Dominated**	**83,620**	**Dominated**
ICER with all changes incorporated						**63,001**	**Dominated**	**83,620**	**Dominated**
Subsequent treatment costs based on trials									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**32,458**	**Dominated**	**120,644**	**4,150**
ICER with all changes incorporated						**62,291**	**Dominated**	**83,492**	**Dominated**
ERG's preferred base case ICER						**62,291**	**Dominated**	**83,492**	**Dominated**
Abbreviations in the table: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year									

Table B. Results of the ERG preferred base case (Incremental)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,492
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The ERG considers the systematic review methods used by the company to be appropriate, suitable eligibility criteria were applied by the company and all relevant clinical efficacy studies relating to lenvatinib and the comparators listed in the NICE final scope are likely to have been identified.

Overall, the ERG considers the trial, HOPE 205, to be largely well conducted and the statistical analyses to be appropriate. A third of the trial population was recruited from the UK and the baseline characteristics of the UK patients were similar to the full trial population, which the ERG and its clinical experts consider to be representative of patients in UK clinical practice eligible for treatment with lenvatinib combination therapy, although, as in trials in general, they represent the slightly younger and fitter proportion of patients found in clinical practice.

All relevant comparators as specified in the NICE final scope for this STA were considered within the CS.

Economic

The economic analysis performed by the company was reasonably well presented in the CS. The economic model design was sound and the ERG did not have any major difficulty in validating the model. A few errors were identified but the company clarified and corrected these issues.

1.4.2 Weaknesses and areas of uncertainty

Clinical

The ERG is concerned about the small sample size of HOPE 205; only around 50 patients were randomised to each treatment group. This introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy.

The baseline characteristics of patients enrolled in HOPE 205 appear relatively well balanced between the trial arms, though some differences potentially indicate a poorer prognosis for the everolimus group compared with patients randomised to lenvatinib combination therapy.

The open label design of HOPE 205 and the lack of blinded outcomes assessment of PFS and tumour response is a potential source of bias. IRR of PFS and tumour response was only done retrospectively.

HRQoL, one of the outcomes of interest listed in the NICE final scope, was not captured in HOPE 205.

The PHs assumption does not hold for PFS and OS in several of the trials in the network, and as no meaningful conclusions can be drawn from the HRs from these trials or the ITC based on these HRs.

To enable a comparison of lenvatinib combination and axitinib, the TARGET trial was included in the network. Based on the difference in prior therapy in TARGET and confounding of OS due to cross-over, which couldn't be adequately adjusted for, no reliable estimate of the relative efficacy of lenvatinib combination therapy versus axitinib could be obtained. The network for the fractional polynomial NMA was therefore simplified by assuming similar efficacy between everolimus and axitinib.

For the best fitting curves for PFS, the ERG's assessment of how well the analysis models the input data as FP curves showed a potential overestimate of PFS in the lenvatinib combination group in HOPE 205, but a good fit for all other treatment groups and trials.

Economic

The company's base case analysis was based on a flawed ITC that violated assumptions of proportional hazards, which are required to provide a robust measure of treatment effectiveness as a hazard ratio. This leads to unreliable measures of treatment effectiveness and, therefore, unreliable cost effectiveness results.

The scenario analysis provided by the company based on fractional polynomials was not implemented correctly beyond 5 years and contained further errors in the model. The ERG considered the company's results of this scenario to be unreliable. However, the ERG considers the fractional polynomial method

the preferred method for estimate treatment effectiveness and, hence, used this method to inform the ERG's preferred base case.

Treatment durations estimated by the company were considered by the ERG to be incorrect. The company appeared to assume that the relative ratios of the median treatment durations observed in the respective trials could be implemented as hazard ratios. The ERG considered this to be an incorrect approach and it resulted in discrepancies between the modelled median treatment durations and the observed durations. The ERG's preferred approach was to fit survival models to treatment discontinuation KM data.

Subsequent treatments that were received in the respective trials were not included in the costs of the economic model. This means the potentially increased effectiveness caused by the subsequent treatments is included in the model but without the trade-off between that increased benefit and the increased costs.

The model had some technical errors such as the half cycle correction being implemented incorrectly, and the utilities being applied inaccurately, leading to slightly erroneous cost effectiveness results.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG explored a scenario analysis around the company's base case to included subsequent treatment costs for those that were received in the respective trials. This had a very small impact on the results.

The ERG's preferred base case incorporated the best fitting fractional polynomial based survival curves for PFS and OS, and the ERG's fitted 2-knot spline curves for TTD. It also incorporated the subsequent treatment costs from the respective trials. This resulted in an increased ICER compared to axitinib, but reduced ICERs for the other comparators.

The ERG performed a range of scenarios around the preferred base case including an alternate fractional polynomial for the OS curve and the use of the lognormal to model TTD. The alternate OS curve had very little impact on the results with a slight increase in the ICERs. The use of the lognormal curves for TTD increased the costs mostly for the lenvatinib group and therefore increased the ICERs.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

In Section 3 of the company submission (CS), the company provides an overview of the health problem, renal cell carcinoma (RCC), including risk factors of developing the disease, diagnosis, prognosis, and available treatment options.

The ERG considers the information presented in Section 3 of the CS to be generally comprehensive and well written. However, the ERG has expanded on a few sections for completeness. All information that appears in boxes in the ERG report is taken directly from the CS unless otherwise stated and the references have been renumbered.

RCC is the most common type of kidney cancer. Kidney cancer is the seventh most common cancer and one of the fastest accelerating cancers in the UK.[1] It is more common in men than women. The incidence is also expected to increase more in men than women, with 28% in men and 18% in women from 2014 to 2035.[2]

The company's overview of RCC is presented in Box 1.

Box 1. Overview of renal cell carcinoma (CS, page 25, Section 3.1)

Kidney cancer is a generic term that includes both the cancers originating in the renal parenchyma itself and those originating in the urothelial epithelium of the renal pelvis, the renal vessels and the connective tissue. The most common type of kidney cancer is renal cell cancer (RCC), which originates in the epithelium of the renal tubules and accounts for about 85% of all diagnosis of kidney cancer. Within RCC, clear cell cancer is by far the most frequent histological subtype, accounting for up to 80% of all cases.
Abbreviations: RCC, renal cell carcinoma

Other histological subtypes of RCC fall under the umbrella term non-clear cell but vary significantly in terms of at which stage they are likely to be diagnosed, their incidence pattern across sex and age, and their prognosis.[3, 4] Within non-clear cell carcinomas, papillary accounts for around 10% of RCC cases, chromophobe about 5% of RCCs, and collecting duct carcinoma around 1%.[3, 4] Papillary and chromophobe RCC tend to have a more favourable prognosis than clear cell RCC, and collecting duct less favourable.[4] Several rare variants have also been identified and around 5% of cases cannot be classified.

There are several well established and associated risk factors related to the development of RCC. In addition to the risk factors of developing renal cancer described by the company in Box 2, occupational exposure to carcinogens such as asbestos, certain medical conditions and medications have also been implicated.[5, 6]

Box 2. Risk factors of renal cancer (CS, page 25, Section 3.1)

Smoking and obesity are well-known risk factors for developing renal cancer. Patients with end-stage renal disease, undergoing hemodialysis for a long time and those who have received a kidney transplant are also at a higher risk of kidney cancer. In addition to these, diabetes and high blood pressure have also been identified as possible risk factors. A small number of kidney cancers are hereditary.

RCC is commonly classified using the tumour-node-metastasis (TNM) staging system by the American Joint Committee on Cancer (AJCC).[7] In the TNM system the T refers to the size and extent of the primary tumour, the N refers to the number of nearby lymph nodes affected by the cancer, and the M refers to whether the cancer has metastasized. The TNM system helps describe cancer in detail, but the TNM combinations are often grouped into four less-detailed stages. For RCC stage I and II tumours are confined to the kidney, the latter being more than 7 cm in size; stage III cancer has started to spread outside the kidney to the adrenal gland or a major vein nearby, it may also have spread to one nearby lymph node; if the RCC has spread further or involves more than one lymph node, the cancer is termed metastatic (stage IV).[8] In Box 3 the company gives the definition of advanced or metastatic RCC in terms of TNM staging and the broader categories of stage I to IV. Throughout the report the ERG will use the term advanced RCC to refer to both advanced and metastatic RCC.

Box 3. Disease staging of advanced RCC (CS, page 25, Section 3.1)

The American Joint Committee on Cancer (AJCC) have designated a tumour–node–metastasis (TNM) staging classification system for RCC. The diagnosis of advanced or metastatic stage IV cancer is made when the tumour has invaded the connective sheath surrounding the kidney (T4NxM0) or when there are distant metastasis, irrespective of the size of the tumour (TxNxM1).[9]
Abbreviations: AJCC, American Joint Committee on Cancer; RCC, renal cell carcinoma; TNM, tumour–node–metastasis

Staging is an important prognostic indicator for RCC. Five-year survival is more than 80% for people with stage I disease and less than 10% for people with stage IV.[10] In 2014, 38% of kidney cancer cases in England were diagnosed at stage I, 15% at stage III, and 21% at stage IV.[11] The symptoms of RCC vary according to the disease stage. Symptoms of advanced RCC may be related to the metastatic spread of the disease rather than the primary tumour. If RCC is suspected, diagnosis is usually made by ultrasound, computerised tomography (CT) or magnetic resonance imaging (MRI), but sometimes a biopsy is required to confirm.[12] Box 4 provides the company overview of the symptoms of RCC at different stages of the disease.

Box 4. Kidney cancer symptoms (CS, pages 26 and 27, Section 3.2)

Early stages of kidney cancer are usually asymptomatic and by the time symptoms appear and the patient seeks medical assistance the disease is very often extended locally or disseminated.

Classically, RCC is diagnosed by the triad of pain in the flank, haematuria and abdominal palpable mass. Nevertheless, more than 50% of cases are now diagnosed incidentally when a renal mass is discovered in an abdominal US examination or MRI scan performed for any other reason.[13]

Health-related quality of life (HRQoL) issues related to tumor burden include anorexia-cachexia syndrome which, in addition to weight loss and lethargy, may involve fever, night sweats, and dysgeusia; anemia, which is often a presenting symptom; hypercalcemia, which may cause confusion and constipation; pain (somatic, visceral, and neuropathic); and venous thromboembolism.[14] RCC usually spreads in the vicinity of the kidney or distantly to lungs, bone, brain and liver [15] and metastases are associated with symptoms specific to the site involved; for example, lung metastases may cause airway obstruction, bleeding, and dyspnea.

Abbreviations: HRQoL, health related quality of life; MRI, Magnetic Resonance Imaging; RCC, renal cell carcinoma

In Box 5 the company describes the commonly used risk rating scales Memorial Sloane Kettering Cancer Centre (MSKCC) and Heng, which allows the RCC to be categorised from favourable to poor on a scale of worsening predicted survival.

Box 5. Prognostic score (CS, page 26, Section 3.1)

There are several prognostic classifications to stratify risk in metastatic RCC. The Memorial Sloane Kettering Cancer Centre (MSKCC) score is based on five criteria (interval from diagnosis to treatment, Karnofsky performance status [PS], and serum levels of LDH, calcium and haemoglobin) and allows risk stratification in three different levels: good, intermediate and poor. This score was further refined by the International Metastatic RCC Database Consortium (IMDC) who identified six prognostic factors for survival: all those in the MSKCC score but the LDH serum level criterion, plus the neutrophil and platelet counts. IMDC criteria are also known as Heng's model.[13, 16]

Abbreviations: IMDC, International Metastatic RCC Database Consortium; LDH, lactate dehydrogenase; MSKCC, Memorial Sloane Kettering Cancer Centre; RCC, renal cell carcinoma

There is no cure for advanced RCC and the goals of treatment are to delay disease progression and extend life while relieving physical symptoms and maintaining function.[17] Box 6 provides an overview of how advanced RCC is treated and how the treatment options for the disease have developed. The different treatment options are discussed in more detail in Section 1.1, and the clinical pathway in Section 2.2.

RCC has a serious effect on patients' physical, social and psychological well-being, particularly when it is advanced or metastatic.[18] Both symptoms and treatment toxicities contribute to the significant physical burden of RCC for patients and their caregivers. The company points out that, "The psychosocial impact of diagnosis with an incurable, poor-prognosis malignancy such as mRCC also is considerable. Among patients participating in a study to develop a kidney cancer-specific symptom index, patient-identified psychosocial concerns included emotional distress, losing hope, worry about the illness progressing, and HRQoL concerns.[19]"(CS, page 28)

Box 6. Treatments for advanced RCC (CS, pages 25 and 26, Section 3.1)

Even though some patients with advanced and metastatic RCC can still benefit from surgery, when the tumour relapses after surgical excision, the disease is spread at the time of diagnosis or the tumour is unresectable, systemic drug treatment is the only remaining option.[16] The choice of the systemic treatment is driven by histological type and risk stratification.

Until late 2005, systemic treatment choices for metastatic RCC were restricted to cytokine therapy. This last decade has witnessed the arrival of targeted therapy with the approval of a number of tyrosine-kinase inhibitors (TKIs) and anti-VEGF antibodies, which have become widely used both in first and second line treatment of advanced RCC.[16]

Abbreviations: RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

2.1.1 Epidemiology

The company provided an overview of the incidence of kidney cancer in the UK in Box 7. The ERG notes that these numbers are not specific to RCC, but acknowledges that more than 80% of kidney cancers are RCC.

Box 7. Incidence and mortality of kidney cancer in the UK (CS, pages 26 and 27, Section 3.2)

Kidney cancer is the seventh most common cancer in the UK (2014), accounting for 3% of all new cases of cancer. There were around 12,500 new cases diagnosed in 2014 with a male to female incidence ratio of 5 to 3. Half (50%) of kidney cancer cases in the UK each year are diagnosed in people aged 70 and over (2012-2014) with the highest incidence in people aged 85-89 (2012-2014). Kidney cancer incidence rates have increased by 41% in the UK over the last decade and are projected to further increase by 26% between 2014 and 2035.[20]

There were around 4,400 kidney cancer deaths in the UK in 2014, accounting for 3% of all cancer deaths. Kidney cancer mortality rates have increased by 6% over the last decade, they are projected to fall by 15% in the UK between 2014 and 2035.[20]

2.2 Critique of company's overview of current service provision

The company provides a summary of NICE's treatment recommendations for advanced RCC based on the NICE pathway on renal cancer, which was updated in February 2017 [21] and NICE technology appraisal guidance in advanced and metastatic renal cancer in Box 8.

Box 8 NICE recommendations for advanced renal cancer (CS, pages 29 and 30, Section 3.5)

First-line treatment

- Pazopanib 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

- Sunitinib 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
- Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma

Second-line treatment

- Everolimus is recommended within its marketing authorisation as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy
- Nivolumab is recommended, within its marketing authorisation, as an option for previously treated advanced renal cell carcinoma in adults
- Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine
- Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma

No third-line treatments are currently recommended by NICE

Abbreviations: ECOG, Eastern Cooperative Oncology Group

The ERG notes that cabozantinib is currently undergoing review by NICE (GID-TA10075) for treating RCC, with guidance expected to be published in August 2017.

As the company states, the NICE pathway for renal cancer only covers first and second line treatment options. However, the ERG notes that the marketing authorisation for everolimus and nivolumab only specifies that these therapies can be used in patients whose cancer has progressed during or after treatment with vascular endothelial growth factor (VEGF) targeted therapy, without specifying line of therapy. Hence, these treatments are likely to be used as second line therapies and beyond. The same applies for cabozantinib which, if recommended by NICE, also is likely to be used second line and later.

The company also presents a summary of clinical guidelines from the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) (Table 1,

Table 2).

ESMO recommendations for first line therapies differ according to risk stratification. Beyond first line, recommendations are based on the treatments administered in previous lines. The NCCN guidelines, which are for relapsed or stage IV and surgically unresectable RCC, differentiates recommendations for clear cell and non-clear cell histology; the ESMO guideline is for clear cell histology only. Both guidelines were updated in 2016 and are mostly in line with NICE recommendations. The exceptions include the guidelines recommending temsirolimus and cytokines as options for first line treatment. The most important difference is that the guidelines have included cabozantinib as a second line treatment option. The ESMO guideline also covers recommendations for third line treatments which include nivolumab, cabozantinib, everolimus or axitinib, depending on the type of prior therapy. ESMO also mentions the combination of lenvatinib and everolimus, but the combination therapy has not been included in the guideline because of the small size of the regulatory trial, HOPE 205.

Table 1. ESMO 2016 guidelines for the management of metastatic RCC of clear cell histology (CS, Figure 10)

First line treatment	Good or intermediate risk		Poor risk	
	Standard: Sunitinib [I, A] Bevacizumab + IFN [I, A] Pazopanib [I, A]		Standard: Temsirolimus [II, A]	
	Option: High dose IL2 [III, C] Sorafenib [II, B] Bevacizumab + low dose IFN [III, B]		Option: Sunitinib [II, B] Sorafenib [III, B] Pazopanib [III, B]	
Second line treatment	Post cytokines		Post TKIs	
	Standard: Axitinib [II, A] Sorafenib [I, A] Pazopanib [II, A]		Standard: Nivolumab [I, A] Cabozantinib [I, A]	
	Option: Sunitinib [III, A]		Option: Axitinib [II, B] Everolimus [II, B] Sorafenib [III, B]	
Third line treatment	Post 2 TKIs	Post TKI and mTOR	Post TKI / nivolumab	Post TKI / Cabozantinib
	Standard: Nivolumab [II, A] Cabozantinib [II, A]	Standard: Sorafenib [I, B] Nivolumab [V, A] Cabozantinib [V, A]	Standard: Cabozantinib [V, A]	Standard: Nivolumab [V, A]
	Option: Everolimus [II, B]	Option: Other TKI [IV, B] Rechallenge [IV, B]	Option: Axitinib [IV, C] Everolimus [IV, C]	Option: Everolimus [V, B] Axitinib [V, B]

	Good or intermediate risk	Poor risk
First line treatment	Standard: Sunitinib [I, A] Bevacizumab + IFN [I, A] Pazopanib [I, A]	Standard: Temsirolimus [II, A]
	Option: High dose IL2 [III, C] Sorafenib [II, B] Bevacizumab + low dose IFN [III, B]	Option: Sunitinib [II, B] Sorafenib [III, B] Pazopanib [III, B]

Abbreviations: mTOR, Mammalian Target of Rapamycin; TKI, Tyrosine Kinase Inhibitor

Levels of evidence: I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomised trials without heterogeneity; II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity; III Prospective cohort studies; IV Retrospective cohort studies or case–control studies; V Studies without control group, case reports, experts opinions

Grades of recommendation: A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended; B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended; C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional;D Moderate evidence against efficacy or for adverse outcome, generally not recommended; E Strong evidence against efficacy or for adverse outcome, never recommended

Table 2. NCCN Guidelines for the management of relapse or stage IV and surgically unresectable RCC (CS, Figure 11)

Clear cell histology First-line therapy*	Clinical trial Pazopanib (category 1, preferred) Sunitinib (category 1, preferred) Bevacizumab + interferon (category 1) Temsirolimus (category 1 for poor-prognosis patients, category 2B for selected patients of other risk groups) Axitinib High-dose IL-2 for selected patients Sorafenib for selected patients
Clear-cell histology Subsequent therapy*	Clinical trial Cabozantinib (category 1, preferred) Nivolumab (category 1, preferred) Axitinib (category 1) Lenvatinib+everolimus (category 1) Everolimus Pazopanib Sorafenib Sunitinib Bevacizumab (category 2B) High-dose IL-2 for selected patients (category 2B) Temsirolimus (category 2B)
Non-clear cell histology Systemic therapy*	Clinical trial (preferred) Sunitinib (preferred) Axitinib Bevacizumab Cabozantinib Erlotinib Everolimus Lenvatinib+everolimus Nivolumab Pazopanib Sorafenib Temsirolimus (category 1 for poor-prognosis patients, category 2A for other risk groups)
* Best supportive care must be included in all case NCCN Categories of evidence and consensus Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate Unless otherwise noted, all recommendations are category 2A	

Box 9 gives the company's description of current UK clinical practice, which is in line with NICE's recommendations and clinical pathway. However, the ERG notes that the company mentions sorafenib as a recommended drug for second line treatment after failure of treatment with a first-line tyrosine kinase inhibitor (TKI), a VEGF-targeted therapy. For clarification, the marketing authorisation for sorafenib is only for advanced RCC when cytokine treatment has failed or cannot be used. As the company indicate, cabozantinib is not currently used in the UK as it is still undergoing assessment by NICE.

Box 9. Current UK clinical practice (CS, pages 27 and 28, Section 3.3)

Most patients are currently being treated in first line with a TKI.[13] Amongst the TKIs, sunitinib and pazopanib are the most commonly used first line treatments worldwide.[13, 15] In England and Wales no other targeted therapies but sunitinib and pazopanib are recommended in first line by NICE.

Sorafenib, everolimus, axitinib, nivolumab and cabozantinib are the VEGF-targeted therapies approved for second line treatment after failure of treatment with a first-line TKI. Axitinib was approved by NICE for second line treatment in February 2015. Until everolimus was recommended by NICE very recently, it was available through the CDF only for those patients who had already received sunitinib or pazopanib and for which second line axitinib was not an option. Sorafenib is not recommended by NICE.

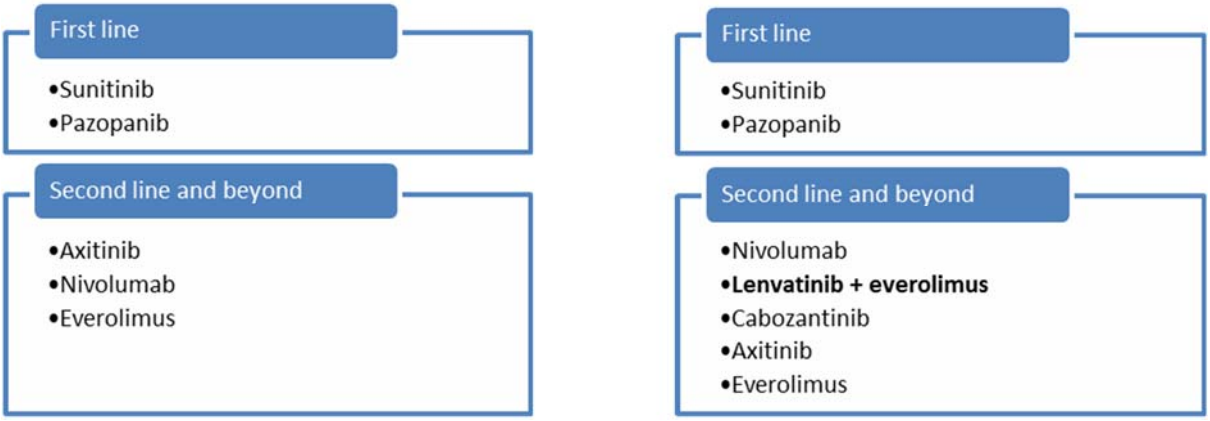
Second line treatment after TKI failure is expected to be challenged by the arrival of nivolumab and cabozantinib,[13] which are very likely destined to become standard treatments for patients already exposed to TKIs in first line. Nivolumab has already been recommended by NICE and cabozantinib is currently undergoing NICE assessment with final guidance expected in June 2017.

Abbreviations: CDF, Cancer Drug Fund; NICE, National Institute for Health and Care Excellence; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

The company's depiction of the current and proposed treatment pathway in England is presented in Figure 1. The ERG notes that if cabozantinib and/or lenvatinib combination therapy become recommended by NICE this will provide further active treatment options for all patients at second line and later lines.

The ERG and its clinical experts agree with the treatment pathways presented by the company (Figure 1), of which the current treatment pathway is in line with NICE's recommendations and treatment pathway for RCC (Box 8).

Figure 1. Current and anticipated future clinical pathways for drug treatment for advanced and metastatic renal cancer in England (adapted from CS, Figure 8)



The ERG agrees with the company that no changes in service provision or infrastructure are likely to be required with the introduction of the lenvatinib combination therapy. Although lenvatinib is a new

TKI it seems to have a similar adverse events profile to other TKIs used in clinical practice. This will be discussed in more detail in Section 4.3.5 and Section □. Everolimus has been used in clinical practice for some time as a second-line option for patients unable to take axitinib, funded through the CDF until a re-assessment by NICE resulting in a recommendation for routine commissioning in February 2017. The company reports that, patients on lenvatinib combination therapy would be expected to be followed up in a similar manner to those that currently receive axitinib and everolimus. Details on the required administration and monitoring of lenvatinib combination therapy are presented in Box 10. The ERG notes that the additional treatment option of lenvatinib combination therapy may not require specific changes to the service provision, but it may increase the burden on hospital clinics. In view of the side effect profile of lenvatinib combination therapy, it may result in extra hospital visits due to the added toxicities of this regimen, as many adverse events are more frequent with the combination (Section 4.3.5).

For the patient, the once daily administration of lenvatinib combination therapy may be more convenient than axitinib, which is taken twice daily. However, for the full dose of lenvatinib plus everolimus therapy that means four tablets per day compared to two for axitinib and only one for everolimus or cabozantinib. In contrast, nivolumab is only administered once every two weeks, but by intravenous injection.

Box 10. Company's proposed resource use for lenvatinib (CS, 22 and 23, Section 2.4)

No additional tests or investigations are needed to identify the population to be treated with lenvatinib in combination with everolimus.

Kisplyx [lenvatinib] treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. Hospital oncology units already have the staffing needed for the administration of cancer treatments and no changes in the pattern of services provided are expected. Since both lenvatinib and everolimus are orally administered drugs, they can be administered at an outpatient clinic and/or taken at home. No additional infrastructure will therefore need to be put in place.

Patients treated with lenvatinib in combination with everolimus should be followed-up and monitored for detection of adverse events as recommended in the SmPC:

- BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter to start antihypertensive therapy as soon as elevated BP is confirmed.
- Urine protein should be monitored regularly with dipsticks.
- Patients should be monitored for clinical symptoms or signs of cardiac decompensation.
- Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment.

- Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment.
- Thyroid function should be monitored before initiation of, and periodically throughout treatment.

Although these precautions add extra time to be devoted to these patients, it is considered that they do not differ from those which are the standard monitoring measures for cancer patients treated with other TKIs.

Abbreviations: BP, blood pressure; ECG, electrocardiogram; SmPC, Summary of Product Characteristics; TKIs, Tyrosine kinase inhibitors

The company has provided estimates of the number of patients eligible for second line systemic treatment for advanced RCC in England and Wales in the CS Section 6 (Table 3). The ERG notes that the company has not given a reference for the estimate of the population of England and Wales or for what year the baseline estimate is referring to. Based on Cancer Research UK's statistics on kidney cancer incidence there were 11,102 new cases of kidney cancer in 2014 in England and Wales compared to the 11,713 stated by the company (year not stated).[22] The company assumes an annual increase in kidney cancer incidence in line with population annual growth rates of 0.71%. The ERG notes that this is lower than the 1.1% annual increase in incidence (calculated by the ERG) based on Cancer Research UK's estimate of an increase in incidence of 26% between 2014 and 2035 referenced in CS Section 3.2. The company estimates that at baseline there will be 990 patients with metastatic RCC eligible for second line therapy. The ERG notes that the number of patients eligible for treatment with lenvatinib combination therapy in the NHS in England is likely to be higher than the company's annual estimates as the annual increase is likely to be higher than that estimated by the company, the company estimate does not include patients with advanced but only metastatic RCC, and because a number of patients will also be eligible for third line treatment. The ERG's clinical experts estimate that between 15-20% of patients would go on to receive third line therapy.

Table 3. Number of patients eligible for second line therapy (adapted from CS, Figure 118, pages 201-202)

		Baseline
Population England and Wales		57,415,704
Incidence of kidney cancer		11,713
Renal Cell Carcinoma (RCC) patients	86%	10,074
a/mRCC patients	25%	2,519
First line - patients systemically treated for mRCC	79.5%	2,003
Second line - patients systemically treated for mRCC	49.4%	990

Abbreviations: a/mRCC, advanced or metastatic renal cell carcinoma; mRCC, metastatic renal cell carcinoma

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE; CS, page 12),[23] together with their rationale for any deviation from the decision problem (Table 4). According to the company, their only deviation from the decision problem was that best supportive care (BSC) was not considered as a relevant comparator in the company submission (CS). This will be discussed further in Section 1.1. The ERG notes that the company did not present any health-related quality of life (HRQoL) data for lenvatinib combination therapy, which will be discussed in Section 3.4.

Table 4. Summary of decision problem as outlined in the company's submission (CS, Figure 1, page 12)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy	Not applicable
Intervention	Lenvatinib in combination with everolimus	Lenvatinib in combination with everolimus	Not applicable
Comparators	• Axitinib • Nivolumab • Everolimus • Best supportive care • Cabozantinib	• Axitinib • Nivolumab • Everolimus • Cabozantinib	BSC was not considered as a comparator in the company submission. This is in line with NICE committee draft recommendations based on clinical expert input during the cabozantinib NICE assessment. (GID-TA10075)
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	Not applicable
Economic analysis	Cost-effectiveness, expressed in terms of QALY. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	Cost-effectiveness, expressed in terms of QALY. Lifelong time horizon In addition, trial-horizon, five and ten year time horizons are provided as sensitivity analysis scenarios	Not applicable
Subgroups to be considered	None	None	Not applicable

Special considerations including issues related to equity or equality	None	None	Not applicable

Abbreviations: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; VEGF, vascular endothelial growth factor

3.1 Population

Clinical effectiveness data in the submission are derived from HOPE 205, a randomised, phase II, open-label, multicentre trial, which was designed to evaluate the efficacy and safety of lenvatinib plus everolimus combination therapy compared with lenvatinib and everolimus monotherapy. Patients eligible for inclusion were adults diagnosed with advanced RCC and disease progression following one prior vascular endothelial growth factor (VEGF)-targeted treatment. Patients were randomised in a 1:1:1 ratio to lenvatinib combination, lenvatinib alone or everolimus alone with around 50 patients in each trial arm. In the CS HOPE 205 is also referred to as Study 205 or E7080-G000-205, however, throughout this report, it will be referred to as HOPE 205.

Eligible patients in Hope 205 had an ECOG performance status of 0 or 1 and an adequate renal, bone marrow, blood coagulation, liver, and cardiac function. Patients with brain metastasis, more than one prior VEGF-targeted treatment and those previously exposed to either lenvatinib or everolimus were excluded from the study.

The majority of patients in HOPE 205 had received either sunitinib (56-71%) or pazopanib (18-26%) as their first VEGF-targeted therapy, which are the two treatments most likely to be given at first-line in UK clinical practice. Thus, the population of HOPE 205 reflects the second-line positioning of lenvatinib combination therapy in the UK based on the type and number of prior therapies received. The trial population is also in line with the final scope issued by NICE which specifies the population of interest to be adults with advanced RCC who have had one prior VEGF-targeted therapy.[23]

Baseline characteristics of the patients in HOPE 205 are generally in keeping with those expected in the advanced RCC population in UK clinical practice. However, the median age was around 60 years, and the trial was limited to patients with a performance status of ≤1; more than 50% of patients had an ECOG performance status of 0, which is reflective of a healthier patient population than would be expected in clinical practice. HOPE 205 was conducted at 37 centres in Czech Republic, Poland, Spain, UK and USA. One third of patients participating in the study were treated in the UK. At the clarification stage the company provided a breakdown of the baselines characteristics of the subgroup of patients from the UK which shows that the characteristics of the UK subgroup are similar to the full trial population (Appendix 10.1).

In summary, the ERG considers the data presented within the submission to be representative of patients with advanced RCC in England and Wales, and to be relevant to the decision problem that is the focus of this STA. The ERG's main concern is the small sample size of the trial population; each trial arm only has around 50 patients.

3.2 Intervention

Lenvatinib, brand name Kisplyx®, is a tyrosine kinase inhibitor (TKI). It has marketing authorisation for use in combination with everolimus, which is a mammalian target of rapamycin inhibitor (mTOR) sold under the name Afinitor® by Novartis. The company's summary of the mechanism of action of lenvatinib and everolimus are presented in Box 11 and Box 12, and illustrated in Figure 2.

Box 11. Mechanism of action of lenvatinib (CS, page 17, Section 2.1)

Lenvatinib is an orally administered multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor [PDGF] receptor PDGFRα; KIT; and RET) involved in tumour proliferation.[24]

The mechanism of action of lenvatinib involves effects on both endothelial cells, which are involved in tumour angiogenesis, and directly on tumour cells.

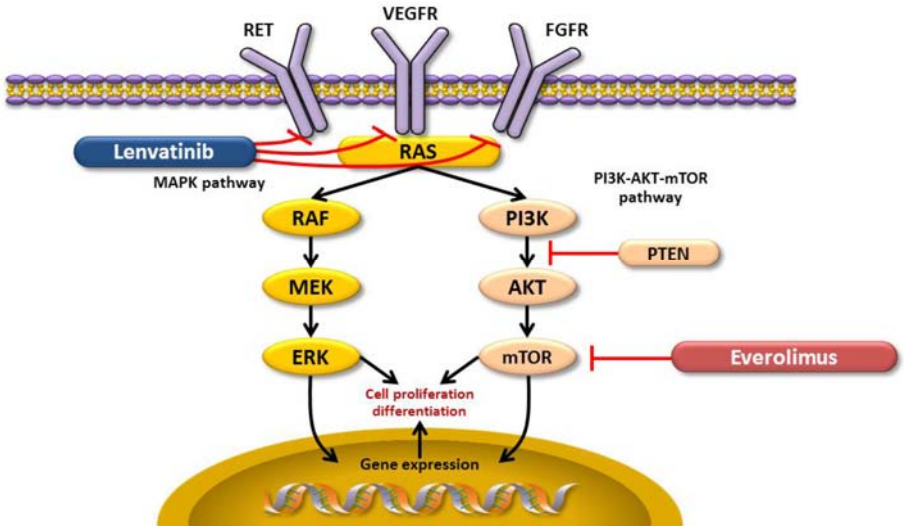
Abbreviations: FGF(R), fibroblast growth factor (receptor); KIT, KIT proto-oncogene receptor tyrosine kinase; PDGF(R), platelet-derived growth factor (receptor); R, receptor; RET, rearranged during transfection tyrosine kinase receptor; RTK, receptor tyrosine kinase; VEGF(R), vascular endothelial growth factor (receptor)

Box 12. Mechanism of action of everolimus (CS, page 19, Section 2.1)

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to an intracellular protein, forming a complex that inhibits mTOR activity. The inhibition of this signalling pathway interferes with the translation and synthesis of proteins involved in the cell cycle, angiogenesis and glycolysis. Everolimus also reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours in vitro and in vivo.[25]

Abbreviations: mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor

Figure 2. Inhibition of receptor tyrosine kinase and mTOR pathways by lenvatinib and everolimus: proposed mechanism of action (CS page 19, figure 6)



As mentioned in Box 11 lenvatinib inhibits FGFR-1, which is a receptor involved in the development of resistance to antiangiogenic therapies such as TKIs.[26] The company rationale for combining lenvatinib and everolimus was to target angiogenesis, tumour cell survival and to potentially block the development of resistance to antiangiogenic therapy.

Lenvatinib was granted European marketing authorisation on 25th August 2016 for use in combination with everolimus for the treatment of adult patients with advanced RCC following one prior VEGF-targeted therapy.[27] Lenvatinib combination therapy was approved by the Food and Drug Administration (FDA) in the USA in the same indication earlier the same year (May 2016).[28] Lenvatinib monotherapy was first approved in 2015, in both Europe and USA, for treatment of differentiated thyroid carcinoma in adults.[27, 29] According to the company, lenvatinib combination therapy has not been subject to any other technology assessment in the UK.

The EMA and FDA requested updated OS analysis and *post-hoc* blinded independent imaging review to confirm the benefit shown in the primary analysis in HOPE 205, which were unblinded and investigator assessed. This will be discussed in more detail in Section 4.2.1 and Section 4.3.

Lenvatinib is supplied as 4mg and 10mg capsules. In the main regulatory trial, HOPE 205, patients received the recommended daily dose of lenvatinib, 18mg (one 10mg capsule and two 4mg capsules) once daily in combination with 5mg of everolimus once daily, which is in line with the EMA marketing authorisation. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent. Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib and/or everolimus. In HOPE 205 the median daily dose of lenvatinib was 13.6mg/day (76% of the intended dose) and of everolimus 4.7mg/day (94% of the intended dose).

Lenvatinib combination therapy should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. Prescribing information and cost of lenvatinib combination therapy are summarised in Table 5.

Table 5. Summary of prescribing information and unit cost for lenvatinib combination therapy (CS, pages 21-22, Figure 7)

Pharmaceutical formulation	Lenvima® is supplied as 4mg and 10mg hard capsules, available in packs of 30.
Acquisition cost (excluding VAT) *	The list price for the 4mg and 10mg packs is £1,437.00.
Method of administration	Oral
Doses	The recommended daily dose of lenvatinib is 18mg (one 10mg capsule and two 4mg capsules) once daily in combination with 5mg of everolimus once daily. The daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/toxicity management plan.
Dosing frequency	Once daily
Average length of a course of treatment	The median duration of treatment for patients taking the lenvatinib and everolimus combination was 8.0 months in the Phase II Study 205.[30]
Average cost of a course of treatment	For lenvatinib, at the list price, based on the median daily dose of 13.6mg in the Phase II Study 205,[31] this equates to 1x10mg tablet and 1x4mg tablet, which is £2,874 per month. For everolimus, at the list price, the median daily dose was 4.7mg in the Phase II Study 205,[31] which is £2,250 per month. Therefore, at a median duration of treatment of 8.0 months,[30] the lenvatinib and everolimus combination works out at an overall cost of £40,992.
Anticipated average interval between courses of treatments	Not applicable.
Anticipated number of repeat courses of treatments	Not applicable.
Dose adjustments	Management of adverse reactions may require dose interruption, adjustment, or discontinuation of the combination therapy. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of the combination of medicines until improvement. For toxicities thought to be related to lenvatinib, upon resolution/improvement of an adverse reaction treatment should be resumed at a reduced dose of 14, 10 or 8mg daily based on the previous dose level. For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate day dosing, or discontinued. For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced prior to reducing everolimus.
Anticipated care setting	Lenvatinib treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. Lenvatinib in combination everolimus will be prescribed in hospital oncology units and dispensed to outpatients.

3.3 Comparators

Comparators listed in the NICE final scope[23] as relevant for this appraisal of lenvatinib combination therapy are:

- axitinib;
- nivolumab;
- everolimus;
- best supportive care;
- cabozantinib.

In the last few years the treatment options for advanced RCC has changed considerably with the development of targeted therapies such as TKIs. Axitinib, which was recommended by NICE in February 2015, has been the main second-line line treatment option in the UK. Everolimus has been available via the CDF for patients unable to take axitinib. However, it was re-appraised by NICE who issued a recommendation in February 2017 for everolimus to be funded through routine commissioning. Nivolumab was recommended by NICE in November 2016 and, based on the opinion of the ERG's clinical experts, it is likely to supersede axitinib as the mainstay of second-line treatment. Cabozantinib is subject to ongoing NICE appraisal (GID-TA10075) with guidance expected August 2017.

Axitinib and cabozantinib are both oral TKIs, similar to lenvatinib, however they all differ in terms of kinetics and which growth factor receptors they inhibit.[26] The mechanism of the mTOR everolimus is described previously in Section 3.2. Nivolumab is a human monoclonal antibody administered by intravenous injection, which induces a targeted immune response to cancer cells by blocking an immune checkpoint protein receptor called programmed cell death protein 1.

HOPE 205, the key trial assessing the efficacy and safety of lenvatinib combination therapy, is a three-arm trial providing head-to-head data for the combination versus lenvatinib and everolimus monotherapy. Lenvatinib monotherapy is not appraised in this STA, hence data from HOPE 205 presented in this report are focused solely on the combination and everolimus groups.

To assess the relative efficacy and safety of lenvatinib combination therapy compared with the other comparators in the NICE final scope, the company performed an indirect treatment comparison (ITC). The ERG's critique on the appropriateness of the trials included in the ITC and the methods used by the company is presented in Section 1.1.

The company did not consider BSC as a relevant comparator in the CS referencing the ongoing NICE technology appraisal of cabozantinib (GID-TA10075). However, the company does present data for lenvatinib combination compared with placebo based on the ITC, which the ERG considers to be a reasonable surrogate for BSC. The ERG agrees with the company that BSC is a comparator of limited importance as there are now several active second-line treatment options for patients with advanced RCC and patients well enough to receive active treatment are unlikely to just receive BSC. Hence, the ERG and its clinical experts agree that for the patient group eligible for treatment with lenvatinib combination therapy, BSC is of limited relevance as a comparator.

3.4 Outcomes

The outcomes listed in the NICE final scope[23] for this appraisal are:

- overall survival;
- progression-free survival;
- response rate;
- adverse effects of treatment;
- health-related quality of life (HRQoL).

The company presents direct evidence for lenvatinib combination therapy versus everolimus monotherapy for all the outcomes listed above with the exception of HRQoL, which according to the CS was not captured in HOPE 205.

All outcome data in HOPE 205 were investigator assessed though the company also presents PFS and response data assessed by an independent radiology review panel as requested by the EMA and FDA. Tumour response data comprised of objective response rate (ORR), complete and partial response, stable disease and progressive disease. Adverse effects of treatment were focused on treatment emergent adverse events (TEAE) of any grade occurring in at least 10% of subjects and grade 3 or 4 TEAEs occurring in ≥5% of subjects in any treatment group. The company also gives an overview of treatment related adverse events (TRAE).

The company presented evidence for lenvatinib combination therapy versus axitinib, nivolumab, everolimus, placebo and cabozantinib through ITCs for OS, PFS, ORR and safety. No comparison between the treatments were presented for HRQoL.

In summary, the company has presented relevant data for all outcomes specified in the NICE final scope[23] with the exception of HRQoL which was not captured in the key trial assessing the efficacy of lenvatinib combination therapy, HOPE 205.

3.5 Timeframe

The company presents data from several different data cuts for HOPE 205. Median follow up reported for the updated analysis in Motzer *et al.* 2015 (data cut off Dec 2014) was 24.2 months in the lenvatinib combination group and 25 months in the everolimus monotherapy group. Median follow-up for the most recent analyses requested by the EMA and the FDA (data cut off July 2015) was not reported in the CS; however, at the data cut off in July 2015 median OS was reached. The ERG considers the duration of follow-up in HOPE 205 to be reasonable for assessing PFS and OS.

3.6 Other relevant factors

There are no known issues relating to equality in this technology appraisal according to the company and the ERG's clinical experts.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The company carried out a literature review to identify evidence of the clinical effectiveness of lenvatinib and comparator therapies used to treat patients with advanced renal cell carcinoma (RCC) in a second-line setting. Additionally, literature searches were carried out to identify evidence of the health-related quality of life (HRQoL) profile of second line therapies for advanced RCC, as well as the economic implications of second-line treatments. A discussion of the economic literature review is discussed further in Section 5.3.

Electronic databases (Embase, Medline, Cochrane library) were searched from inception until October 2016 (17th October for clinical efficacy studies and 25th October for HRQoL studies). The search was limited by language to only include English language studies. The company specify study design was filtered using indexed keywords and free text terms to identify randomised control trials (RCT), meta-analyses, pooled analyses and systematic reviews (SR), however, the company did not include the study design terms used for this filter. Search terms were used for the disease area including 'renal cell carcinoma', combined with terms relating to disease severity 'advanced / metastatic.' Free text terms were used to identify studies investigating particular lines of treatment including: 'prior' or 'previously treated' in addition to 'first' and 'second.' The company acknowledged that despite the population of interest being prior treated patients, first line therapy terms were included to identify studies that would later be manually excluded by the company. The ERG argues the use of search terms for line of treatment used by the company would not adequately limit the evidence to the population of interest and therefore are unnecessary. Interventions were searched using search terms for both brand and generic name of the intervention. Outcomes search terms were used for the HRQoL evidence search, with terms including 'quality of life' and specifying well known instruments of HRQoL such as: 'European organization for research treatment of cancer core questionnaire' and the 'Kings Health Questionnaire'. The ERG considers the search strategy and search terms used by the company to be comprehensive and appropriate.

Conference proceedings were searched including: American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), American Association for Cancer Research (AACR), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The company provide no rationale why these conferences were chosen and others in the field were not searched. The ERG notes the company does not provide dates for which years these conference proceedings were searched.

The company also searched clinical registries for relevant evidence in November 2016. Registries searched included: Clinicaltrials.gov, International standard randomised controlled trial number register (ISRCTN), UK clinical trials gateway, WHO international clinical trial registry platform. The company specify that these registries were searched using search terms for treatments, the company do not specify which treatments these were. The searches were not restricted by date or by current recruitment status of the study.

A manual grey literature search of online sources was also conducted by the company. These included: The International Network of Agencies for Health Technology Assessment (INAHTA), Canadian Agency for Drugs and Technologies in Health (CADTH), National Institute of Health and Clinical Excellence (NICE); Scottish Medicine Consortium (SMC), Australian Pharmaceutical Benefits Scheme (PBS), New Zealand Pharmaceutical Management Agency (PHARMAC), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), UK Department of Health, UK Office for National Statistics, Cancer Research UK, American Cancer Society (ACS). The ERG notes that ESMO and Cancer Research UK sources were searched for thyroid cancer rather than RCC. Lenvatinib is a treatment licensed for thyroid cancer[27] therefore searching these resources for known side effects of lenvatinib would be appropriate. The company provide no details as to how this grey literature was used to inform the literature review for lenvatinib or its relevant comparators in RCC patients.

The ERG considers the evidence search carried out by the company to investigate the clinical effectiveness of lenvatinib and its comparators as second line treatments for advanced RCC to be comprehensive and appropriate. Sufficient searches were carried out using key databases, conference proceedings, clinical registries and grey literature.

4.1.2 Inclusion criteria

4.1.2.1 Inclusion criteria for direct evidence

The company used the same eligibility criteria for both the evidence search relating to lenvatinib clinical effectiveness studies, as well as studies investigating comparator treatments for second line patients with advanced RCC that inform the indirect treatment comparison (ITC).

Table 6: Summary of review eligbility criteria (Adapted from CS, Figure 12, page 37)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	Lenvatinib Cabozantinib Nivolumab Temsirolimus Everolimus	Not second line a/mRCC treatment after one prior anti-VEGF therapy Surgical /Radiotherapy /Diagnostic intervention

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	Pazopanib Sunitinib Sorafenib Bevacizumab Axitinib	
Outcomes	Progression free Survival Overall survival Response Rate Adverse events Quality of life	
Study design	Randomised controlled trials Systematic reviews Meta-analysis	Experimental or non-human studies Not a randomised trial or meta-analysis/systematic review Subgroup analyses/ abstracts/ publications of already identified trial with no additional information provided
Language restrictions	English	Non-English language

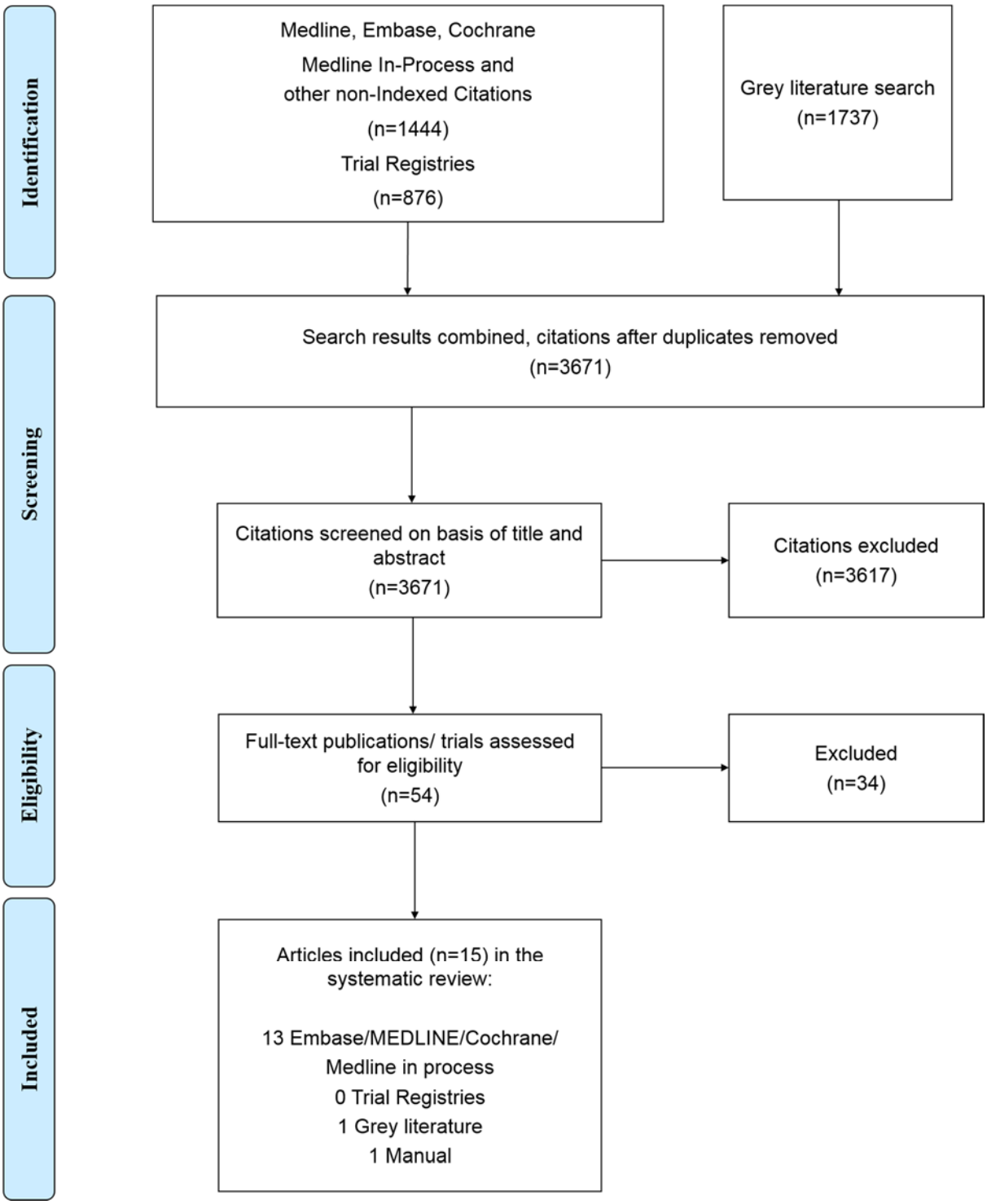
The ERG notes that the eligibility criteria supplied by the company are very broad. The population were defined by disease only 'advanced or metastatic RCC'. Restrictions based on line of treatment and exposure to prior treatment were listed as exclusion criteria for intervention/comparators. Eligible interventions were second line after one prior anti-VEGF treatment. Surgical, radiotherapy or diagnostic interventions were also not eligible. These criteria are in line with the NICE final scope[32]: 'adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy'. The NICE scope does specify an adult population that was not specified by the company in the eligibility criteria. The interventions listed were inclusive of treatments that were not listed in the NICE final scope[32] including: temsirolimus, pazopanib, sunitinib, sorafenib, bevacizumab. The ERG considers it appropriate to include comparators outside of the scope if they are used in the same population as these may provide additional connections in an ITC. The outcomes listed in the eligibility criteria are in keeping with those listed in the NICE final scope.[32] The company restricted the eligible study design to RCTs, SRs and meta-analyses. The ERG considers this appropriate as there is RCT evidence available in this disease area. The company also restricted evidence to English language only studies, limiting relevant evidence by language can potentially lead to relevant evidence being overlooked.

Overall the ERG considers the eligibility criteria outlined by the company to be appropriate for the decision problem outlined in the NICE final scope.[32] Some interventions eligible for inclusion in the review were outside the NICE scope,[32] however these were likely included to identify trials that could help form a fully connected network.

4.1.3 Critique of screening process

A summary of the screening process carried out by the company to identify clinical efficacy evidence relating to lenvatinib and comparator treatments for the treatment of advanced RCC second line is summarised in Figure 3.

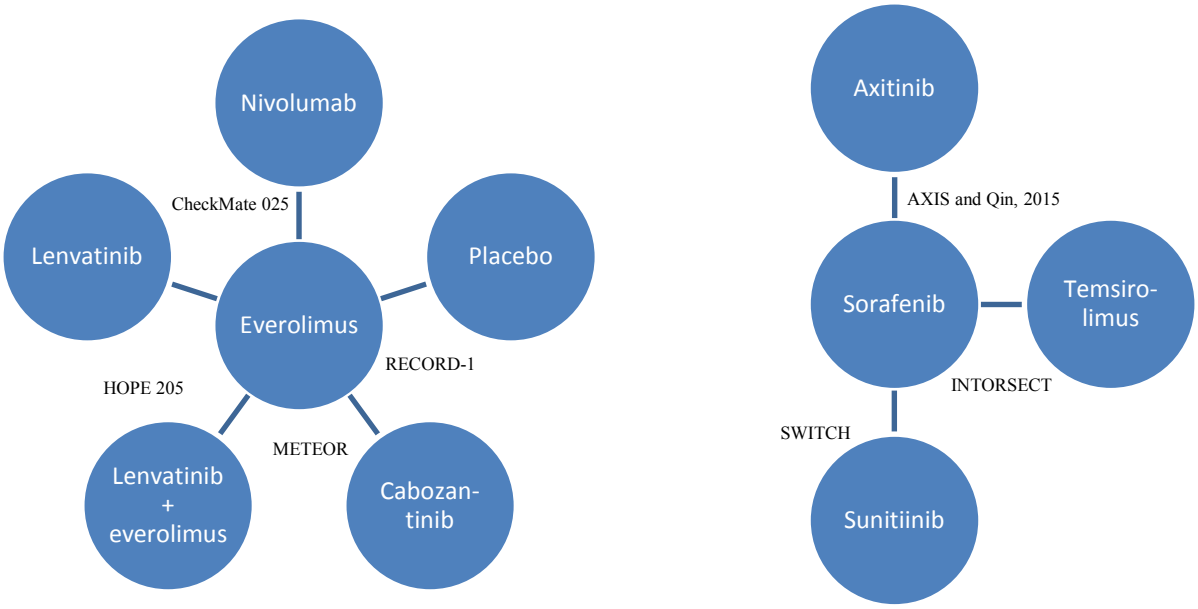
Figure 3. The PRISMA diagram of the company's systematic literature search (Adapted from clarification response C2)



The company identified 3671 unique records from database searches, trial registries and grey literature search. A total of 3617 records were excluded at the title and abstract stage, which left 54 records to be assessed at full text stage. Of these the company excluded 34 records. According to the CS PRISMA diagram a total of 15 articles were included (13 from the database searches, one from the grey literature and one added manually) that describe eight RCTs.[31, 33-39] The ERG notes that in the CS Appendix 8.3 it appears the total number of included records was 21; however, after removing duplicates across different databases 15 records remained.

The eight RCTs identified investigated ten different treatment regimens in patients with advanced RCC that had failed one prior anti-VEGF therapy. HOPE 205 was the only study investigating lenvatinib in combination with everolimus.[31] A summary of the studies identified and their interventions is shown in Figure 4.

Figure 4. Trials identified in indirect treatment comparison literature review (Adapted from CS, Figure 35, page 65)



Four studies (Checkmate 025[38]; METEOR[37]; HOPE 205[31] and RECORD-1[36]) investigated interventions including: nivolumab, cabozantinib, lenvatinib+everolimus or placebo (considered interchangeable with best supportive care) with the common comparator of everolimus. Four further studies had a common comparator to sorafenib: one study investigating temsirolimus compared with sorafenib (INTORSECT[39]) one comparing sunitinib with sorafenib (SWITCH[33]) and two studies comparing axitinib with sorafenib (AXIS,[40] Qin 2015[34]).

For the ITC network the company excluded the INTORSECT[39] and SWITCH[33] trial that investigated temsirolimus and sunitinib respectively as they did not contribute to the network in connecting relevant comparators. The company also chose to exclude the Qin 2015[34] trial as they considered it was less representative than the AXIS[40] trial. Both trials compared axitinib to sorafenib, however the Qin 2015[39] study was a smaller trial with a predominately Asian patient group, a more selective population than the mixed racial characteristics found in AXIS.[40] Additionally Qin 2015[39] consisted of 50% of patients that had received prior cytokine therapy compared to AXIS[40] that had 30% of patients exposed to prior cytokines. The ERG agrees with the exclusion of studies relating to temsirolimus and sunitinib due to their lack of relevance in the presented network. The rationale for excluding the Qin 2015[39] study due to its limited representability in population and prior cytokine exposure is also considered appropriate by the ERG.

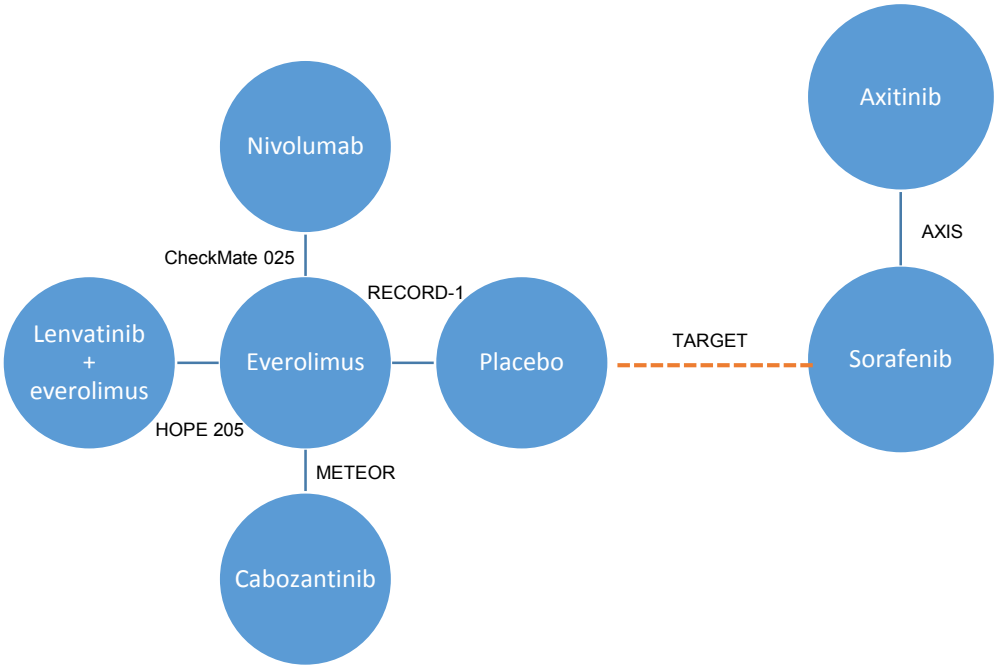
The ERG notes the company provide a table of excluded studies from the ITC, summarised in Table 7. Here the company include Qin 2015[39] with the reason for exclusion. However, no details were supplied by the company regarding the exclusion of the INTORSECT or SWITCH studies. The company also list the exclusion of Ratain 2006[41], a study that compared sorafenib to placebo. This study was not listed in the original eight RCTs identified in the search and screening process. Therefore, the ERG speculates the inclusion of this study is an error by the company.

Table 7: Trials excluded from the indirect treatment comparison with reason for exclusion (Adapted from CS, Figure 38, page 68)

Treatment	References	Reason for exclusion
Sorafenib network		
Axitinib Qin 2015	Qin S, Bi F, Jin J, Cheng Y, et al. (2015) "Axitinib versus sorafenib as a second-line therapy in Asian patients with metastatic renal cell carcinoma: results from a randomised registrational study." Onco Targets Ther 8: 1363-1373.[34]	Less comparable patient population than pivotal AXIS trial (Asian, less prior VEGF)
Placebo Ratain 2006	Ratain MJ, Eisen T, Stadler WM, et al. (2006) "Phase II Placebo-Controlled Randomized Discontinuation Trial of Sorafenib in Patients With Metastatic Renal Cell Carcinoma" J Clin Oncol 24(16):2505-2512.[41]	Randomised discontinuation design. Limited reporting of outcomes.

The final ITC network presented in the CS consisted of six studies (Checkmate 025,[38] HOPE 205,[31] METEOR,[37] RECORD-1,[36] TARGET[42] and AXIS[40], Figure 5). Four trials that investigated relevant NICE scope comparators: nivolumab, cabozantinib, lenvatinib+everolimus or placebo/BSC were included, all of which had a common comparator of everolimus. (Checkmate 025[38], RECORD-1[36], HOPE 205[31], METEOR[37]). To create a completed network including axitinib, a listed relevant comparator in the NICE scope, the company included the TARGET trial.[42] This trial compared sorafenib to placebo, creating an indirect link between axitinib and everolimus through sorafenib and placebo. The company acknowledge that TARGET patient population is not fully representative of other trials also included in the ITC, with patients in the TARGET trial having received prior cytokines rather than one prior anti-VEGF treatment.

Figure 5. Network of trials in the indirect treatment comparison (Adpated from CS, Figure 36, page 66)



In summary, the ERG considers the screening process carried out by the company to be largely appropriate and sufficient in identifying all relevant clinical efficacy studies relating to lenvatinib and other relevant comparators as listed in the NICE final scope (axitinib, nivolumab, everolimus, cabozantinib and best supportive care/placebo). However, there is some uncertainty around the screening process as there were inconsistencies in the PRISMA diagram. There are also some concerns over the suitability of all trials included in the ITC, in particular the TARGET[42] trial, because patients had prior treatment with cytokines rather than with anti-VEGF therapy. The studies included in the ITC, methods and the results are discussed further in Section 4.4.

4.1.4 Quality assessment

4.1.4.1 Quality assessment of HOPE 205

The company carried out a quality assessment of HOPE 205[31] using the Centre for Reviews and Dissemination of the University of York criteria for risk of bias in RCTs.[43] The criteria consists of seven domains: random allocation, allocation concealment, baseline characteristics, blinding, imbalances in discontinuations, outcome reporting, and intention to treat analysis. A summary of the company's assessment is provided in Table 8. The ERG carried out an independent assessment of the quality of HOPE 205, which is presented alongside the company's assessment in Table 8.

Table 8: Quality assessent of lenvatinib study HOPE 205 (Adapted from CS, Figure 22, pages 51-52)

Trial	HOPE 205 Company assessment	ERG Assessment
Was the method used to generate random allocations adequate?	Yes	Yes, patients were randomised using an IVRS. Randomisation was stratified by two factors: haemoglobin and corrected serum calcium.
Was the allocation adequately concealed?	Yes	Yes, patients were randomly allocated in a 1:1:1 ratio to one of three treatments (lenvatinib combination therapy, lenvatinib alone or everolimus alone).
Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	No, there was imbalances between treatment groups. There was a higher proportion of patients in the everolimus group that had a higher number of metastases sites (60%) compared to the lenvatinib+everolimus group (35%). In the everolimus group there were a higher proportion of patients with each of the 4 types of metastases sites (bones, liver, lung, lymph nodes) compared to lenvatinib+everolimus group. A higher proportion of patients in lenvatinib+everolimus group had prior sunitinib (71%) compared to everolimus group (56%).
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No. Open-label study. Uncertain impact for response assessment for PFS and ORR. No impact for OS.	No, the study had an open label design. Tumour response was investigator assessed and therefore PFS and ORR may be at risk of performance bias. OS is an objective measure and unlikely to be influenced.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No, patients discontinuation was largely due to disease progression and was fairly equal between treatment groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No, all outcomes of interest were reported: PFS, OS, OFF, DCR, CBR, and durable SD were reported.
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Censoring of patients lost to follow-up or alive.	Yes, intention to treat analysis was used. Patients lost to follow up or alive at data cut off were censored.
Abbreviation: CBR, clinical benefit ratio; DCR, disease control rate; IVRS, interactive voice response system; ORR, objective response rate, OS, overall survival; PFS, progression free survival, SD, stable disease.		

The company's quality assessment of HOPE 205 showed an overall low risk of bias with appropriate random allocation using an interactive voice response system (IVRS), no baseline characteristic differences, no disproportionate discontinuations between groups, all outcomes reported as stated and an intention to treat analysis used for all clinical efficacy outcomes. The study was however an open

label trial and therefore care providers and patients were aware of the treatment they received. The company acknowledge an uncertainty of how an unblinded investigator may impact assessment of progression free survival (PFS) and overall response rate (ORR). Tumour response assessment was carried out by the unblinded investigator and an independent review was carried out retrospectively to adhere to the EMA and FDA requests for independently assessed PFS and response data. Based on the investigator assessment the trial is at risk of some detection bias however the retrospective independent assessment mitigates any risk of bias.

Overall the ERG agrees with the company's assessment of HOPE 205. However, the ERG disagrees with the company with regards to baseline characteristic differences, particularly relating to prior therapies, metastases sites, and numbers of metastases; with a larger proportion of patients in the everolimus group having a higher number of metastases sites compared with the lenvatinib combination group. The sites of metastases were disproportionate with more patients in the everolimus group having metastases across the four different sites (bone, liver, lymph nodes and lung) compared to the other treatment groups. With regards to prior treatments, more patients in the lenvatinib combination group had received prior sunitinib compared to the everolimus group. These baseline differences can have prognostic implications for patients, such as everolimus group patients having a higher number of bone metastases that can result in poorer prognosis. Therefore, these imbalances between groups are a potential source of bias. The baseline characteristics of HOPE 205[31] are discussed further in Section 4.2.2.

4.1.4.2 Quality assessment for indirect treatment comparison studies

The company carried out quality assessment of trials identified as potentially relevant for the ITC network (Checkmate 025,[38] METEOR,[37] RECORD-1,[36] AXIS,[40] INTORSECT,[39] Qin 2015,[34] SWITCH[33]) using the NICE methodology checklist for RCTs.[44] However, the ERG notes that, no quality assessment was carried out for the TARGET[42] trial, a key trial in the network as it forms the only link for a comparison with axitinib.

A summary of the quality assessment carried out by the company is presented in Table 9. Each study was assessed on the following domains: randomisation, treatment allocation, baseline characteristics, blinding, length of follow up and outcome assessment. The company's quality assessment found a low risk of bias for most domains across all trials, however, there were domains of potentially high risk of bias in the majority of studies concerning blinding. Seven of the eight RCTs were open label trials (HOPE 205,[31] Checkmate 025,[38] METEOR,[37] AXIS,[40] INTORSECT,[39] Qin 2015[34] and SWITCH[33]) therefore due to a lack of blinding patients and investigators were aware of treatment allocation. The majority of studies (METEOR,[37] RECORD-1,[36] AXIS, [40] INTORSECT, [39] Qin 2015[34]) had independent outcome assessors to overcome the potential bias due to open label design. The HOPE 205[31] study had an independent assessment however this was carried out *post hoc* to adhere to the EMA and FDA

request for an independent assessment of PFS and response data. Two studies (Checkmate 025[38] and SWITCH[33]) were investigator assessed and open label, highlighting a potential for detection bias.

The ERG's quality assessment of the studies included in the ITC was mostly in agreement with the company. The ERG highlights that in both Qin 2015[34] and SWITCH[33] there were small differences in baseline characteristics: the proportion of patients that had varying sites of metastases in the Qin 2015[34] study differed between the two treatment groups. Performance status between the treatment groups in SWITCH also differed. These differences can have implications in patient prognosis, potentially influencing the subsequent impact of treatment response. Therefore for both Qin 2015[34] and SWITCH[33] there is an unclear risk of bias for this particular domain.

The ERG's assessment of TARGET found the trial to have a high or unclear risk of bias in multiple domains. The trial had limited reporting on the methods used for randomisation and allocation concealment. The main trial was double-blind, however, patients could continue treatment after progression and those originally randomised to placebo could cross over to receive sorafenib unblinded. In addition, overall survival and progression free survival data was immature and therefore at a high risk of bias.

4.1.5 Summary of systematic review

The ERG considers the systematic reviews methods used by the company to be appropriate. Relevant databases, conference proceedings, clinical registries and grey literature were systematically searched for relevant studies. Suitable eligibility criteria were applied by the company that included the comparators listed in the NICE final scope as well as additional comparators which could help connect the network. All relevant clinical efficacy studies relating to lenvatinib and the comparators listed in the NICE final scope are likely to have been identified. However, to create a completed network the company included the TARGET trial in which patients had had prior cytokine treatment rather than prior anti-VEGF therapy. The company's discussion of the quality and validity of the trials included in the CS was reasonable with the majority of studies indicating and overall low risk of bias. However, no quality assessment was carried out for the TARGET trial, a key trial in the network as it forms the only link for a comparison with axitinib. The ERG assessment of TARGET found the trial to have a high or unclear risk of bias in multiple domains.

Table 9: Quality assessment by the company of randomised control trials included in the mixed treatment comparison literature review (Adapted from Appendix 8.3, Table 3.4.1, pages 23-24)

Study	**Selection Bias**			**Performance Bias**			**Attrition Bias**			**Detection Bias**				
	Was an appropriate method of randomization	Was an adequate concealment of allocation	Were the groups comparable at baseline	Did comparison groups receive the same care?	Were participants receiving care kept blind?	Were individuals administering care kept blinded?	All groups were followed up for an equal length of time	Were groups comparable for treatment completion?	Were groups comparable with respect to the availability of outcome data?	Had the study had an appropriate length of follow-up	Had the study a precise definition of outcome	Was a valid and reliable method used to determine the outcome?	Were the investigation kept blind to participant exposure?	Were investigators kept blind to other confounding and prognostic factors?
HOPE 205	Yes	N/A open label	Yes with the exception of the proportion of patients who has three or more metastases and the proportion of patients who has received sunitinib	Yes	No	No but outcomes independently assessed	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Not clear
CHECKMATE 025[38]	Yes	N/A open label	Yes	Not clear	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
METEOR [37]	Yes	N/A open label	Yes	N/A open label	Yes	Yes	No	No but outcome independ	Yes	Yes	Yes	Yes	Yes	Yes

								ently assessed						
RECORD-1[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes
AXIS[35]	Yes	N/A open label	Yes	Yes	Yes	Yes, although patients without hypertension and with good tolerability in the axitinib group were allowed to increase their doses, whereas those in the sorafenib group were not	No	No but outcome independently assessed	Yes	Yes	Yes	Yes	Yes	Yes
INTORSECT[39]	Yes	N/A open label	Yes	N/A	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes
Qin 2015[34]	Yes	N/A open label	Yes	Yes	Yes	Yes	No	No but outcome independently assessed	Yes	Yes	Yes	Yes	Yes	Yes
SWITCH[33]	Not clear	N/A open label	Not clear	N/A open label	Yes	Not clear	No	No	Yes	Yes	Yes	Yes	Yes	Yes

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Through the systematic search conducted by the company, it identified one RCT, HOPE 205, providing head-to-head evidence for lenvatinib in combination with everolimus versus everolimus monotherapy, one of the comparators relevant to this STA. No head-to-head trials were identified comparing lenvatinib combination therapy versus the other comparators in the NICE scope:[23] axitinib, nivolumab, cabozantinib and BSC. To provide comparative data for lenvatinib combination therapy versus these comparators the company conducted an ITC of RCTs identified in their search. Details of these trials and the methods used for the ITC are described and discussed in Section 1.1.

4.2.1 Trial conduct

HOPE 205 is an open label, phase II, multicentre randomised controlled trial. The trial was conducted at 37 centres in Czech Republic, Poland, Spain, the USA and the UK. One third of patients in the trial were recruited from the UK. Patients were randomised 1:1:1 to lenvatinib combination therapy, everolimus monotherapy, and lenvatinib monotherapy using an interactive voice response system. The primary objective of the trial was to compare PFS of lenvatinib combination therapy and lenvatinib monotherapy versus everolimus monotherapy. Lenvatinib monotherapy is outside the scope of this STA, hence the description and critique of HOPE 205 presented in this report are focused solely on the combination and everolimus groups of the trial.

Study treatment was administrated orally once daily in 28-days continuous cycles. Patients randomised to lenvatinib combination therapy received lenvatinib 18mg/day (one 10mg and two 4mg capsules) plus everolimus 5mg/day (one 5mg tablet); patients randomised to everolimus monotherapy received everolimus 10mg/day (two 5mg tablets). Dose reductions and dose interruptions done in accordance with prescribing information were allowed to manage toxicities of the study drugs.

Randomisation was stratified by haemoglobin and corrected serum calcium levels, two out of five factors determining a patients MSKCC risk score and two of six Heng risk score factors. The other factors contributing to MSKCC are time from diagnosis to systemic treatment, lactate dehydrogenase (LDH) level and Karnofsky performance status.[45] The Heng score does not take into account LDH levels but includes neutrophil and platelet counts.[46] According to the ERG's clinical experts MSKCC or Heng risk score would have been more relevant as stratification factor than limiting to haemoglobin and corrected serum calcium levels, but the ERG notes that the patient groups in HOPE 205 appear balanced in terms of MSKCC and Heng risk score.

Patients eligible for entering the study were adults aged ≥18 years who were diagnosed with unresectable or advanced RCC and histological or cytological confirmation of predominant clear cell

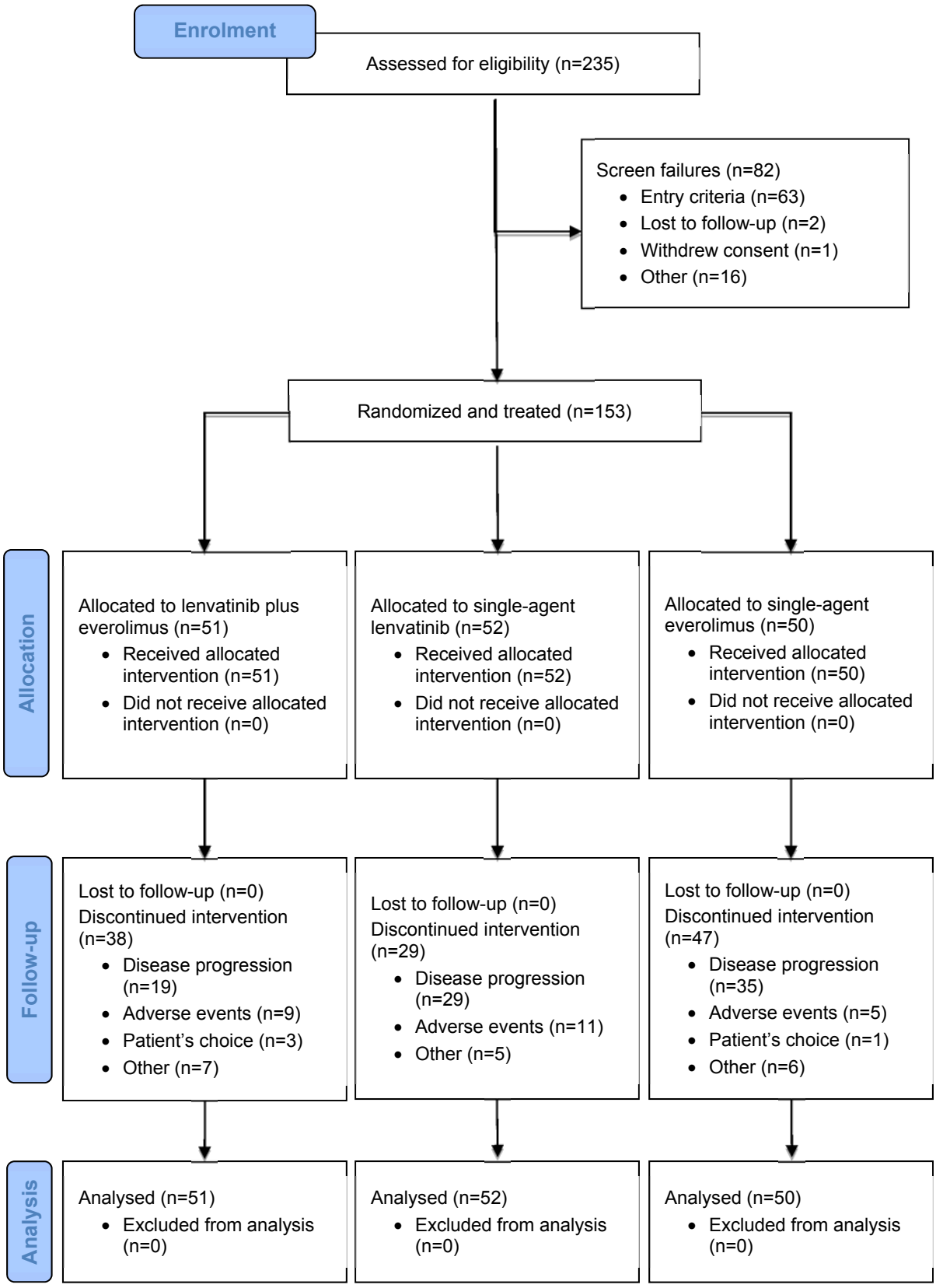
RCC with at least one measurable lesion according to RECIST criteria. They also had to have radiographic evidence of disease progression on or within 9 months of stopping prior therapy with one prior VEGF-targeted therapy, an ECOG performance status of 0 or 1 and an adequate renal, bone marrow, blood coagulation, liver, and cardiac function. Patients previously exposed to either lenvatinib or everolimus were excluded from the study.

Patient recruitment took place between March 2012 and June 2014. The primary analysis, which took place in June 2014, required that a total of at least 60 PFS events were observed for the comparison of the combination versus the everolimus group. Patients still on treatment at the time of data cut-off for the primary analysis continued the treatment they were randomised to during an extension phase. Patients received study treatment until disease progression, development of unacceptable toxicity, or withdrawal of consent. After discontinuation of study treatment patients were followed up for survival every eight weeks until death or until they withdrew consent. The EMA and FDA requested an updated OS analysis with data cut-off in July 2015 at which 63% of patients had died.

Tumour assessments were performed every eight weeks during treatment or sooner if there was evidence of progressive disease. Up until the primary analysis in June 2014 patients who had stopped study treatment without progression were to continue having tumour assessments every eight weeks until disease progression was documented or another anticancer therapy was initiated, after June 2014 patients who discontinued study treatment without disease progression were to have tumour assessments performed as clinically indicated using the investigator's discretion. Patients who discontinued study treatment were followed for survival every 12 weeks as long as they were alive or until they withdrew consent.

Several amendments to the study protocol have been made throughout the study (CS, Appendix 8.4), however, the ERG notes that all amendments were minor and are not deemed to affect the quality or applicability of the trial results. The patient flow diagram for all three trial arms in HOPE 205 is provided in Figure 6. Around 50 patients were randomised to each trial arm and all randomised patients received the correct treatment and were included in the analyses. No patients were lost to follow up, however, 74.5% of patients in the lenvatinib combination group and 94% of patients on everolimus monotherapy discontinued the randomised study therapy. The majority of patients discontinued therapy due to progression. It is unclear from the CS for which data cut the numbers in Figure 6 are from, however, the numbers seem to correspond with the patient flow diagram presented in the CSR from the 13 June 2014 data cut-off.

Figure 6. CONSORT Flow diagram HOPE 205 (CS, clarification response C6)



The primary outcome of the study was progression free survival (PFS), defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by the investigator using RECIST 1.1. Secondary outcomes included:

- overall survival (OS) - time from the date of randomisation until date of death from any cause;
- objective response rate (ORR) - the proportion of patients who had best overall response (BOR) of complete response (CR) or Partial response (PR) as determined by the investigator using RECIST 1.1;
- disease control rate (DCR) - the proportion of patients who had BOR of CR or PR or SD (minimum duration from randomization to SD ≥7 weeks);
- durable stable disease (SD) - the proportion of patients with duration of SD ≥23 weeks;
- clinical benefit rate (CBR) - the proportion of patients who had BOR of CR or PR or durable SD;
- tolerability and safety of the study drugs.

The trial was open label with investigators and patients aware of which treatment each patient was prescribed. All outcomes were investigator assessed, which was also unblinded. As discussed in the quality assessment of HOPE 205 in Section 4.1.4, unblinded outcome assessment is likely to have an impact on PFS and response assessments, but not OS as it is an objective outcome. In response to a request from the regulatory agencies, a *post-hoc* analysis of tumour response using independent radiological review was undertaken.

The ERG considers the trial to be largely well conducted, but is concerned about the small sample size of the study, which is in line with the phase II trial design, but it introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy. In addition, the ERG is concerned about the open label design and the lack of blinded outcomes assessment of PFS and tumour response, which was only done retrospectively on the request of EMA/FDA. Furthermore, data for PFS was only presented for the primary analysis, which was planned for when around 60% of patients in each treatment group had progressed. More mature PFS data should be available and could have been presented. The ERG also notes that HRQoL, one of the outcomes of interest listed in the scope, was not captured in HOPE 205.

4.2.2 Baseline characteristics

The baseline characteristics of patients in HOPE 205 are presented in Table 10. The average age was around 60 years of age, ~70% of patients were male, and slightly more than half of patients had an ECOG performance status of 0. The baseline characteristics of patients in the lenvatinib combination therapy and the everolimus monotherapy groups were relatively well balanced in terms of Heng and MSKCC risk groups. However, in the everolimus group there was a larger proportion of patients with more than one metastasis, resulting in slightly more patients having bone, liver, lung and lymph node metastases compared with the lenvatinib combination group. Bone and liver metastases are associated with a poorer prognosis than metastases in other locations. These differences may potentially indicate a worse prognosis for patients in the everolimus monotherapy group compared with patients in the combination therapy group. However, the ERG notes that the number of patients are very small and the potential impact of the differences should be interpreted with caution.

The majority of patients had received sunitinib or pazopanib as first-line VEGF-targeted therapy (Table 11), which is in line with NICE recommendations and UK clinical practice. Patients in the everolimus monotherapy group had a slightly shorter duration of prior VEGF-targeted therapy and fewer patients with complete or partial response to first-line VEGF-targeted therapy compared with patients in the lenvatinib combination group. Although the differences between the trial arms are based on very small numbers of patients, and may be due to chance, they are consistent with a potentially worse prognosis for the patients in the everolimus group compared with patients randomised to lenvatinib combination therapy. The potential impact of these differences would likely lead to an overestimate of the lenvatinib combination therapy compared with everolimus monotherapy. However, the ERG emphasise that this is based on a very small number of patients.

A substantial proportion of patients in HOPE 205 were recruited from UK centres. The baseline characteristics of patients enrolled in the UK were similar to the full trial population (Appendix 10.1). According to the ERG's clinical experts, the UK subgroup and the full trial population are representative of advanced RCC patients eligible for treatment in England and Wales. However, the trial population represents a slightly younger and fitter proportion of patients found in clinical practice.

Table 10. Baseline demographic and disease characteristics of participants in HOPE 205 (adapted from CS, page 49, Figure 20)

Baseline characteristic	Lenvatinib combination therapy (n=51)	Everolimus monotherapy (n=50)
Age (years)	61 (44–79)	59 (37–77)
Sex		
Men	35 (69%)	38 (76%)
Women	16 (31%)	12 (24%)

ECOG Performance status		
0	27 (53%)	28 (56%)
1	24 (47%)	22 (44%)
MSKCC risk group		
Favourable	12 (24%)	12 (24%)
Intermediate	19 (37%)	19 (38%)
Poor	20 (39%)	19 (38%)
Heng risk group*		
Favourable	8 (16%)	9 (18%)
Intermediate	32 (64%)	29 (58%)
Poor	10 (20%)	12 (24%)
Haemoglobin, n (%)		
≤130 g/L (men) or ≤115 g/L (women)	33 (65%)	31 (62%)
>130 g/L (men) or >115 g/L (women)	18 (35%)	19 (38%)
Corrected serum calcium, n (%)		
≥2.5 mmol/L	6 (12%)	8 (16%)
<2.5 mmol/L	45 (88%)	42 (84%)
Number of metastases		
1	18 (35%)	5 (10%)
2	15 (29%)	15 (30%)
≥3	18 (35%)	30 (60%)
Sites of metastasis		
Bone	12 (24%)	16 (32%)
Liver	10 (20%)	13 (26%)
Lung	27 (53%)	35 (70%)
Lymph nodes	25 (49%)	33 (66%)
Country**		
UK	17 (33.3%)	18 (36.0%)
Czech Republic	13 (25.5%)	5 (10.0%)
Poland	8 (15.7%)	9 (18.0%)
Spain	8 (15.7%)	4 (8.0%)
United States	5 (9.8%)	14 (28%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center
Data are number of patients (%), or median (range). * One patient in the lenvatinib plus everolimus group was excluded because of missing baseline laboratory values. ** Country specific information provided at the clarification stage.

Table 11. Previous treatments in HOPE 205 (adapted from CS, page 50, Figure 21)

Baseline characteristic	**Lenvatinib combination therapy (n=51)**	**Everolimus monotherapy (n=50)**
Previous nephrectomy†	44 (86%)	48 (96%)
Previous VEGF-targeted therapy‡		
Axitinib	1 (2%)	0
Bevacizumab	0	4 (8%)
Pazopanib	9 (18%)	13 (26%)

Baseline characteristic	Lenvatinib combination therapy (n=51)	Everolimus monotherapy (n=50)
Sorafenib	1 (2%)	2 (4%)
Sunitinib	36 (71%)	28 (56%)
Tivozanib	3 (6%)	2 (4%)
Other	1 (2%)	1 (2%)
Median duration of previous VEGF-targeted therapy (months)*	9.8 (2.0–66.2)	8.9 (1.6–57.8)
Best response for previous VEGF-targeted therapy		
Complete response	1 (2%)	0
Partial response	14 (28%)	10 (20%)
Stable disease	20 (39%)	21 (42%)
Progressive disease	7 (14%)	15 (30%)
Not evaluated or unknown	9 (18%)	4 (8%)
Previous checkpoint inhibitor therapy	1 (2%)	2 (4%)
Previous interferon therapy	4 (8%)	7 (14%)
Previous radiotherapy	6 (12%)	11 (22%)

Abbreviations: VEGF, Vascular endothelial growth factor
† One patient in the lenvatinib group had two nephrectomy procedures (partial and left radical) but was only counted once. ‡ All patients had one previous VEGF-targeted therapy. *Clarification response C8.

4.2.3 Statistical approach

The statistical approach for HOPE 205 is described in the CS Section 4.4. The primary outcome in HOPE 205 was PFS. The trial was powered to detect a hazard ratio (HR) for PFS of 0.67 with 70% power using an (1-sided) alpha of 0.15 for the comparison of the combination group versus the everolimus monotherapy group. The ERG notes that the power of the trial to correctly reject the null hypothesis and to detect a statistically significant difference between treatments was low as generally a value of power greater than or equal to 80% is used. For this a total of 90 PFS events were required across all three treatment groups and at least 60 PFS events (59% of patients progressed) were needed for each of the comparisons of the combination versus the everolimus group, and the lenvatinib versus the everolimus group. The assumed median PFS for everolimus 10mg was 5 months based on historical data, corresponding to an estimated median PFS of 7.5 months for lenvatinib combination therapy.

For OS patients who were lost to follow-up and those who were alive at the date of data cut-off were censored at the date they were last known to be alive. The PFS censoring rules as defined in the statistical analysis plan (SAP) followed the FDA Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).[47] Patients who stopped therapy due to clinical progression with no radiologic confirmation were censored at their last radiologic date. For endpoints which determined the percentage of responders, patients with unknown response were treated as non-responders.

PFS and OS were presented as median and Kaplan-Meier (KM) plots for each treatment group, and as HR with corresponding 95% confidence intervals (CIs) between treatment groups, which was estimated using a stratified Cox regression model (stratified by haemoglobin and corrected serum calcium) with treatment as a factor. HRs are conditional on the proportional hazard (PH) assumption being fulfilled which the company assessed by visual inspection of the log-cumulative hazard plot and the PH test based on residuals for PFS and OS.

Response rates with 95% CIs (ORR, DCR, CBR, and durable SD rate) were calculated using the Clopper and Pearson exact method. Differences between treatment groups were presented as rate ratios (RR) with corresponding 95% CIs and p values using the Fisher's exact (2-sided) test.

Intention-to-treat (ITT) analyses were performed for all efficacy outcomes using the Full Analysis Set (FAS) included all randomised patients. Adverse events were analysed using the Safety Analysis Set (SAS) which included all patients who received at least one dose of study medication and had at least one post-baseline safety evaluation.

The ERG notes that pre-planned subgroups mentioned in the CS included haemoglobin level (≤13g/dL vs >13g/dL for males and ≤11.5g/dL vs >11.5g/dL for females) and corrected serum calcium (≥10mg/dL vs <10mg/dL). However, results are presented for additional exploratory subgroup analyses for PFS including: age, sex, race, ECOG PS, region, and baseline hypertension status. The ERG notes that there is no mention of these subgroups in the study protocol and therefore assumes that they were *post-hoc* analyses.

Overall, the ERG considers the statistical approach taken by the company to be appropriate. Though HOPE 205 was only powered to have a 70% chance of detecting a difference between the treatments.

4.2.4 Summary statement

One trial, HOPE 205 comparing lenvatinib combination therapy and everolimus monotherapy, provides the only direct evidence informing the efficacy and safety of lenvatinib combination therapy. Trials informing the indirect comparisons of the lenvatinib combination therapy versus other comparators of interested are discussed in Section 4.1 and Section 1.1.

HOPE 205 is a well conducted multicentre, open label, phase II trial, with around 50 patients in each treatment group. Patients were randomised 1:1 to 18mg/day of lenvatinib plus 5mg/day of everolimus or 10mg/day of everolimus monotherapy. Patients eligible for entering the study were adults who were diagnosed with unresectable or advanced predominantly clear cell RCC whose disease had progressed on or within 9 months of stopping prior therapy with one prior VEGF-targeted therapy.

All outcomes were investigator assessed although the regulatory agencies EMA and FDA requested *post-hoc* IRR of PFS and response data. The patient's baseline characteristics appear relatively well balanced between the trial arms, though some differences potentially indicate a poorer prognosis for the everolimus group compared with patients randomised to lenvatinib combination therapy. However, the number of patients are very small and the potential impact of the differences should be interpreted with caution. A third of the trial population was recruited from the UK and the baseline characteristics of the UK patients are similar to the full trial population. Based on the baseline characteristics, the full trial population is representative of patients in UK clinical practice, although they represent the slightly younger and fitter proportion of patients found in clinical practice. The primary outcome in HOPE 205 was PFS; other outcomes assessed in the trial included OS, tumour response, and safety. ITT analyses were performed for all efficacy outcomes and adverse events were analysed using the Safety Analysis Set.

Overall, the ERG considers the trial to be largely well conducted and the statistical analyses to be appropriate. However, the ERG is concerned about the small sample size of the study, which introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy. In addition, the ERG is concerned about the open label design and the lack of blinded outcomes assessment of PFS and tumour response, which was only done retrospectively on the request of EMA/FDA. The ERG also notes that HRQoL, one of the outcomes of interest listed in the scope, was not captured in HOPE 205.

4.3 Clinical effectiveness results HOPE 205

This section describes the results of HOPE 205, the only trial identified by the company that provides direct evidence of the clinical effectiveness of lenvatinib combination therapy.

Data in HOPE 205 were analysed at several different time points, summarised in Table 12. The ERG notes that the primary analysis took place June 2014, the same time as recruitment closed, and hence minimum follow up was close to none. At this time point 62% of patients had progressed and 45% had died in the combination and everolimus monotherapy groups. At the pre-specified update analysis in December 2014 this had increased slightly as 66% of patients had progressed and 47% had died in the two treatment groups of interest to this appraisal. At the OS analysis in July 2015, requested by the EMA and FDA, 68% had died and minimum follow up was around 12 months. The difference between the EMA and FDA analyses of PFS (investigator assessed, data cut June 2014) and OS (data cut July 2015) lies in the use of different stratification variables: the IVRS (interactive voice recording system) dataset was used for the FDA while CRF (case report form) data was used for the EMA. At the clarification stage the company provided more details about the impact of the different analyses: "The FDA requested that, for the calculation of the HRs (hazard ratios) of PFS and OS, the stratification

factors were based on the value in the IVRS system, instead of the actual CRF values as used in the original CSR (clinical study report) analysis. The FDA reasoned that the primary analysis of a registration trial had to follow the intent-to-treat principle and the IVRS stratification factor is considered to be ITT, regardless of what was pre-specified in the statistical analysis plan." (Clarification response A4). In the CS the company presents the EMA results, however, in this report the FDA results (kindly provided at the clarification stage) are also presented.

In this section data are presented based on the pre-specified investigator assessment and the *post-hoc* independent review (where available). Data are presented for the latest data cut-off presented in the CS, which is June 2014 for PFS and tumour response, and July 2015 for OS.

Table 12. Data cut summary (adapted from Figure 29, CS, page 58)

Data cut	Description	Reference
Protocol specified primary analysis Date: June 2014 Median OS follow-up: 18.5 months for LEN+EVE and 16.5 months for EVE Completion LEN+EVE and EVE OS*: 45% PFS*: 62%	This data cut was originally planned in the clinical trial protocol. The stratification variable used and the power for each analysis was pre-specified. The Motzer (2015) publication included an initial data cut and an updated data cut.	Motzer *et al.* 2015. Eisai Ltd Study 205 Clinical Study report
Protocol specified update analysis Date: December 2014 Median OS follow-up: 24.2 months for LEN+EVE and 25 months for EVE Completion LEN+EVE and EVE OS*: 56%	This data cut was originally planned in the clinical trial protocol. The stratification variable used and the power for each analysis was pre-specified. The Motzer (2015) publication included an initial data cut and an updated data cut.	Motzer *et al.* 2015. Eisai Ltd Study 205 Clinical Study report
Date: July 2015 (OS); June 2014 (PFS) Completion LEN+EVE and EVE OS*: 68% PFS*: 62%	EMA requested a longer follow-up for overall survival to reduce uncertainty in the OS estimated of Motzer (2015).	Eisai Ltd Summary of Clinical Efficacy
Date: July 2015 (OS); June 2014 (PFS) Completion LEN+EVE and EVE OS*: 68% PFS*: 62%	FDA re-stratification FDA requested a changed in the OS and PFS cox model calculation i.e. a change in the calculation of the stratification variables. The same data as the EMA was used.	FULL PRESCRIBING INFORMATION (FDA label), LENVIMA® (lenvatinib) capsules, for oral use, Reference ID: 3931091, 2015
Abbreviations: EVE, everolimus; LEN, lenvatinib; OS, overall survival; PFS, progression free survival *calculated by the ERG based on the lenvatinib combination therapy and the everolimus monotherapy groups.		

4.3.1 Progression free survival

As mentioned above PFS data were only presented for the primary analysis data cut-off in June 2014. At that time 62% of patients in the lenvatinib combination therapy and everolimus monotherapy groups had progressed. Median follow-up was 13.9 months for the combination group and 17.5 months for the everolimus group.

The company presented their assessment of the PH assumption for PFS in HOPE 205 in CS Section 5.3 which showed that the hazard plots for the treatment groups are not straight or parallel, but cross and converge at different time point for PFS. However, the PH test based on residuals did not show a significant result (p-value = 0.5461) for PFS. The ERG notes that the contradictory results of the log-cumulative hazard plots and the statistical test reflect the uncertainty in the PH assumption assessment as the test is underpowered due to the small sample size in HOPE 205.

Median PFS, as assessed by the trial investigators, was 14.6 months for the combination group, compared with 5.5 months for the everolimus group. The combination group showed a statistically significant improvement in PFS compared with the everolimus group both in the EMA analysis (HR 0.40, 95% CI: 0.24 to 0.68, p=0.0005) and in the FDA analysis (HR 0.37, 95% CI: 0.22 to 0.62, Table 13, Figure 7).

Post-hoc assessment of PFS by independent radiological review (IRR) showed similar results though the difference between the treatment groups was slightly smaller; median PFS was 12.8 months in the combination group and 5.6 months for the everolimus group (HR 0.45, 95% CI: 0.26 to 0.79, p=0.003; Table 13, Figure 8).

Table 13. Progression-Free Survival – Full Analysis Set (adapted from Figure 23 and 25, CS, pages 53 and 54)

	Investigator Assessment		**Independent Imaging Assessment**	
	lenvatinib combination therapy (n=51)	Everolimus (n=50)	lenvatinib combination therapy (n=51)	Everolimus (n=50)
Median PFS months (95% CI)[a]	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)	12.8 (7.4, 17.5)	5.6 (3.6, 9.3)
At 9 months	56.7 (40.7, 69.9)	33.4 (19.6, 47.8)	NR	NR
At 12 months	50.9 (34.8, 64.9)	21.2 (9.9, 35.5)	NR	NR
HR (95% CI)[b] EMA	0.40 (0.24, 0.68)		0.45 (0.26, 0.79)	
HR (95% CI)[b] FDA	0.37 (0.22, 0.62)		NR	
p-value[c]	0.0005		0.003	

Abbreviations: CI, Confidence interval; NR, not reported; PFS, Progression-free survival
a: Point estimates are based on Kaplan-Meier method and 96% CIs are based on the Greenwood formula using log-log transformation.
b: Stratified HR is based on a stratified Cox regression model including treatment as a covariate factor and baseline ECOG scores, hemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.
c: p-values based on stratified Log Rank test.

Figure 7. Kaplan-Meier plot of progression-free survival based on investigator assessment (CS, page 54, Figure 24)

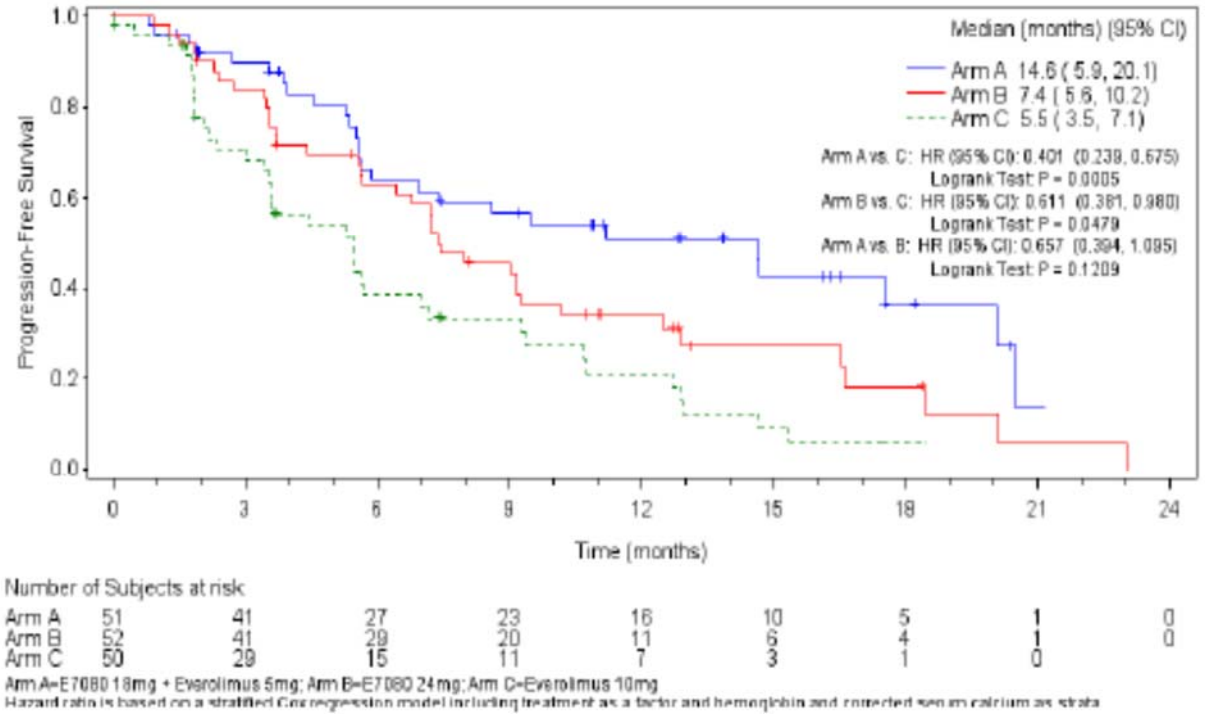
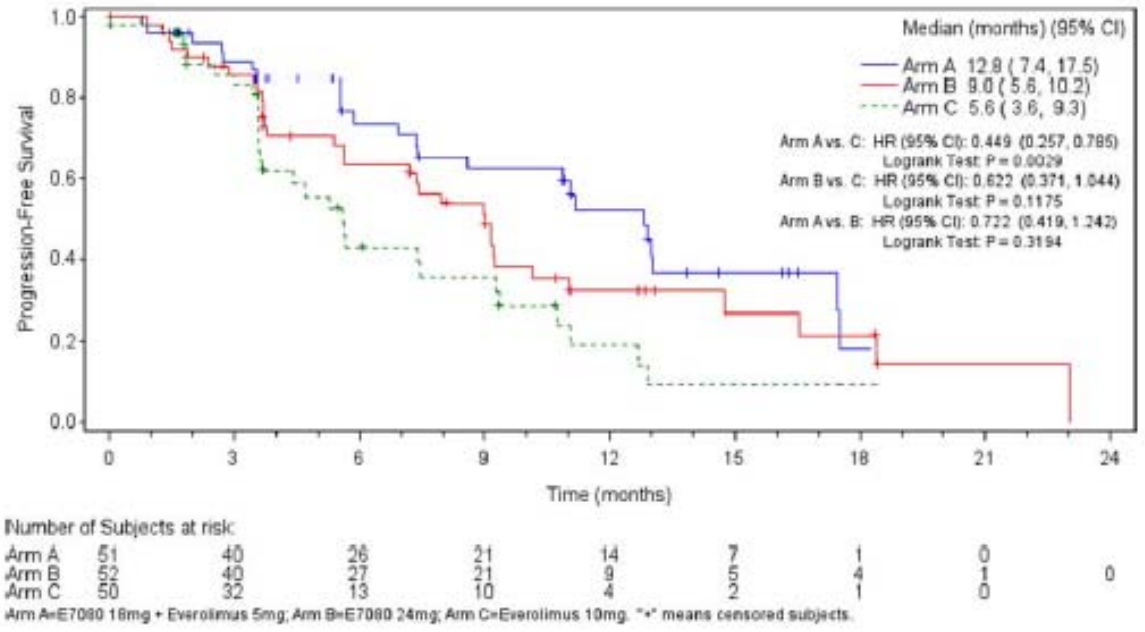


Figure 8. Kaplan-Meier plot of progression-free survival based on independent assessment (CS, pg 55, Figure 26)



4.3.2 Overall survival

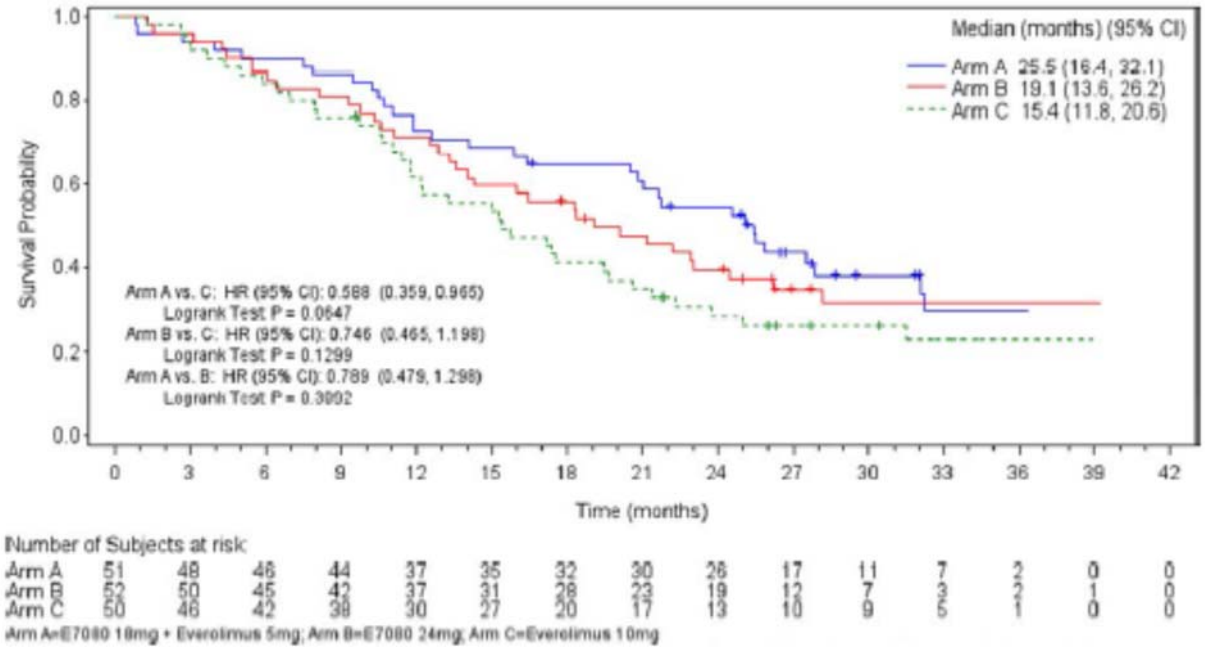
At the updated analysis in July 2015, requested by the EMA and FDA, 32 patients (62.7%) in the combination group and 37 patients (74.0%) in the everolimus group had died. Median follow up was 32.0 and 32.7 months for the combination and everolimus group respectively. In the EMA analysis OS was statistically significantly longer for patients on lenvatinib combination therapy compared with patients receiving everolimus monotherapy based on the cox model (HR 0.59, 95% CI: 0.36 to 0.97), however, the p-value for the log rank test did not reach statistical significance (p=0.065, Table 14, Figure 9). The FDA analysis favoured lenvatinib combination therapy but did not reach statistically significance (HR 0.67, 95% CI: 0.42 to 1.08). Median survival was 25.5 months for the combination group and 15.4 months for the everolimus group.

The company's assessment of the log-cumulative hazard plot for OS showed that the hazard plots for both treatment groups cross and converge at various time point indicating that the PH assumption may not hold. However, the PH test based on residuals did not show a significant result (p-value = 0.4412), which indicates that the curves do not deviate from the PH assumption (CS Section 5.3). Similar to the assessment of PH for PFS, the ERG notes that the contradictory results of the log-cumulative hazard plots and the statistical test reflect the uncertainty in assessment as the test is underpowered due to the small sample size in HOPE 205.

Table 14. Overall survival – Full Analysis Set (CS, page 59, Figure 30)

	Lenvatinib combination therapy (n=51)	**Everolimus monotherapy (n=50)**
Deaths (n)	32 (62.7%)	37 (74.0%)
OS (months) Median (95% CI)	25.5 (16.4, 32.1)	15.4 (11.8, 20.6)
Lenvatinib combination therapy vs everolimus monotherapy		
Stratified HR (95% CI) EMA	0.59 (0.36, 0.96)	
Stratified HR (95% CI) FDA	0.67 (0.42, 1.08)	
p-value based on stratified log-rank test	0.065	
Overall survival rate (%) (95% CI)		
At 12 months	72.5 (58.1, 82.7)	61.6 (46.6, 73.5)
At 18 months	64.7 (50.0, 76.1)	41.1 (27.3, 54.3)
Abbreviations: CI, Confidence Interval; NE, Not estimable. Data cut-off date = July 31st, 2015.		

Figure 9. Kaplan-Meier estimate of updated overall survival, by treatment group (CS, page 59, Figure 31)



4.3.3 Tumour response

As for PFS, tumour response data were presented for the primary analysis data cut-off in June 2014. Based on the planned IA more patients treated with lenvatinib combination therapy achieved a complete (one patient) or partial (21 patients) response than patients treated with everolimus monotherapy (zero complete responders and three partial responses), the difference being statistically significant (RR 7.2, 95% CI: 2.3 to 22.5, p<0.0001) in favour of the combination group (Table 15). Median time to response was similar in the combination and everolimus groups and corresponded with the first protocol-specified tumour assessment timepoint: 8.2 weeks and 8.0 weeks, respectively.

The ERG notes that there is a discrepancy between the median duration of response reported in the CS, which indicates a larger difference between the treatment groups (13 months in the lenvatinib combination group and 8.5 months in the everolimus group), and the CSR in which median duration of response was reported to be 8.3 months in the combination group and 7.5 months in the everolimus group.

The EMA and FDA requested a *post-hoc* analysis of tumour response based on IRR. According to the company, the IRR for HOPE 205 is highly uncertain and so they focused on IA tumour response. The ERG agrees that there is substantial uncertainty due to the low number of events and low number of patients, but considers this is to be true for both IA and IRR. Hence, the ERG deems the results by IRR to be less biased and more reliable than IA response. The IRR showed similar result to the IA but with

slightly lower ORR for both groups which meant that a rate ratio could not be calculated as there were no CR or PR in the everolimus group (Table 15).

There were more patients with stable disease in the everolimus group than in the combination group (Table 16), which is also reflected by the higher Durable Stable Disease Rate in the everolimus group compared with the combination group. All other response outcomes (progressive disease, DCR, CBR) consistently favoured the combination group over the everolimus group (Table 16).

Table 15. Tumour Response based on investigators assessment and independent radiology review – Full Analysis Set (CS, page 60, and CS Appendix 8.5, Table 3.4.1)

	Investigator Assessment		**Independent Imaging Assessment**	
	Lenvatinib combination therapy (n=51)	Everolimus monotherapy (n=50)	Lenvatinib combination therapy (n=51)	Everolimus monotherapy (n=50)
ORR (CR+ PR) (n%)	22 (43.1)	3 (6.0)	18 (35.3)	0 (0.0)
95% CI	(29.3, 57.8)	(1.3, 16.5)	(22.4, 49.9)	(0.0, 7.1)
Rate Ratio (95% CI)	7.2 (2.3, 22.5),		NE	
p-value	<0.0001		<0.0001	
Abbreviations: CI, confidence interval; CR, complete response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response.				

Table 16. Summary of Tumour Response based on investigators assessment – Full Analysis Set (CS, page 62, Figure 33)

	Lenvatinib combination therapy (n=51)	**Everolimus monotherapy (n=50)**
Complete response (CR), n (%)	1 (2.0)	0
Partial response (PR), n (%)	21 (41.2)	3 (6.0)
Stable disease (SD), n (%)	21 (41.2)	31 (62.0)
Progressive disease (PD), n (%)	2 (3.9)	12 (24.0)
Not assessed, n (%)	6 (11.8)	4 (8.0)
Objective Response Rate (CR+PR), n (%)	22 (43.1)	3 (6.0)
95% CI	(29.3, 57.8)	(1.3, 16.5)
Disease Control Rate (CR+PR+SD ≥ 7weeks), n (%)	43 (84.3)	34 (68.0)
95% CI	(71.4, 93.0)	(53.3, 80.5)
Durable Stable Disease Rate (SD ≥ 23 weeks), n (%)	13 (25.5)	18 (36.0)
95% CI	(14.3, 39.6)	(22.9, 50.8)
Clinical Benefit Rate (CR+PR+SD ≥ 23 weeks)	35 (68.6)	21 (42.0)
95% CI	(54.1, 80.9)	(28.2, 56.8)
Abbreviations: CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease		

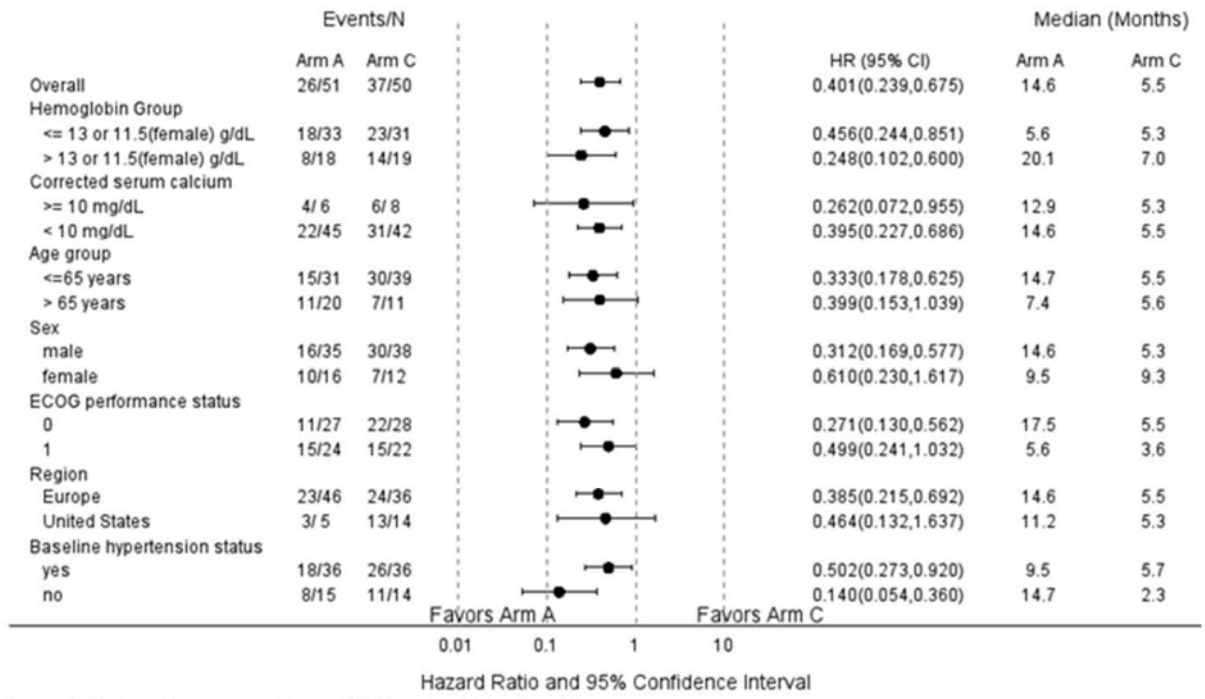
4.3.4 Subgroup analyses

The ERG notes that the company only mentioned haemoglobin and corrected serum calcium as pre-specified subgroups in the CS, however, the subgroups listed in

Figure 10 were all specified in the CSR. The ERG notes that according to the CSR the subgroups for the analysis were determined after database lock.

Subgroup analyses of PFS based on ECOG PS at baseline, age, sex, region, baseline hypertension status, risk categories of the Memorial Sloan-Kettering Cancer Center (MSKCC), corrected serum calcium, and haemoglobin showed consistent improvements (at least numerically) in PFS for the combination group in all subgroups compared with the everolimus group. The ERG notes that these analyses are considered exploratory as they are limited by the small sample size within each subgroup.

Figure 10. Forest Plot of HRs for PFS by Subgroup (Combination Group vs Everolimus Group) – Full Analysis Set (CS, page. 63, Figure 34)



Arm A=E7080 18mg + Everolimus 5mg; Arm B=E7080 24mg; Arm C=Everolimus 10mg
Hazard ratio is based on a Cox regression model including treatment, subgroup and treatment-by-subgroup interaction as factors.

4.3.5 Adverse effects

Based on data at the Jun 2014 data cut-off, median daily dose of lenvatinib was 13.6mg, 75% of the recommended daily dose of 18mg (Table 17). For everolimus median daily dose was 4.7mg, approximately 94% of the intended daily dose of 5mg in the combination group, and 9.7mg in the everolimus monotherapy group (97% of the intended daily dose of 10mg). The ERG notes that some patients got more than the daily intended dose of both lenvatinib and everolimus; the highest dose of lenvatinib was 133% of the recommended daily dose and 125% for everolimus in the combination group

whereas no patients went above the intended daily dose of everolimus in the monotherapy group. The ERG speculate that, this may be due to the complexity of the dosing schedule for the lenvatinib combination therapy where patients have to take three lenvatinib tablets of two different doses plus one everolimus tablet each day.

Median duration of treatment was longer in the lenvatinib combination group at 7.6 months compared with 4.1 months in the everolimus group. At the July 2015 data cut-off the median duration of treatment in the combination group had increased slightly to 8.0 months; in the everolimus group median duration of treatment was unchanged.

Median time to first lenvatinib dose reduction was 1.6 months in the combination group. Median time to first everolimus dose reduction was 4.8 months in the combination group and 2.5 months in the everolimus monotherapy group (Table 17).

A larger proportion of patients had dose interruptions of lenvatinib (80.4%) and/or everolimus (76.5%) in the combination group compared with everolimus in the monotherapy group (54.0%). 70.6% of patients in the combination group also had dose reduction of lenvatinib; though only one patient (2%) in the combination group had a dose reduction of everolimus, compared with 13 patients (26.0%) in the everolimus monotherapy group (Table 17). The majority of dose interruptions and reductions were due to adverse events (Table 18).

All patients in the trial had at least one treatment emergent adverse event (TEAE). Grade 3 or higher TEAEs were more frequent in the combination group (72.5%) than the everolimus group (54.0%).

Serious AEs occurred at a slightly higher incidence in the combination group (54.9%) than in the everolimus group (42%). Fatal AEs were rare; one patient died due to cerebral haemorrhage in the combination group (2.0%) and two patients in the everolimus group (respiratory failure and sepsis, 4.0%).

More patients treated with lenvatinib combination had a TEAE leading to treatment adjustment (88.2%) compared with the everolimus group (60.0%); 23.5% of patients discontinued lenvatinib combination treatment due to adverse events compared with 12.0% of patients in the everolimus group.

The number of treatment related adverse events (TRAEs) were similar to TEAEs; all but one patient experienced at least one TRAE. Grade 3 or higher TRAEs were more frequent in the combination group (64.7%) than the everolimus group (42.0%), and as expected most adverse events leading to treatment adjustments were related to the study treatments (Table 19). The two SAE deaths in the everolimus group were not deemed to be treatment related though one death in the lenvatinib combination group was linked to the study treatment.

Table 17. Extent of exposure to study treatment – safety analysis set, data cut-off June 2014 (adapted from CS, pages 80 and 81, Figure 44, Figure 45, and Figure 46)

	Lenvatinib combination therapy (n=51)		**Everolimus monotherapy (n=50)**
Duration of treatment (months*)			
Mean (SD)	9.4 (6.6)		6.2 (5.2)
Median	7.6		4.1
Range	0.7-22.6		0.3-20.1
Mean daily dose per patient (mg/day)	Lenvatinib	Everolimus	
Mean (SD)	13.3 (4.0)	4.4 (0.82)	9.0 (1.5)
Median	13.6	4.7	9.7
Range	6-24	2-6	4-10
Percent intended dose (%)			
Mean (SD)	73.8 (22.3)	88.0 (16.42)	89.6 (14.6)
Median	75.4	93.7	97.0
Range	31-133	34-125	44-100
Number of patients with, n (%)			
Dose reduction	36 (70.6)	1 (2.0)	13 (26.0)
Dose interruption	41 (80.4)	39 (76.5)	27 (54.0)
Time to dose reduction (months), median (95% CI)	1.6 (1.2, 2.3)	4.8 (0.9, 6.0)	2.5 (1.4, 5.6)

Abbreviations: CI, confidence interval; SD, standard deviation

*Changed by ERG from days, as stated in the CS, to months in line with the CSR.

Table 18. Overview of treatment emergent adverse events (adapted from CS, page 82, Figure 47)

	Lenvatinib combination therapy (n=51)	**Everolimus monotherapy (n=50)**
	n (%)	n (%)
	n (%)	n (%)
Any TEAEs	51 (100.0)	50 (100.0)
TEAEs with CTCAE Grade ≥3	37 (72.5)	27 (54.0)
SAEs	28 (54.9)	21 (42.0)
Deaths	1 (2.0)	2 (4.0)
Other SAEs	27 (52.9)	21 (42.0)
TEAEs leading to study treatment adjustment	45 (88.2)	30 (60.0)
TEAEs leading to study treatment withdrawal	12 (23.5)	6 (12.0)
TEAEs leading to dose reduction	34 (66.7)	8 (16.0)
TEAEs leading to dose interruption	35 (68.6)	25 (50.0)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; TEAE, treatment emergent adverse event

Table 19. Overview of treatment related adverse events (adapted from CS, page 86, Figure 50)

	Lenvatinib combination therapy (n=51)	Everolimus monotherapy (n=50)
	n (%)	n (%)
Any TRAEs	51 (100.0)	49 (98.0)
TRAEs with CTCAE Grade ≥3	33 (64.7)	21 (42.0)
STRAEs	16 (31.4)	11 (22.0)
Treatment related deaths	1 (2.0)	0
Other STRAEs	15 (29.4)	11 (22.0)
TRAEs leading to study treatment adjustment	42 (82.4)	22 (44.0)
TRAEs leading to study treatment withdrawal	8 (15.7)	3 (6.0)
TRAEs leading to dose reduction	33 (64.7)	7 (14.0)
TRAEs leading to dose interruption	33 (64.7)	19 (38.0)
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; STRAE, serious treatment related adverse event; TRAE, treatment related adverse event		

Table 20 lists TEAEs occurring in at least 10% of patients in the lenvatinib combination or everolimus monotherapy groups. The most frequently reported TEAEs (>30% of patients in either treatment group) in the combination group were diarrhoea (84.3%), decreased appetite (51.0%), fatigue (47.1%), vomiting (45.1%), nausea (41.2%), hypertension (41.2%), cough (37.3%), hypertriglyceridemia (35.3%), hypercholesterolemia (33.3%), and weight decreased (31.4%). These events are consistent with the safety profile of lenvatinib in combination with everolimus from the SmPC; however, this is primarily based on lenvatinib monotherapy in differentiated thyroid cancer (458 patients) and only 62 RCC patients, allowing characterisation only of common adverse drug reactions.

These are also consistent with the most frequently reported (≥30% of patients in either treatment group) TRAEs, all of which occurred more frequently with the combination treatment than with everolimus monotherapy were diarrhoea, decreased appetite, hypertension, fatigue, nausea, vomiting, weight decreased, hypothyroidism, hypertriglyceridemia, and dysphonia. The most frequent TRAE in the everolimus group was stomatitis, which is consistent with the known safety profile of everolimus.

Table 20. Treatment-emergent adverse events occurring in at least 10% of patients in either treatment group – safety analysis set (adapted from CS, page 83, Figure 48)

	Lenvatinib combination therapy (n=51) n(%)	Everolimus monotherapy (n=50) n(%)
Diarrhoea	43(84.3)	17(34.0)
Decreased appetite	26(51.0)	9(18.0)
Fatigue	24(47.1)	16(32.0)
Vomiting	23(45.1)	5(10.0)
Nausea	21(41.2)	8(16.0)
Hypertension	21(41.2)	5(10.0)

Cough	19(37.3)	15(30.0)
Hypertriglyceridaemia	18(35.3)	12(24.0)
Hypercholesterolaemia	17(33.3)	8(16.0)
Weight decreased	16(31.4)	4(8.0)
Stomatitis	15(29.4)	21(42.0)
Epistaxis	9(17.6)	11 (22.0)
Abdominal pain	9 (17.6)	1 (2.0)
Abdominal pain upper	9 (17.6)	4 (8.0)
Insomnia	9(17.6)	1 (2.0)
Anaemia	8(15.7)	13 (26.0)
Hyperglycaemia	8(15.7)	11 (22.0)
Musculoskeletal chest pain	8 (15.7)	2 (4.0)
Blood thyroid stimulating hormone increased	7 (13.7)	1 (2.0)
Constipation	6(11.8)	9 (18.0)
Dyspepsia	6(11.8)	5 (10.0)
Pruritus	6(11.8)	7 (14.0)
Nasopharyngitis	6(11.8)	6 (12.0)
Oral pain	6 (11.8)	1 (2.0)
Hypokalaemia	6(11.8)	1 (2.0)
Mouth ulceration	5 (9.8)	5 (10.0)
Upper respiratory tract infection	3 (5.9)	5 (10.0)
Pneumonitis	3(5.9)	6 (12.0)
Dyspnoea exertional	2 (3.9)	5 (10.0)
Lower respiratory tract infection	1 (2.0)	6 (12.0)
Rash macular	1 (2.0)	5 (10.0)

Table 21 gives a summary of grade 3 and 4 TEAEs occurring in at least 5% of patients in either treatment group. More patients treated with lenvatinib combination were reported to have grade 3 TEAEs than in the everolimus monotherapy group. The most common grade 3 TEAEs were in line with common TEAEs of any grade and included: diarrhoea (19.6%), hypertension (13.7%), fatigue (9.8%), anaemia (7.8%), vomiting (7.8%), decreased appetite (5.9%), and nausea (5.9%). Additional grade 3 TEAE included hypertriglyceridemia (7.8%), thrombocytopenia (5.9%), and dehydration (5.9%). Most common grade 3 event in the everolimus monotherapy group was anaemia (12%). There were few grade 4 events in either trial arm with no more than one patient in either the lenvatinib combination or the everolimus monotherapy group with a specific grade 4 event.

Table 21. Grade 3 and 4 Treatment-emergent adverse events occurring in at least 5% of patients in either treatment group (adapted from CS, page 85, Figure 49)

	Lenvatinib combination therapy (n=51)		**Everolimus monotherapy (n=50)**	
	Grade 3	Grade 4	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)
Patients with any TEAE	36 (70.6)	7 (13.7)	26 (52.0)	6 (12.0)
Diarrhoea	10 (19.6)	0	1 (2.0)	0
Hypertension	7 (13.7)	0	1 (2.0)	0

	Lenvatinib combination therapy (n=51)		Everolimus monotherapy (n=50)	
Fatigue	5 (9.8)	0	0	0
Anaemia	4 (7.8)	0	6 (12.0)	0
Hypertriglyceridaemia	4 (7.8)	0	4 (8.0)	0
Vomiting	4 (7.8)	0	0	0
Decreased Appetite	3 (5.9)	0	0	0
Nausea	3 (5.9)	0	0	0
Dehydration	3 (5.9)	0	0	0
Thrombocytopenia	3 (5.9)	1 (2.0)	0	0
Dyspnoea	0	1 (2.0)	4 (8.0)	0
Hyperglycaemia	0	0	4 (8.0)	1 (2.0)
Pneumonitis	0	0	3 (6.0)	0
Abbreviations: TEAE, treatment emergent adverse event				

The ERG notes that the FDA has raised concerns about the serious adverse events requiring dose reduction or interruption in HOPE 205, which are listed in Table 22. The FDA has determined that an analysis of spontaneous post-marketing adverse events reported will not be sufficient to assess the known serious risks of diarrhoea, fatigue, vomiting, haemorrhage, and renal failure occurring with lower doses of lenvatinib in combination with everolimus. Hence, the FDA has requested another clinical trial to assess these known serious risks.[48] The requested study is expected to be completed in November 2020 and the Final Study Report submitted in July 2021.

[redacted]

4.3.6 Summary of clinical effectiveness HOPE 205

- Lenvatinib combination therapy showed a statistically significant improvement in PFS (median PFS 14.6 months) compared with everolimus (median PFS 5.5 months) in the IA analysis (HR 0.40, 95% CI: 0.24 to 0.68, p=0.0005). *Post-hoc* assessment of PFS by IRR showed similar

results; median PFS was 12.8 months in the combination group and 5.6 months for the everolimus group (HR 0.45, 95% CI: 0.26 to 0.79, p=0.003).

- In the EMA analysis of the latest data cut, OS was statistically significantly longer for patients treated with lenvatinib combination therapy (median survival 25.5 months) compared with patients receiving everolimus monotherapy (median survival 15.4 months) based on the cox model (HR 0.59, 95% CI: 0.36 to 0.97), however, the p-value for the log rank test did not reach statistical significance (p=0.065). The FDA analysis also favoured lenvatinib combination therapy but did not reach statistically significance (HR 0.67, 95% CI: 0.42 to 1.08).

- Based on the IA more patients treated with lenvatinib combination therapy achieved a complete or partial response than patients treated with everolimus monotherapy, the difference being statistically significant (RR 7.2, 95% CI: 2.3 to 22.5, p<0.0001) in favour of the combination group. The IRR showed similar result to the IA but with slightly lower ORR for both groups.

- Subgroup analyses of PFS based on ECOG PS at baseline, age, sex, region, baseline hypertension status, MSKCC risk category, corrected serum calcium, and haemoglobin showed consistent improvements in PFS for the combination group compared with the everolimus group.

- All patients in the trial had at least one treatment emergent adverse event (TEAE). Serious AEs occurred at a slightly higher incidence in the combination group (54.9%) than in the everolimus group (42%). The most frequently reported TEAEs in the combination group compared with the everolimus group were diarrhoea (84.3% vs 34.0%), decreased appetite (51.0% vs 18.0%), fatigue (47.1% vs 32.0%), vomiting (45.1% vs 10.0%), nausea (41.2% vs 16.0%), hypertension (41.2% vs 10.0%), cough (37.3% vs 30.0%), hypertriglyceridemia (35.3% vs 24.0%), hypercholesterolemia (33.3% vs 16.0%), and weight decreased (31.4% vs 8.0%). The most common grade 3 TEAEs were diarrhoea (19.6% vs 2.0%, lenvatinib combination vs everolimus), hypertension (13.7% vs 2.0%), fatigue (9.8% vs 0%), anaemia (7.8% vs 12.0%), hypertriglyceridemia (7.8% vs 8.0%), and vomiting (7.8% vs 0%).

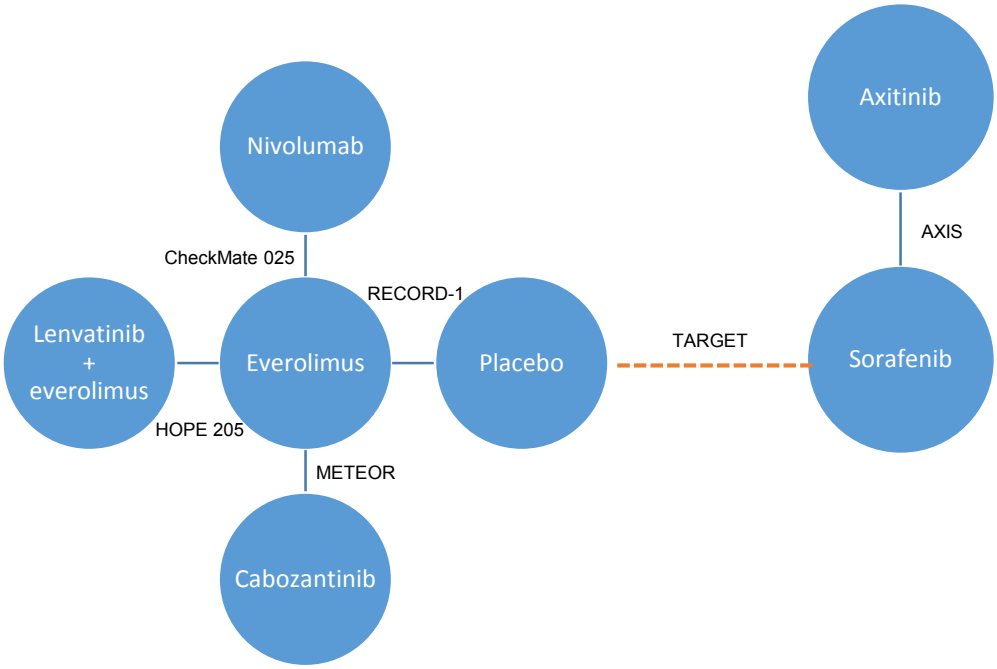
4.4 Indirect treatment comparison

Due to the absence of head-to-head trials comparing lenvatinib combination therapy with nivolumab, cabozantinib, axitinib, and BSC in patients with advanced RCC who have progressed after one prior VEGF-targeted treatment, the company conducted an indirect treatment comparison (ITC). The studies included in the ITC were identified via a standard systematic literature review; the methods used to identify the studies included in the ITC and the quality assessment of the included studies are described in Section 4.1.

4.4.1 Included studies

Five trials comparing treatments for patients with advanced RCC who had failed at least one prior VEGF-targeted therapy were included; AXIS (axitinib versus sorafenib), CheckMate 025 (nivolumab versus everolimus), HOPE 205 (lenvatinib combination therapy versus everolimus), METEOR (cabozantinib versus everolimus), and RECORD-1 (everolimus versus placebo). A summary of the included studies is presented in Table 23. A network could be connected enabling comparisons of lenvatinib combination therapy with nivolumab, cabozantinib and placebo (Figure 11). The ERG considers it reasonable to use placebo as a surrogate for BSC. No trials meeting the eligibility criteria were identified which would enable a comparison with axitinib. The company, therefore, included the trial TARGET (sorafenib versus placebo), which links the axitinib RCT AXIS to the network. As discussed in Section 4.1, it is unclear how TARGET was identified and if there are other trials that could facilitate connections in the network that have been overseen. In TARGET, patients who had had prior anti-VEGF targeted therapy were excluded; instead patients were eligible for study entry if they had had one prior systemic therapy, with the majority of patients having previously received cytokine treatment. This is in contrast to the other trials included in the network where all or at least a relatively large subgroup of patients had prior anti-VEGF targeted treatments. The company acknowledge that type of prior treatment may have a marked effect on PFS and OS, and hence including TARGET in the network may violate the transitivity assumption.

Figure 11. Network of trials included in the ITC for a/mRCC (CS, page 66, Figure 36)



The company reports that CheckMate 025 and METEOR both allowed patients who had failed at least one anti-VEGF therapy, with close to 30% of patients having failed more than one. The ERG notes that the eligibility criteria for RECORD-1 was also one or two prior anti-VEGF therapies; 26% of patients had received two prior TKIs. However, RECORD-1 did not exclude patients who had also had other prior therapies such as cytokines. In HOPE 205 all patients had received only one prior anti-VEGF therapy. In AXIS two thirds of patients had received prior anti-VEGF therapy, but subgroup data were available for around half of patients who had had prior sunitinib therapy.

AXIS, CheckMate 025, HOPE 205 and METEOR were all open label, whereas both placebo controlled trials (RECORD-1 and TARGET) were double blind. All trials were phase III with the exception of HOPE 205 which is a phase II trial with a smaller sample size.

Table 23. Summary of trials included in the network

Study	Study design	Treatments	N	Prior therapies permitted
AXIS	Phase III open label RCT	Axitinib	361	1 systemic therapy (54% TKI, 35% cytokines, 11% other); other prior therapies permitted
		Sorafenib	362	
CheckMate 025	Phase III open label RCT	Nivolumab	410	1or 2 prior antiangiogenic; no prior mTORi permitted
		Everolimus	411	
HOPE 205	Phase II open label RCT	Lenvatinib combination therapy	51	1 prior TKI; other prior therapies permitted
		Everolimus	50	

METEOR	Phase III open label RCT	Cabozantinib	330	1 or more prior TKIs; no prior mTORi permitted
		Everolimus	328	
RECORD-1	Phase III double blind RCT	Everolimus	277	1 or 2 prior TKI; bevacizumab & cytokines permitted; no prior mTORi permitted
		Placebo	139	
TARGET	Phase III double blind RCT	Sorafenib	451	1 systemic therapy (~80% cytokines); no prior VEGF targeted therapy permitted
		Placebo	452	
Abbreviations: RCT, randomised control trials; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamaycin inhibitor.				

Baseline characteristics were generally balanced between trial arms in all studies included in the network (Table 26), and the trial populations were relatively similar between studies in terms of mean age, gender mix and ethnicity, where reported (Table 26). However, a larger proportion of patients had a worse performance status (ECOG 1 or 2, Karnofsky <80) in AXIS, HOPE 205 and TARGET compared with patients in CheckMate 025, METEOR and RECORD-1. This was also reflected in the MSKCC risk score with a larger proportion of patients with a poor risk score in AXIS and HOPE 205 compared with the other trials. Of the included trials AXIS and HOPE 205 are, therefore, the most representative of second-line RCC patients in clinical practice, based on performance status. However, both trial populations still have a better performance status than would be expected in clinical practice. In all trials most patients (86% to 97%) had had prior nephrectomy. The proportion of patients with prior radiotherapy was lower in HOPE 205 than the other trials, where reported, and there was an imbalance between the trial arms.

RECORD-1 and TARGET both permitted crossover to the investigational treatment post progression. At the final data-cut (Nov 2008) of RECORD-1, 80% of patients randomised to placebo had crossed over to receive open-label everolimus. In TARGET 48% of patients randomised to placebo crossed over to receive sorafenib after the interim analysis, in May 2005. In AXIS, CheckMate 025, HOPE 205, and METEOR large proportions of patients went on to receive other anti-VEGF and mTOR therapies after progression on the trial intervention (Table 25). In these trials, slightly more patients randomised to everolimus/sorafenib received subsequent therapies than patients randomised to the other intervention.

Table 24. Summary of prior therapies in trials included in the network (adapted from CS, Appendix 8.5, Table 3.1.1)

Study	**Treatments**	**Prior VEGF-targeted therapy %**		**Prior sunitinib %**	**Cytokine as only prior systemic therapy %**	**Prior RT %**	**Prior Nephrectomy %**
		1	**≥2**				
AXIS	Axitinib	65	0	54	35	NR	91
	Sorafenib	65	0	54	35	NR	
CheckMate 025	Nivolumab	72	28	60	0	NR	89
	Everolimus	72	28	59	0	NR	87

HOPE 205	Lenvatinib combination therapy	100	0	71	0	12	86
	Everolimus	100	0	56	0	22	96
METEOR	Cabozantinib	71	29	64	0	33	85
	Everolimus	70	30	62	0	33	85
RECORD-1	Everolimus	74	26	71	0	31	97
	Placebo	74	26	69	0	27	96
TARGET	Sorafenib	0	0	0	83	27	94
	Placebo	0	0	0	81	24	93
Abbreviations: RT, radiotherapy; VEGF, vascular endothelial growth factor							

Table 25. Subsequent therapies (adapted from CS, Appendix 8.5, Table 2.3.1)

Trial	**Control patients cross-over to investigational treatment**	**Continued treatment with study drug after progression**	**Subsequent systemic therapies**	
Everolimus trials			Treatment	Everolimus
HOPE 205* (lenvatinib plus everolimus)	Not permitted	Not permitted	Any: 35% Any VEGF: 18% Axitinib 12% Everolimus 10%	Any: 36% Any VEGF 26% Axitinib 24% Everolimus 4%
CheckMate 025 (nivolumab)	Not permitted	Not reported	Any: 55% Everolimus 26% Axitinib 24% Pazopanib 9%	Any: 63% Axitinib 36% Pazopanib 16% Sorafenib 9%
METEOR (cabozantinib)	Not permitted	Treatment continued while clinical benefit was observed	Any: 50% Any VEGF 24% Everolimus 29% Axitinib 17%	Any: 55% Any VEGF 47% Axitinib 27% Sunitinib 10%
RECORD-1 (placebo)	80%	Not permitted	NR	NR
Sorafenib trials			Treatment	Sorafenib
AXIS (axitinib)	Not permitted	Not permitted	Any: 54% Any VEGF 33% Any mTOR 39% Everolimus 16%	Any: 57% Any VEGF 32% Any mTOR 41% Everolimus 8%
TARGET (placebo)	48%	Patients who responded could continue sorafenib	NR	NR
Abbreviations: mTOR, mammalian target of rapamaycin; VEGF, vascular endothelial growth factor *Subsequent therapies at data cut July 2015, kindly provided at the clarification stage.				

Table 26. Summary of baseline characteristics in trials included in the network (adapted from CS, Appendix 8.5, Table 3.1.1)

Study	Treatments	Age, median	Male %	Ethnicity white %	ECOG/Karnofsky performance status[a] %			MSKCC %		
					0/90-100	1/70-80	2/<70	Favourable	Intermediate	Poor
AXIS	Axitinib	61	73	77	54	45	<1	28	37	33
	Sorafenib	62	71	74	55	44	0	28	36	33
CheckMate 025	Nivolumab	62	77	86	68	32	<1	35	49	16
	Everolimus	62	74	89	65	35	<1	36	49	15
HOPE 205	Lenvatinib combination therapy	61	69	NR	53	47	-	24	37	39
	Everolimus	59	76	NR	56	44	-	24	38	38
METEOR	Cabozantinib	63	77	82	68	32	-	45	42	12
	Everolimus	62	73	80	66	34	-	46	41	13
RECORD-1	Everolimus	61	78	NR	63	36	-	29	56	15
	Placebo	60	76	NR	68	33	-	28	57	15
TARGET	Sorafenib	58	70	NR	49	49	2	52	48	-
	Placebo	59	75	NR	46	52	1	51	49	-

Abbreviations: NR, not reported; MSKCC, Memorial Sloane Kettering Cancer Center Risk Score

The company checked the consistency across the network by comparing median PFS and OS, and ORR for each of the everolimus groups and the sorafenib groups across trials (CS Appendix 8.5 Table 3.2.1). Median PFS and OS differ, and ORR show large variations between trials, but also within trials depending on number and type of prior therapy, and if the assessment had been done by the investigators or by IRR. The ERG notes that naive comparisons of median PFS and OS for all everolimus trial arms and all sorafenib trial arms are not expected to give the same values. The decision of which trials should be included in a network should be based on any potential treatment effect or prognostic modifiers, in terms of the trial designs, trial conduct and patient's baseline characteristics, being similar enough in the trials that the relative efficacy of treatments are expected to be the same if patients had been randomised to the same two treatments in any of these trials. E.g. based on the effect of type of prior treatment (cytokines or TKI) on the relative efficacy of axitinib versus sorafenib in AXIS, the ERG considers it reasonable to exclude TARGET (prior cytokines) from the network as the population is too different from the populations in the other included studies. Although number of prior VEGF-targeted therapies and performance status differs between the trials in the network and these factors have been shown to influence PFS and OS, it is unclear if they effect the interventions in the network differently. By combining these trials in the network the company assumes that the relative efficacy between each comparison within the network will be independent of these factors. The ERG agrees with the company's assumption and approach to combine these trials in a network, with the exception of TARGET for the reasons mentioned previously.

The outcomes analysed in the ITCs were:

- progression free survival (PFS);
- overall survival (OS);
- objective response rate (ORR); and
- safety:
    - proportion of patients experiencing at least one severe (grade 3 or 4) AE;
    - proportion of patients experiencing at least one AE leading to discontinuation of study treatment.

4.4.2 Statistical methods

In the CS the relative efficacy of lenvatinib combination therapy versus each comparator was estimated using the Bucher method[49] in which the relative efficacy of drug A versus drug C can be estimated indirectly if the efficacy of A versus B and B versus C are known. Indirect estimates of the relative treatment effect of lenvatinib combination therapy versus nivolumab, cabozantinib and placebo were conducted using the Bucher method with everolimus as the common comparator. The relative efficacy of lenvatinib combination therapy versus axitinib was achieved by repeating the Bucher method in a multi-step indirect comparison. Although not explicit in the CS, the ERG assumes that the multiple steps consisted of using the Bucher method to calculate the indirect estimate of lenvatinib combination therapy versus placebo (HOPE 205 and RECORD-1), axitinib versus placebo (AXIS and TARGET) and finally using these two estimates to get the relative efficacy of lenvatinib combination therapy versus axitinib.

ORR and safety, which are both binary outcomes, are presented as odds ratio (OR), relative risk (RR) and risk difference (RD) calculated from the proportion of patients experiencing each outcome. When no events were observed in a treatment group, 0.5 was added to each cell of the 2-by-2 table. The ERG notes that this was not done consistently as the IRR of ORR in HOPE 205 had zero events in the everolimus monotherapy group, but the company did not us this data as, "sensitivity analyses based on the IRR results are highly uncertain" (CS Appendix 8.5 page 14).

For PFS and OS the company used the published HRs and associated 95% CIs. HRs are conditional on the proportional hazards (PHs) assumption being fulfilled and any ITC based on HRs would need to assume that the PHs assumption holds within and between each of the trials included. The ERG notes that the PHs assumption has been tested previously for PFS and OS in all the trials included in the network, with the exception of HOPE 205, in the CS for the STAs of cabozantinib.[50] Based on the assessment by the company in the STA of cabozantinib the PHs assumption holds for OS and PFS in METEOR, RECORD-1 and AXIS, but not in CheckMate 025 or TARGET (Table 27).

Table 27. Proportional hazards test for OS and PFS (adapted from cabozantinib STA, Committee papers, Section 3, Company submission from Ipsen, Table 32)[50]

Study Name	Proportional hazards assumption holds?	
	OS	PFS
METEOR	Yes	Yes*
RECORD-1	Yes	Yes
CheckMate 025	No	No
TARGET	No	No
AXIS	Yes	Yes
*PH holds at the significance level of 0.05 for PFS endpoint but doesn't hold at the significance level of 0.1 (p=0.0593).		

As described in Sections 4.3.1 and 1.1.1 the company tested the PH assumption for PFS and OS in HOPE 205, with the PH test based on residuals not showing a significant result which indicates that the curves do not deviate from the PH assumption. However, due to the small sample size in HOPE 205 the test is likely underpowered to detect a significant difference, which was also reflected by the visual inspection of the log-cumulative hazard plots which indicate that the PHs assumption may not hold.

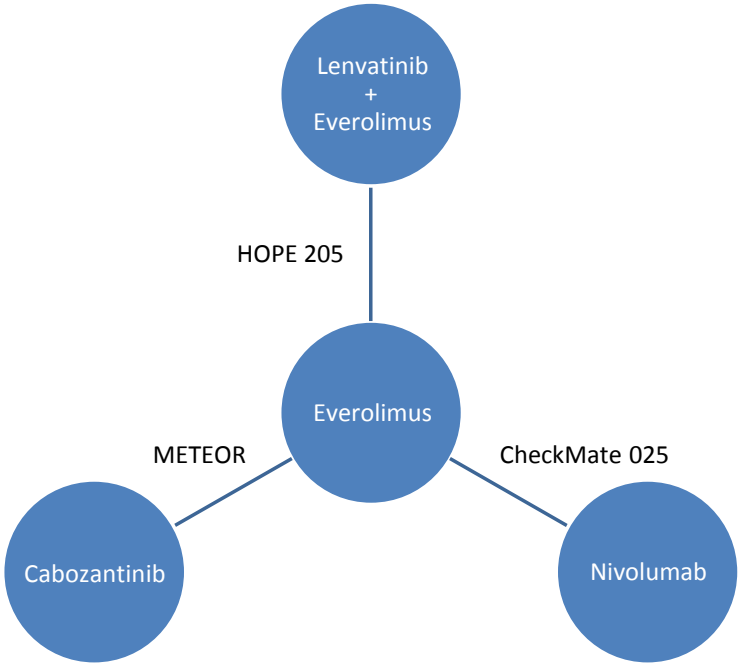
At the clarification stage, the company also provided their own assessment of PHs in CheckMate 025 and METEOR, which showed similar results to the assessment in the cabozantinib STA: for PFS the PH assumption was violated in CheckMate 025 and METEOR, for OS the PHs assumption held within METEOR, but not for CheckMate 025.

As the PHs assumption is not fulfilled for PFS or OS for CheckMate 025, TARGET and potentially METEOR, the ERG considers it inappropriate to base the analysis of these outcomes on any indirect comparison method which relies on the PHs assumption. However, as the ITC analyses of PFS and OS, using the Bucher methods based on HRs, informs the company's base case in the economic model these results are presented in this report, but the ERG would like to emphasise the difficulty in deriving a meaningful interpretation of these results.

At the clarification stage the company re-assessed PFS and OS in a Bayesian network meta-analysis (NMA) using fractional polynomials, which does not rely on the PH assumption being fulfilled.

The company acknowledge that the analysis of lenvatinib combination therapy versus axitinib is problematic due to the lack of consistency between the included trials. As mentioned previously, patients in TARGET had mainly received cytokine therapy prior to entering the trial and none had received prior VEGF-targeted therapies. OS for the comparison of lenvatinib combination therapy versus axitinib is also confounded by cross-over to the interventional therapy in both TARGET and RECORD-1. For the NMA, the company therefore assumed that axitinib and everolimus monotherapy have similar efficacy; an assumption which is in accordance with the NICE appraisal committee for cabozantinib (GID-TA10075) and nivolumab (TA417).[51, 52] The network for the NMA was therefore condensed to include HOPE 205, CheckMate 025, and METEOR as shown in Figure 12.

Figure 12. Network of trials included in the ITC for advanced RCC



Abbreviations: ITC, indirect treatment comparison; RCC, renal cell carcinoma.

For the NMA, the company used a method described by Jansen et al. 2011 with parametric fractional polynomial survival functions.53 With fractional polynomials, the treatment effect is represented by multiple parameters and the hazard is modelled over time which allows a wide family of survival functions to be estimated. The method used for the NMA is described in Box 13. The ERG has examined the programming code supplied by the company and could replicate the company's results. Hence, the ERG considers that the fractional polynomial method has been implemented appropriately. The company digitally extracted survival data from the relevant KM curves for CheckMate 025 and METEOR; for each treatment, survival time, censored events, total number of events, and the number at risk were extracted from the KM data. The company only considered fixed effect models, stating that random effects models may be less stable due to only three trials being available across the four treatments of interest. The ERG agrees with the company's approach to only run fixed effect models since the network is star shaped with no cross-links between treatments and only one trial is available for each comparison. Hence, there is nothing to inform the between trial heterogeneity. Similarly, the ERG accepts that the time available to the company has limited their opportunity to explore all possible second order fractional polynomial models.

Box 13. Fractional polynomial method (late clarification response pages 4 and 5)

First order fractional polynomial for hazard function:

$$\ln(h_{jkt}) = \beta_{0jk} + \beta_{1jk} t^{P1}$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix} = \begin{cases} \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} \; if \; k = b \\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} + \begin{pmatrix}\delta_{0jk}\\ \delta_{1jk}\end{pmatrix} \; if \; k \neq b \end{cases}$$

$$\text{where } \begin{pmatrix}\delta_{0jk}\\ \delta_{1jk}\end{pmatrix} = \begin{pmatrix}d_{0k}\\ d_{1k}\end{pmatrix} - \begin{pmatrix}d_{0b}\\ d_{1b}\end{pmatrix}$$

Second order fractional polynomial for hazard function:

$$\ln(h_{jkt}) = \begin{cases} \beta_{0jk} + \beta_{1jk} t^{P1} + \beta_{2jk} t^{P2} \; if \; P1 \neq P2 \\ \beta_{0jk} + \beta_{1jk} t^{P1} + \beta_{2jk} t^{P1} \ln(t) \; if \; P1 = P2 \end{cases} \quad with \; t^0 = \ln(t)$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\\ \beta_{2jk}\end{pmatrix} = \begin{cases} \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} \; if \; k = b \\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} + \begin{pmatrix}\delta_{0jk}\\ \delta_{1jk}\\ \delta_{2jk}\end{pmatrix} \; if \; k \neq b \end{cases}$$

$$\text{where } \begin{pmatrix}\delta_{0jk}\\ \delta_{1jk}\\ \delta_{2jk}\end{pmatrix} = \begin{pmatrix}d_{0k}\\ d_{1k}\\ d_{2k}\end{pmatrix} - \begin{pmatrix}d_{0b}\\ d_{1b}\\ d_{2b}\end{pmatrix}$$

where *j* denotes study (1 to 3), *k* denotes treatment (1 to 4), *b* denotes 'baseline' treatment (everolimus) and *t* denotes time.

Thus, h_{jkt} is the hazard rate for intervention *k* in trial *j* at time *t* with parameters β which comprises the vectors μ for the 'baseline' treatment (everolimus) and δ for the difference in log hazard curves for treatment *k* relative to 'baseline' (everolimus). Under the proportion hazards assumption d_1 is zero and thus non zero estimates of d_1 reflect the change in the log hazard ratio over time.

Model parameters were estimated using Markov Chain Monte Carlo (MCMC) method in WinBugs. Two chains were run for 50,000 iterations and discarded as 'burn-in, and then the model was run for a further 50,000 iterations for inference. Non-informative priors were used for μ and d. Diagnostic plots were examined for convergence including the Gelman-Rubin statistic. The powers for the fractional polynomials were chosen from the set: -2, -1, -0.5, 0, 0.5, 1, and 2, although due to time constraints not all possible second order models were considered. The Deviance Information Criterion (DIC) was used to compare the goodness of fit. The model with the lowest DIC provides the 'best' fit to the data.

Abbreviations: DIC, deviance information criterion; MCMC, Markov Chain Monte Carlo

4.4.3 Data

The company's analysis of PFS and ORR used the primary analysis in each trial, that is IA for HOPE 205 and CheckMate 025, and IRR for AXIS, METEOR, RECORD-1 and TARGET. For PFS in HOPE 205, the company's reasoning was to avoid potential biased due to informative censoring as the independent reviewer was not able to review further scans after the investigator deemed the patient's tumour to have progressed. At the clarification stage, the company provided further rational for using IA rather than IRR in the analyses, "the protocol specified progression would be ascertained based on investigator assessment which resulted in some patients being classified with progressive disease before the *ad hoc* analysis by the IRR committee. These patients may have then switched to subsequent therapy and had no further scans available for IRR, introducing potential bias in the IRR results." (clarification response A3). The ERG notes that it is unclear if patients who were deemed to have progressed by the investigator, but not by the IRR, were censored at the time of IA progression from the IRR assessment. If so, then the *ad hoc* IRR in HOPE 205 is unlikely to be different from IRR in an open label trial with pre-specified IA and IRR. For ORR in HOPE 205, there were no events in the everolimus monotherapy group and the company deemed the IRR too uncertain to use rather than imputing 0.5 where there were no events. The ERG considers the IRR for PFS and ORR for all trials to be more reliable and should be used where possible. The company did not provide an updated analysis of PFS using NMA fractional polynomial based on IRR for HOPE 205, however, for the ITC of PFS and ORR the company's preferred analysis is presented alongside sensitivity analyses provided, which are based on each assessment methodology separately.

The company's primary analyses were based on the full populations for all trials. For the ITC of PFS, OS and ORR the company also provides sensitivity analyses based on subgroups of patients with one prior VEGF targeted therapy and with prior sunitinib where available.

As mentioned previously RECORD-1 and TARGET both permitted crossover to the investigational treatment post-progression. Crossover was adjusted using different methodologies in the trials; RECORD-1 used the rank-preserving structural failure time (RPSFT) model[54] and TARGET censored placebo patients who were still alive at the time of crossover. The ERG notes that at the cross-over point in TARGET only 41% of the protocol defined 540 deaths had been observed; the pre-crossover results are thus immature due to the early censoring. Moreover, patients were not censored at random and this informative censoring is likely to bias the results, although it isn't possible to predict the direction of the bias. The RPSFT model used for RECORD-1 requires additional censoring of patient level data and so the precision of the HR estimate is lower than that for the ITT estimate. However, this method is preferable to censoring of patients at time of crossover. For the primary ITC analysis for OS the company used the unadjusted results, however, the crossover adjusted results were also provided for completeness.

For all outcomes the latest data cut reported for each study was used in the ITC.

For the fractional polynomial NMA the company digitalised the published KM curves for OS and PFS for CheckMate 025 and METEOR and used individual patient data (IPD) for HOPE 205.

4.4.4 Results

4.4.4.1 PFS

ITC - Bucher method

The company acknowledges that number and type of prior therapy, as well as independent or investigator assessment of response may impact PFS, but conducted the ITC of lenvatinib combination therapy versus the other treatments despite these differences as they did not substantially modify the HRs within the everolimus trials (HOPE 205, CheckMate 025, METEOR, RECORD-1). The ERG notes that the PHs assumption does not hold for all trials in the network, and as no meaningful conclusions can be drawn from the HRs from these trials, using the Bucher method will only propagates this flaw into the ITC results and it is therefore inappropriate.

The ITC, which informed the company base case showed [redacted] between lenvatinib combination therapy and everolimus [redacted], nivolumab [redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy. There was [redacted] in PFS between lenvatinib combination therapy and cabozantinib ([redacted]). Based on this analysis lenvatinib combination therapy may also be superior to axitinib, but the company highlights that this result should be interpreted with caution due the prior therapy for patients in TARGET being primarily cytokines rather than one prior VEGF-targeted therapy. The ERG highlights that the assumption of PHs is not fulfilled for PFS in CheckMate 025, TARGET, and potentially METEOR and so no meaningful conclusions can be made including these trials in an analysis based on PHs. However, if the PHs assumption would have been fulfilled for all comparisons within the network, the ERG's preferred analysis would have been independent assessment for all trials and one prior VEGF-targeted therapy where possible, the exclusion of TARGET, and hence axitinib, from the network due to the lack of prior VEGF-targeted therapies and insufficient crossover adjustment.

Table 28. Indirect treatment comparisons of progression-free survival: hazard ratio (95% CI) for lenvatinib combination therapy versus other treatments (CS, page 72, Figure 39)

Treatment	Main analysis as reported by trial[a,b]	Independent assessment[b]	One prior VEGF[a]	Prior sunitinib[a]
Everolimus [c]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]

Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]

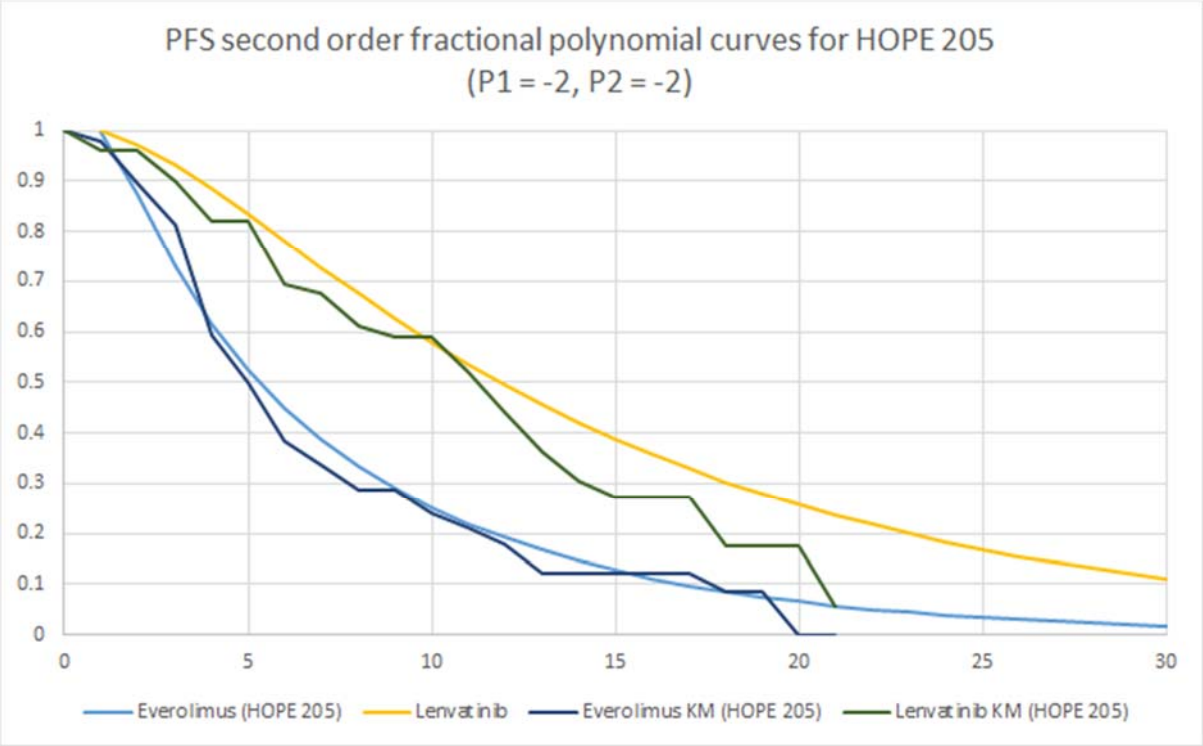
Abbreviations: CI, confidence interval; NA, not available; VEGF, vascular endothelial growth factor.
[a] Investigator assessment for E7080-205 and CHECKMATE-025 and independent assessment for METEOR, RECORD-1, TARGET and AXIS.
[b] 1 prior VEGF for E7080-205, 1-2 prior VEGF for CHECKMATE-025, ≥1 prior VEGF for METEOR, prior sunitinib and/or sorafenib (1-2 prior VEGF) for RECORD-1, 0 prior VEGF (cytokines only) for TARGET and 0-1 prior VEGF (sunitinib or cytokines) for AXIS.
[c] Direct comparison based on E7080-205.
[d] Using investigator assessment for both E7080-205 and RECORD-1 estimate is similar 0.12 (0.07-0.22).
[e] Except for TARGET which was conducted in patients with no prior VEGF treatment.

NMA - fractional polynomials

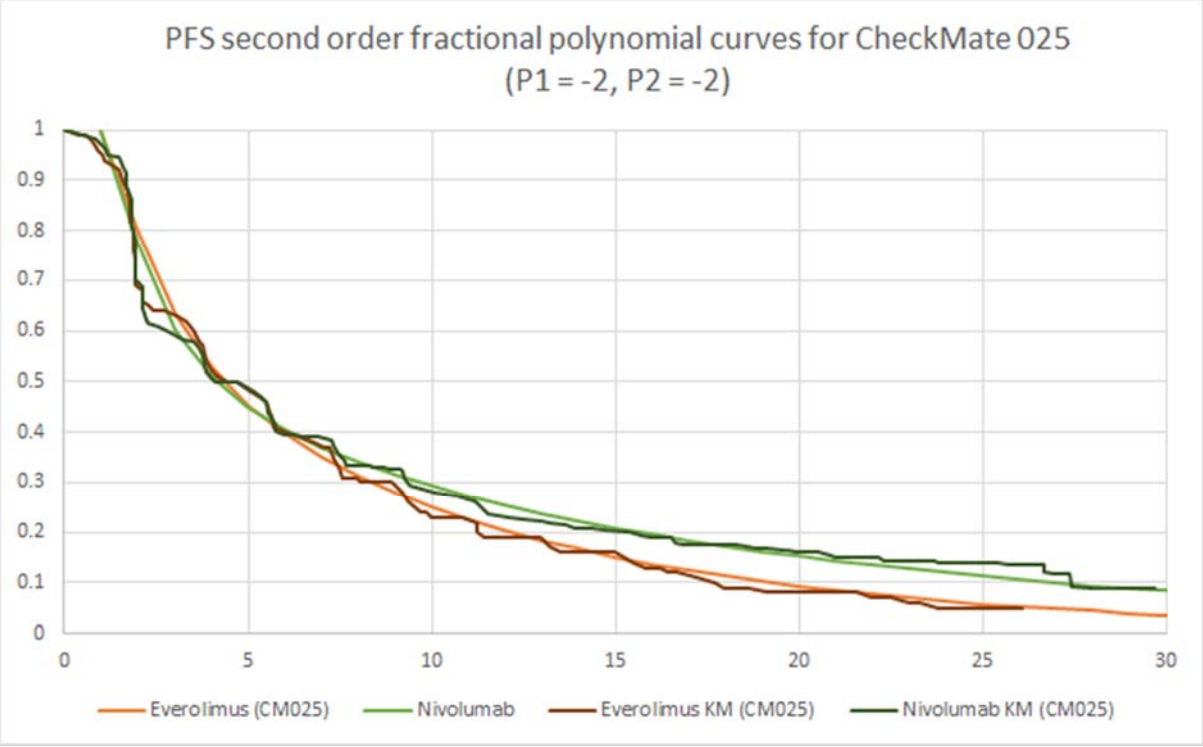
The 'best' model fit for PFS was a second order fractional polynomial model (P1=-2, P2=-2). The company visually inspected the fit of the model output overlaid on the underlying KM data for each treatment. However, as the company points out the model fit statistics are based on the average fit across the network; that is, the fractional polynomial may not fit any individual treatment well but, on average, the family of curves is the best fit for the network. Due to the absolute differences in the underlying data (median PFS differed for each of the everolimus groups across the trials, as shown by the company's check of the consistency across the network), the NMA-based curves will not necessarily fit each underlying treatment KM curve well as the NMA-based curves are dependent on the baseline chosen, which in this case is based on the three everolimus curves. The ERG, therefore, considers the plots presented by the company to be of limited value as a validation of model fit. As an alternative, the ERG produced trial-based fractional polynomial curves for the best fitting model to test how well the analysis models the underlying KM data as a FP curve, that is the survival curve for each treatment for each trial, before any adjustments to the common baseline across the network. Due to time constraints, the ERG only digitised the KM curves for CheckMate 025 and used the KM data for Hope 205 supplied by the company. Visual inspection of these curves overlaid on the underlying KM data shows a good fit for both trial arms in CheckMate 025 and the everolimus group in HOPE 205, but potentially an overestimate of PFS in the lenvatinib combination group in the same trial (Figure 13).

Figure 13. Second-order trial based fractional polynomial curves (P1=-2, P2=-2) overlaid on extracted KM data.

A



B



A: HOPE 205; B: CheckMate 025. On the y-axis is the hazard ratio and on the x-axis is months since start of therapy.
Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

[redacted]

[redacted]

[redacted]

4.4.4.2 OS

ITC - Bucher method

The ITC, based on the Bucher method and the assumption of PHs, which informed the company base case showed [redacted] between lenvatinib combination therapy and nivolumab ([redacted]), cabozantinib ([redacted]) or axitinib ([redacted]) based on the primary analyses using full trial populations (variety of prior therapies) and ITT analysis (ignoring crossover). The difference in OS was [redacted] between lenvatinib combination therapy and everolimus ([redacted]) and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1. The company points out that the results for the multi-step indirect comparison of lenvatinib combination therapy and axitinib should be interpreted with caution. The ERG highlights that the assumption of PHs is not fulfilled for OS in CheckMate 025 and TARGET and hence no meaningful interpretation of HRs can be made between lenvatinib combination therapy and nivolumab or axitinib. However, if the PHs assumption would have been fulfilled for all comparisons within the network, the ERG's preferred analysis would have been one prior VEGF-targeted therapy where possible, and the exclusion of TARGET, and so axitinib, from the network due to the lack of prior VEGF-targeted therapies and insufficient crossover adjustment. The ERG notes that the company's primary analysis ignores crossover but that crossover adjusted data for RECORD-1 (everolimus versus placebo) and TARGET (sorafenib versus placebo) are reported by the company in the footnote of Table 29.

Table 29. Indirect treatment comparisons of overall survival: hazard ratio (95% CI) for lenvatinib combination therapy versus other treatments (CS, page 74, Figure 40)

Treatment	Latest data cut[a]	One prior VEGF	Prior sunitinib
Everolimus [b]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]
Placebo [c]	[redacted]	[redacted]	[redacted]
Axitinib [d]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; NA, not available; RPSFT, rank preserving structural failure time; VEGF, vascular endothelial growth factor.
a 1 prior VEGF for E7080-205, 1-2 prior VEGF for CHECKMATE-025, ≥1 prior VEGF for METEOR, prior sunitinib and/or sorafenib (1-2 prior VEGF) for RECORD-1, 0 prior VEGF (cytokines only) for TARGET and 0-1 prior VEGF (sunitinib or cytokines) for AXIS.
b Direct comparison based on E7080-205.
c Based on the intention to treat analysis of RECORD-1 which permitted patients on placebo to cross over to everolimus. Using the RPSFT estimates from RECORD-1 the indirect estimate of lenvatinib plus everolimus versus placebo is 0.35 (0.12-1.08).
d Based on the intention to treat analysis of RECORD-1 and TARGET which permitted patients on placebo to cross over to everolimus and sorafenib respectively. Using the RPSFT estimates from RECORD-1 and censoring at time of cross-over for TARGET the indirect estimate of lenvatinib plus everolimus versus axitinib is 0.47 (0.15-1.50).

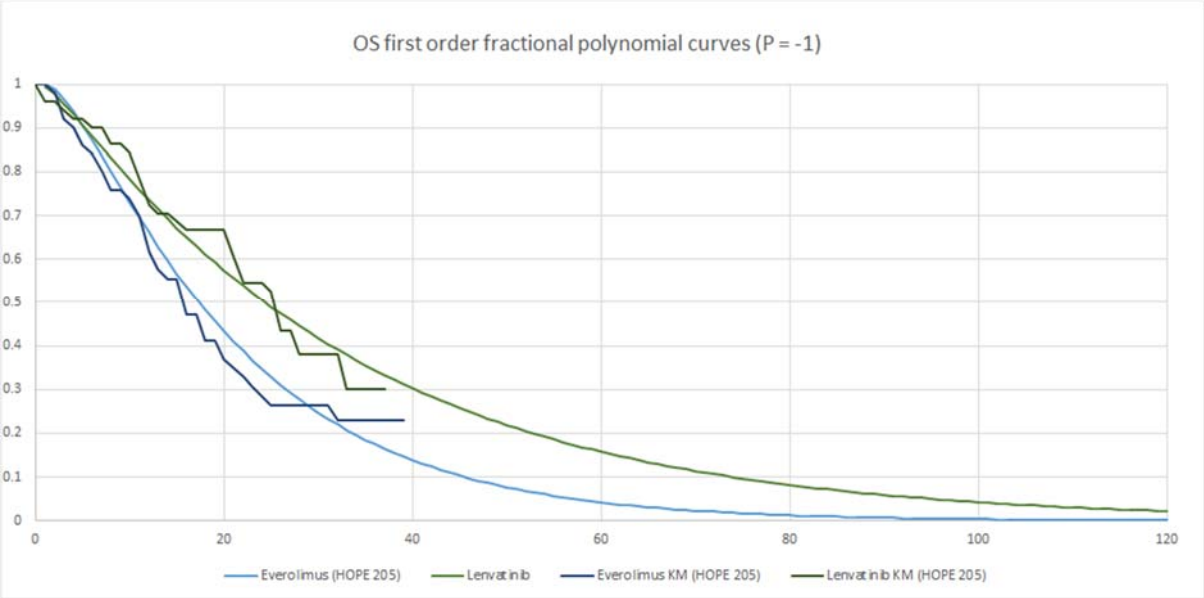
NMA - fractional polynomials

The 'best' model fit for OS was a first order fractional polynomial model (P1=-1, DIC 640.3). Similar to PFS, the company provided plots of the NMA-based curves overlaid on the underlying KM data for each treatment. For the reasons mentioned previously the ERG considers these plots to be of limited value as a validation of model fit. Instead, the ERG produced trial based fractional polynomial curves for the best fitting model to test how well the analysis models the underlying KM data as a FP curve for each treatment in each trial. Due to time constraints, the ERG only digitised the KM curves for CheckMate 025 and used the KM data for Hope 205 supplied by the company. Visual inspection of these curves overlaid on the underlying KM data shows a good fit for both trial arms in both CheckMate 025 and HOPE 205 (Figure 16).

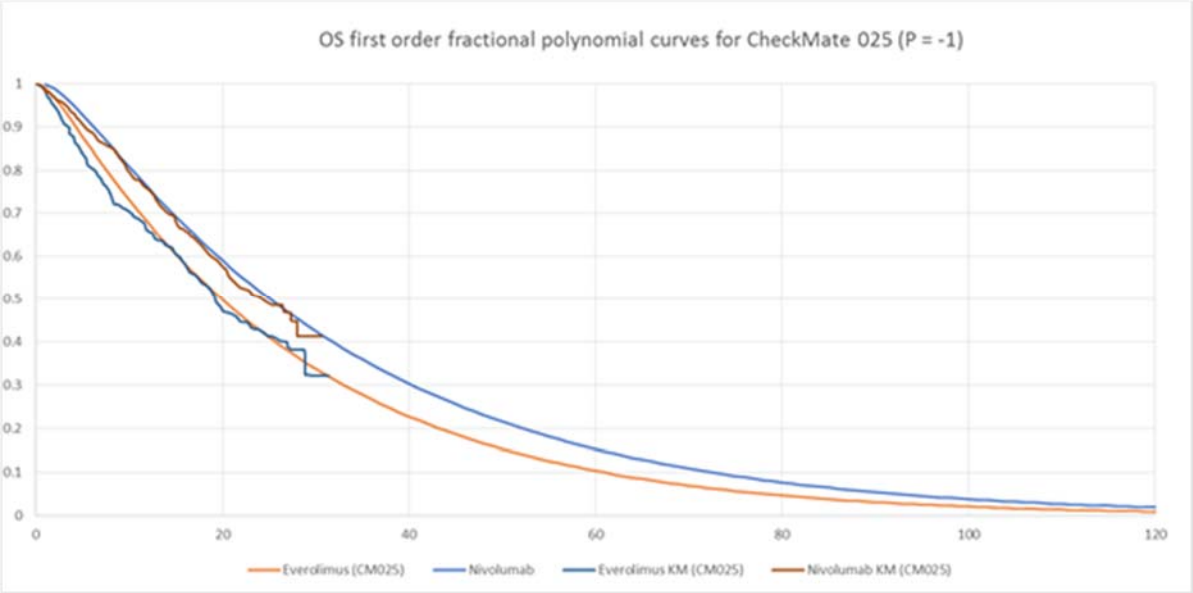
The ERG notes that there are several first and second order curves with similar DICs. The company visually inspected the curves for some of these: the models with the second lowest DIC (P1=-2, P2=0, DIC 641.5), third lowest DIC (P1=-2, DIC 641.6), and with the best fit for lenvatinib combination therapy, but not overall (P1=-1, P2=0, DIC 644.6). The ERG assessed the visual fit of all the curves with a similar DIC. Only one curve, other than the 'best' fitting (P1=-1), appeared to provide a plausible curve and that was the first order FP with P = -0.5, which was used by the ERG in a scenario analysis around the ERG's preferred base case, which is presented in Section 6.4.1.

Figure 16. Second-order trial based fractional polynomial curves (P1=-2, P2=-2) overlaid on extracted KM data.

A



B



A: HOPE 205; B: CheckMate 025. On the y-axis is the hazard ratio and on the x-axis is months since start of therapy.
Abbreviations: KM, Kaplan-Meier; OS, overall survival.

[redacted]

[redacted]

4.4.4.3 ORR

ORR data are based on the latest available data cut and the primary analysis, whether investigator assessed (IA) of independent radiology review (IRR). The *post-hoc* IRR analysis of HOPE 205 resulted

in no patients in the everolimus group being assessed with complete or partial response compared to three patients based on IA. Due to the small sample size and the small number of events, the ERG considers the ORR results to be highly uncertain, irrespective of outcome assessment used, but considers the IRR results to be more comparable with those from METEOR and RECORD-1. Due to the inconsistency in prior therapies across the network, the ERG also considers that the assumption of similar efficacy between everolimus and axitinib, would have been a reasonable alternative to the multi-step ITC of lenvatinib combination therapy versus axitinib via the TARGET trial.

There was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy [redacted] and placebo [redacted] in favour of lenvatinib combination. The difference between lenvatinib combination therapy and nivolumab [redacted], cabozantinib [redacted] and axitinib [redacted] also favoured lenvatinib combination therapy, [redacted].

Subgroup analyses restricting trial population of METEOR and CheckMate 025 to one prior VEGF-targeted therapy or AXIS to prior sunitinib were not possible as this information was not published.

Table 30. Indirect treatment comparisons of overall response rate: lenvatinib combination therapy versus other treatments (CS, page 76, Figure 41)

Single step ITC	**Treatment n/N (%)**	**Everolimus n/N (%)**	**Odds Ratio (95% CI)**	**Relative Risk (95% CI)**
Lenvatinib plus everolimus vs Everolimus	22/51 (43.1)	3/50 (6.0)	[redacted]	[redacted]
Nivolumab vs Everolimus	103/410 (25.1)	22/411 (5.4)	[redacted]	[redacted]
Cabozantinib vs Everolimus	57/330 (17.3)	11/328 (3.4)	[redacted]	[redacted]
Placebo vs Everolimus	0/138 (0.0)	5/272 (1.8)	[redacted]	[redacted]
Lenvatinib plus everolimus vs Nivolumab			[redacted]	[redacted]
Lenvatinib plus everolimus vs Cabozantinib			[redacted]	[redacted]
Lenvatinib plus everolimus vs Placebo			[redacted]	[redacted]
Multi-step ITC	**Drug A n/N (%)**	**Drug B n/N (%)**	**Odds Ratio (95% CI)**	**Relative Risk (95% CI)**
Lenvatinib plus everolimus (A) vs Everolimus (B)	22/51 (43.1)	3/50 (6.0)	[redacted]	[redacted]
Everolimus (A) vs Placebo (B)	5/272 (1.8)	0/138 (0.0)	[redacted]	[redacted]
Placebo (A) vs Sorafenib (B)	0/337 (0.0)	7/335 (2.1)	[redacted]	[redacted]
Sorafenib (A) vs Axitinib (B)	34/362 (9.4)	70/361 (19.4)	[redacted]	[redacted]
Lenvatinib plus everolimus vs Axitinib			[redacted]	[redacted]

Abbreviations: CI, confidence interval; n/N, number with event/number in efficacy population; vs, versus.
Indirect estimates are presented in italics.

4.4.4.4 Safety

Indirect comparisons of safety to axitinib was not feasible due to the lack of overall safety reporting in RECORD-1, TARGET and AXIS. Indirect estimates of lenvatinib combination therapy versus nivolumab, cabozantinib and placebo are presented in Table 31 for each safety outcome where possible.

Median duration of treatment with everolimus monotherapy was relatively similar between the studies; 4.1 months in HOPE 205, 3.7 months in CheckMate 025, 4.4 months in METEOR, and 4.6 months RECORD-1.

Data on grade 3 or 4 adverse events were only reported in HOPE 205 and METEOR. There [redacted] in the proportion of patients experiencing at least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib based on the ITC [redacted].

Summary data on treatment-related severe AEs were reported in HOPE 205 and CheckMate 025. There was a higher proportion of patients experiencing at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted].

HOPE 205, CheckMate 025, METEOR and RECORD-1 all reported the proportion of patients who discontinued study treatment due to AEs. There was [redacted] difference in discontinuation due to AEs between lenvatinib combination therapy and cabozantinib [redacted], but [redacted] patients discontinuing treatment due to AE with the lenvatinib combination therapy compared with nivolumab ([redacted]) and placebo ([redacted]).

Table 31. Indirect comparisons of safety: lenvatinib combination therapy versus other treatments (CS, page 78, Figure 43)

Comparison	Treatment n/N (%)	Everolimus n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
At least one grade 3 or 4 AE					
Lenvatinib plus everolimus vs Everolimus	36/51 (70.6%)	25/50 (50.0%)	[redacted]	[redacted]	[redacted]
Cabozantinib vs Everolimus	235/331 (71.0%)	193/322 (59.9%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Cabozantinib			[redacted]	[redacted]	[redacted]
At least one treatment related grade 3 or 4 AE					
Lenvatinib plus everolimus vs Everolimus	32/51 (62.7%)	21/50 (42.0%)	[redacted]	[redacted]	[redacted]

Nivolumab vs Everolimus	76/406 (18.7%)	145/397 (36.5%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Nivolumab			[redacted]	[redacted]	[redacted]
Discontinuation due to AE					
Lenvatinib plus everolimus vs Everolimus	12/51 (23.5%)	6/50 (12.0%)	[redacted]	[redacted]	[redacted]
Nivolumab vs Everolimus[a]	31/406 (7.6%)	52/397 (13.1%)	[redacted]	[redacted]	[redacted]
Cabozantinib vs Everolimus	40/331 (12.1%)	34/322 (10.6%)	[redacted]	[redacted]	[redacted]
Placebo vs Everolimus	5/135 (3.7%)	28/269 (10.4%)	[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Nivolumab			[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Cabozantinib			[redacted]	[redacted]	[redacted]
Lenvatinib plus everolimus vs Placebo			[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CI, confidence interval; n/N, number with event/number in safety population; vs, versus.
Notes: Indirect estimates are presented in italics.
[a] CheckMate 025 reported discontinuation due to treatment-related AE.

4.4.5 Summary of clinical effectiveness ITC

- Indirect comparisons were needed to estimate the relative efficacy of lenvatinib combination therapy versus nivolumab, cabozantinib, axitinib and BSC (placebo). Five trials comparing treatments for patients with advanced RCC who had failed at least one prior VEGF-targeted therapy were identified; AXIS (axitinib versus sorafenib), CheckMate 025 (nivolumab versus everolimus), HOPE 205 (lenvatinib combination therapy versus everolimus), METEOR (cabozantinib versus everolimus), and RECORD-1 (everolimus versus placebo). TARGET (sorafenib versus placebo), which only enrolled patients who had not had prior anti-VEGF targeted therapy, was also included to form a connected network.

- Baseline characteristics were generally balanced between trial arms in all studies included in the network, and the trial populations were relatively similar between studies, however, the trials differed in terms of number and type of prior therapies, subsequent therapies, and outcome assessment.

- The relative efficacy of lenvatinib combination therapy versus each comparator for OS and PFS was estimated using HRs and the Bucher method, which are conditional on the PHs assumption being fulfilled. However, the PHs assumption does not hold for PFS in CheckMate 025, METEOR and TARGET, and for OS in CheckMate 025 and TARGET. Therefore, the company re-assessed PFS and OS in a Bayesian NMA using fractional polynomials, which does not rely

on the PHs assumption being fulfilled. For the NMA the company assumed that axitinib and everolimus monotherapy have similar efficacy.

- The company's primary analyses were based on the full populations and the primary analysis for all trials irrespective of number and type of prior therapy, and investigator or independent outcome assessment.

- The ERG highlights that no meaningful interpretation of the resulting HRs and 95% CIs for PFS can be made between lenvatinib combination therapy and nivolumab or axitinib as the PHs assumption does not hold. However, the results of the ITC, using the Bucher method, [redacted] between lenvatinib combination therapy and axitinib [redacted], everolimus [redacted], nivolumab [redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy. There was [redacted] in PFS between lenvatinib combination therapy and cabozantinib.

- The ERG tested how well the model captures the underlying PFS KM data as a FP curve, which showed a good fit for both trial arms in CheckMate 025 and the everolimus group in HOPE 205, but potentially an overestimate of PFS in the lenvatinib combination group in the same trial.

- [redacted] The ITC, based on the Bucher method, showed [redacted] in OS between lenvatinib combination therapy and nivolumab ([redacted]), cabozantinib ([redacted]) or axitinib ([redacted]) based on the full trial populations (variety of prior therapies) and ITT analysis (ignoring cross-over). The difference in OS was [redacted] between lenvatinib combination therapy and everolimus ([redacted] and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1.

- [redacted]

[redacted]The ERG tested how well the model captures the underlying OS KM data, which showed a good fit for both trial arms in both CheckMate 025 and HOPE 205. However, there are several first and second order curves with a similar DIC for OS. However, there are several first and second order curves with a similar DIC for OS. The ERG's inspection of the different curves shows that only one other fractional polynomial provides plausible curves.

- Based on the ITC using the Bucher method, there [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy [redacted] and placebo [redacted] in favour of lenvatinib combination. The difference between lenvatinib combination therapy and nivolumab [redacted], cabozantinib [redacted] and axitinib [redacted] also favoured lenvatinib combination therapy, [redacted].

- There was [redacted] in the proportion of patients experiencing at least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib based on the ITC [redacted]. A higher proportion of patients experienced at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted]. There was [redacted] difference in discontinuation due to AEs between lenvatinib combination therapy and cabozantinib ([redacted]), but [redacted] patients discontinuing treatment due to AE with the lenvatinib combination therapy compared with nivolumab ([redacted]) and placebo ([redacted]).

4.5 Conclusions of the clinical effectiveness section

- One trial, HOPE 205, provides the only direct evidence informing the efficacy and safety of lenvatinib combination therapy. HOPE 205 is a well conducted, open label, phase II, multicentre trial, with a third of patients recruited from the UK. The primary objective of the trial was to compare PFS of lenvatinib combination therapy versus everolimus monotherapy. Secondary outcomes included OS, tumour response, and safety. HRQoL was not captured in HOPE 205. All outcomes were investigator assessed although IRR of PFS and tumour response was done retrospectively.

- Patients eligible for entering the study were adults who were diagnosed with unresectable or advanced predominantly clear cell RCC whose disease had progressed on or within 9 months of stopping prior therapy with one prior VEGF-targeted therapy.

- Lenvatinib combination therapy showed a statistically significant improvement in PFS (median PFS 14.6 months) compared with everolimus (median PFS 5.5 months) in the IA analysis (HR 0.40, 95% CI: 0.24 to 0.68, p=0.0005). *Post-hoc* assessment of PFS by IRR showed similar results; median PFS was 12.8 months in the combination group and 5.6 months for the everolimus group (HR 0.45, 95% CI: 0.26 to 0.79, p=0.003).

- Subgroup analyses of PFS based on ECOG PS at baseline, age, sex, region, baseline hypertension status, MSKCC risk category, corrected serum calcium, and haemoglobin showed consistent improvements in PFS for the combination group compared with the everolimus group.

- OS was statistically significantly longer for patients treated with lenvatinib combination therapy (median survival 25.5 months) compared with patients receiving everolimus monotherapy (median survival 15.4 months) based on the Cox model (HR 0.59, 95% CI: 0.36 to 0.97), however, the p-value for the log rank test did not reach statistical significance (p=0.065).

- Based on the IA more patients treated with lenvatinib combination therapy achieved a complete or partial response than patients treated with everolimus monotherapy, the difference being statistically significant (RR 7.2, 95% CI: 2.3 to 22.5, p<0.0001) in favour of the combination group. The IRR showed similar result to the IA but with slightly lower ORR for both groups.

- Serious AEs occurred at a slightly higher incidence in the combination group (54.9%) than in the everolimus group (42%). The most common grade 3 TEAEs were diarrhoea (19.6% vs

2.0%, lenvatinib combination therapy vs everolimus), hypertension (13.7% vs 2.0%), fatigue (9.8% vs 0%), anaemia (7.8% vs 12.0%), hypertriglyceridemia (7.8% vs 8.0%), and vomiting (7.8% vs 0%).

- Indirect comparisons were needed to estimate the relative efficacy of lenvatinib combination therapy versus nivolumab, cabozantinib, axitinib and BSC (placebo). Five trials comparing treatments for patients with advanced RCC who had failed at least one prior VEGF-targeted therapy were identified; AXIS (axitinib versus sorafenib), CheckMate 025 (nivolumab versus everolimus), HOPE 205 (lenvatinib combination therapy versus everolimus), METEOR (cabozantinib versus everolimus), and RECORD-1 (everolimus versus placebo). TARGET (sorafenib versus placebo), which only enrolled patients who had not had prior anti-VEGF targeted therapy, was also included to form a connected network.

- Baseline characteristics were generally balanced between trial arms in all studies included in the network, and the trial populations were relatively similar between studies, however, the trials differed in terms of number and type of prior therapies, subsequent therapies, and outcome assessment.

- The relative efficacy of lenvatinib combination therapy versus each comparator was initially estimated using HRs, which are conditional on the PHs assumption being fulfilled. However, the PH assumption does not hold for PFS and OS in several of the trials in the network. Therefore, the company assessed PFS and OS in a Bayesian NMA using fractional polynomials, which does not rely on the PH assumption being fulfilled.

- Based on the difference in prior therapy in TARGET and confounding of OS due to cross-over, which couldn't be adequately adjusted for, axitinib and everolimus were assumed to have similar efficacy for the NMA.

- The relative efficacy of lenvatinib combination therapy versus each comparator for response and safety was estimated using RRs and the Bucher method. The company's primary analyses were based on the full populations and the primary analysis for all trials irrespective of number and type of prior therapy, and investigator or independent outcome assessment.

- [redacted]

[redacted] There are several first and second order curves with a similarly good fit for OS. The ERG's inspection of the different curves shows that only one other fractional polynomial provides plausible curves.

- There was a statistically significant difference in ORR between lenvatinib combination therapy and everolimus monotherapy (RR 7.2; 95% CI: 2.3 to 22.5) and placebo (RR 40.3; 95% CI: 1.8 to 899) in favour of lenvatinib combination. The difference between lenvatinib combination therapy and nivolumab (RR 1.53; 95% CI: 0.45 to 5.21), cabozantinib (RR 1.40; 95% CI: 0.38 to 5.13) and axitinib (RR 1.29; 95% CI: 0.02 to 89.55) also favoured lenvatinib combination therapy, but without reaching statistical significance.

- There was no statistically significant difference in the proportion of patients experiencing at least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib (RR 1.19; 95% CI: 0.84 to 1.69). A higher proportion of patients experienced at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted]. There was [redacted] difference in discontinuation due to AEs between lenvatinib combination therapy and cabozantinib ([redacted]), but [redacted] patients discontinuing treatment due to AE with the lenvatinib combination therapy compared with nivolumab ([redacted]) and placebo ([redacted]).

4.5.1 Clinical issues

- The ERG is concerned about the small sample size of HOPE 205; only around 50 patients were randomised to each treatment arm. This introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy.

- The open label design of HOPE 205 and the lack of blinded outcomes assessment of PFS and tumour response is a potential source of bias. IRR of PFS and tumour response was only done retrospectively.

- HRQoL, one of the outcomes of interest listed in the scope, was not captured in HOPE 205.

- The baseline characteristics of patients enrolled in HOPE 205 appear relatively well balanced between the trial arms, though some differences potentially indicate a poorer prognosis for the everolimus group compared with patients randomised to lenvatinib combination therapy.

- The PHs assumption does not hold for PFS in CheckMate 025, METEOR and TARGET, and for OS in CheckMate 025 and TARGET. Therefore, no meaningful interpretation of HRs can be made between lenvatinib combination therapy and nivolumab or axitinib based on the ITC using the Bucher method.

- The TARGET trial was included to enable a comparison between lenvatinib combination therapy and axitinib. Based on the difference in prior therapy in TARGET and confounding of OS due to cross-over, which couldn't be adequately adjusted for, no reliable estimate of the relative efficacy of lenvatinib combination therapy versus axitinib could be obtained. The network for the fractional polynomial NMA was therefore simplified by assuming similar efficacy between everolimus and axitinib.

- For the best fitting curves for PFS, the ERG's test of how well the model predicts the input data showed a potential overestimate of PFS in the lenvatinib combination group in HOPE 205, but a good fit for all other treatment groups and trials.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft® Excel based economic model. Table 32 summarises the location of the key economic information within the company's submission (CS).

Table 32. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.3
Overview and critique of economic evaluation	5.4
Quality assessment	5.4.1
Population	5.4.2
Interventions and comparators	5.4.3
Model approach and model structure	5.4.4
Treatment effectiveness	5.4.5
Treatment discontinuation	5.4.6
Adverse events	5.4.7
Health-related quality of life	5.4.8
Resource use and costs	5.4.9
Results	5.5
Abbreviations used in table: CS, company's submission.	

5.2 Summary of the company's key results

The company's deterministic base case results are given in Table 33 and the results of the probabilistic sensitivity analysis are given in Table 34.

Table 33. Results of company's base case analysis (Clarification responses document)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
LEN+EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,971
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,167
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,299
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,404

Table 34. Mean probabilistic ICERs (company's clarification responses document)

Treatment	Lenvatinib comb. vs Axitinib	Lenvatinib comb. vs Cabozantinib	Lenvatinib comb. vs Nivolumab	Lenvatinib comb. vs Everolimus
Deterministic ICER (£)	32,971	2,167	7,299	122,404
Mean probabilistic ICER (£)*	47,343	279,561	29,567	154,941
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LEN+EVE, lenvatinib combined with everolimus. *The ERG was unable to obtain mean ICERs similar to those reported by the company.				

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review to identify cost-effectiveness studies assessing any of the comparators included in this appraisal, in adult patients with advanced renal-cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

An overview of the search is presented in Section 5.1 of the CS, and the search terms and results reported in Appendix 8.3. The company searched the following online databases: MEDLINE and MEDLINE In-process; Embase; EconLit; and The Cochrane Library. In addition to the online databases the company reports searching the following online sources:

- The International Network of Agencies for Health Technology Assessment (INAHTA);
- Canadian Agency for Drugs and Technologies in Health (CADTH);
- National Institute of Health and Clinical Excellence (NICE);
- Scottish Medicine Consortium (SMC);
- Australian Pharmaceutical Benefits Scheme (PBS);
- New Zealand Pharmaceutical Management Agency (PHARMAC);
- European Society for Medical Oncology (ESMO);
- National Comprehensive Cancer Network (NCCN);
- UK Department of Health;
- UK Office for National Statistics (ONS);
- Cancer Research UK;

- American Cancer Society (ACS).

The searches were carried out on 21st October 2016 and the results were restricted to English language studies published from 2005 onwards. Population search terms (Advanced/metastatic RCC) were combined with intervention terms (lenvatinib, in addition to specified comparators in the decision problem and first-line therapies). The inclusion and exclusion criteria applied in the search are summarised in Table 35.

Table 35. Inclusion and exclusion criteria applied in search for cost-effectiveness studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	Lenvatinib Cabozantinib Nivolumab Temsirolimus Everolimus Pazopanib Sunitinib Sorafenib Bevacizumab Axitinib	Not second line a/mRCC treatment after one prior anti-VEGF therapy Surgical /Radiotherapy /Diagnostic intervention
Outcomes	Economic aspects, such as: costs and resource utilisation, economic evaluations, including cost-effectiveness, cost-utility and cost-benefit, economic models such as decision analytic model and Markov model, burden of illness.	
Study design	Systematic reviews Meta-analysis Pooled analyses	Reviews, case reports, editorials, letters, notes/comments, errata
Language restrictions	English	Non-English language

A total of 28 publications were reviewed for inclusion, of which 23 were included. Nine studies (7 HTAs[55-61] and 2 economic evaluations[62, 63]) were considered particularly relevant to the UK and were quality assessed by the company. The following interventions as second-line treatments for RCC were assessed across the identified studies: nivolumab, axitinib, everolimus, sunitinib, and sorafenib. The studies included by the company are summarised in Table 36.

The ERG considers the inclusion and exclusion criteria applied by the company to be appropriate and the search terms used in line with published guidelines by the Canadian Agency for Drugs and Technology in Health. The company provided the following justification during the clarification stage for restricting the search to studies published after 2005, "*As the first TKIs in this indication were only*

approved by the European Medicines Agency in July 2006, this restriction was considered appropriate and sufficient to capture all the relevant cost-effectiveness studies within this patient population." The ERG considers this to be reasonable. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

The ERG is aware of economic evaluation studies in non-UK settings that have been captured by the company's literature search for randomised clinical trials described in Section 4.1.1, yet have not been captured in the search for cost-effectiveness studies. It is unclear to the ERG how these studies could have been missed and whether any other studies relevant to a UK decision making context have been missed.

Table 36. Summary of studies included in systematic literature review for cost-effectiveness studies (CS, pg 96-100, Figure 54)

Study and Year	Country	Model Time Horizon	Intervention and Comparator(s)	Methods	QALYs (intervention, comparator)	Costs (£) (intervention, comparator)	Resource Utilisation Information	ICER (per QALY gained)
NICE everolimus appraisal committee (2011) (additional detail from Pitt *et al.* 2009)[55, 64]	UK	144 weeks Updated model: 312 weeks	Everolimus plus BSC vs BSC	Markov model The model included 4 health states: 1. Stable disease with no Aes 2. Stable disease with Aes 3. Progressed disease 4. Death - Cycle length = 8 weeks, no half-cycle correction	Mean of 0.607 QALYs for BSC plus everolimus, compared to 0.302 QALYs for BSC plus placebo	Not reported	Not available	ICER: (everolimus plus BSC vs BSC) Manufacturer submission (updated values): Cost per QALY = £49,272 with PAS ERG re-analysis = agreed with manufacturers updated values
NICE sorafenib and sunitinib appraisal committee (2009) (additional detail from Thompson *et al.* 2010)[56, 65]	UK	10 years	Sorafenib vs BSC Sunitinib vs BSC	Markov model Sorafenib: The model included 3 health states: 1. Progression-free survival 2. Progressed disease 3. Death - 6 week cycle Sunitinib: The model included 3 health states: 1. Progression-free survival 2. Progressed disease 3. Death - 6 week cycle	Sunitinib vs BSC sunitinib increased OS by 0.77 years and PFS by 0.54 years and resulted in an additional 0.60 QALYs compared with BSC.		Healthcare resource use was estimated in the absence of specific published literature.	ICER (sorafenib vs BSC) Manufacturer submission: Cost per QALY = £62,256 with PAS ERG re-analysis: Cost per QALY = £102,498 with original price DSU re-analysis: Cost per QALY = £65,929 with PAS and new price ICER (sunitinib vs BSC) Manufacturer submission: Cost per QALY = £37,519 with PAS ERG re-analysis:

								Not evaluated as data considered inadequate
NICE axitinib appraisal committee (2015) (additional detail from Riemsma *et al.* 2012)[57, 66]	UK	10 years	Axitinib vs BSC	Markov model The model included 3 health states: 1. Progression-free survival 2. Progressive disease 3. Death - Cycle length = 4 weeks	Not reported	Not reported	company submission included detailed information on healthcare resource utilisation which was based on previous NICE submissions and validated with expert clinical opinion. A scenario analysis examined the impact of assuming management by oncologist rather than GP.	ICER (axitinib vs BSC) Manufacturer submission: Prior cytokine group; Cost per QALY = £55,284 with PAS Prior sunitinib group; Cost per QALY = £33,538 with PAS Committee re-analysis: Prior cytokine group; Cost per QALY = ~£36,500 to ~55,300 with PAS Prior sunitinib group; Cost per QALY = ~£33,500 to ~£52,900 with PAS
NICE nivolumab appraisal committee Papers (2016)[58]	UK	30 years	Nivolumab with everolimus, axitinib and best supportive care (BSC)	Partitioned-survival (AUC) model The model included 6 health states: 1. PFS on treatment 2. PFS off treatment 3. Post-progression survival (PPS) on treatment 4. Post-progression survival (PPS) off	QALY gain for nivolumab against everolimus was 0.63 QALY gain for nivolumab against axitinib was 1.07 QALY gain for nivolumab	Not reported	company submission included detailed information on healthcare resource utilisation which was based on previous NICE submissions and estimated	company's base case: ICER Nivolumab vs axitinib: £43,109 ICER Nivolumab vs everolimus: £86,136 ICER Nivolumab vs BSC: £57,096 ERG's preferred analysis: ICER Nivolumab vs axitinib: £74,132

				treatment 5. Terminal care 6. Death - Cycle length = 1 week	against BSC was 1.43		by clinicians currently practicing in the UK.	ICER Nivolumab vs everolimus: £91,989 ICER Nivolumab vs BSC: £61,317 Updated ICER's: When the confidential discounts for nivolumab and axitinib were included, the company's revised base case and the majority of the ERGs revised base case were below £50,000/QALY gained for nivolumab compared with any comparator.
SMC Nivolumab 1188/16 (2016)[61]	Scotland	30 years	Nivolumab vs axitinib or everolimus	Markov model The model included 6 health states: 1. PFS on treatment 2. PFS off treatment 3. Post-progression survival (PPS) on treatment 4. Post-progression survival (PPS) off treatment 5. Terminal care 6. Death - Cycle length = 1 week	QALY gain for nivolumab against everolimus was 0.61 • QALY gain for nivolumab against axitinib was 1.05 • LY gain for nivolumab against everolimus was 0.84 • LY gain for nivolumab against axitinib was 1.30	Incremental cost of nivolumab compared to everolimus is £59,949. Incremental cost of nivolumab compared to axitinib is £57,419	No details reported	ICER (nivolumab vs everolimus) £98,558 ICER (nivolumab vs axitinib) £54,747
SMC Axitinib 855/13 (2013)[59]	Scotland	10 years	Axitinib vs BSC using indirect comparison (AXIS).	Not explicitly stated – assumed Markov model	Not reported	Not reported	Clinical management costs were estimated	ICER (axitinib vs BSC) Sunitinib refractory population;

				The model included 3 health states: 1. Progression free survival 2. Progressive disease 3. Death - Cycle length = 4 weeks			from a previous HTA review. No further details were provided.	Cost per QALY = £33,837 with PAS Cytokine refractory population; Cost per QALY = £56,343 with PAS For this population, using the lognormal parametric function the ICER was: Cost per QALY = £61,100 with PAS Reducing the dose intensity to 80% the ICER was: Cost per QALY = £44,400 with PAS
SMC Sunitinib 343/07 (2007)[60]	Scotland	6 years	Sunitinib vs BSC.	Not reported	Not reported	Not reported	Resource use and unit cost data were sourced from published literature and supplemented with opinion from clinical experts. No further details were provided.	ICER (sunitinib vs BSC) Cost per LYG = £30,066 Cost per QALY = £39,000
Hoyle *et al.* 2010[62]	UK	10 years	Sorafenib vs BSC	Markov-type decision analytic model The model included 3 health states: 1. Progression-free survival 2. Progressive disease 3. Death - Cycle length = 6 weeks	• Lys: BSC = 1.30, sorafenib = 1.66 • QALYs: BSC = 0.91, sorafenib = 1.18 Discounted (sorafenib vs BSC):	Total cost: BSC = £3,797 sorafenib = £23,860 Discounted: (sorafenib vs BSC) = £20,063	Assumptions were based on guidelines outlining current practice and information provided by clinical experts.	ICER: (sorafenib vs BSC) Cost per LYG = £54,565 Cost per QALY = £75,398

					0.37 LY 0.27 QALY		Detailed information is provided.	
Chandiwana *et al.* 2014[63]	UK	12 years	Everolimus vs axitinib	Markov model The model included 3 health states: 1. Stable disease 2. Progressive disease 3. Death - Cycle length = monthly	QALY (everolimus vs axitinib) is 0.65 vs 0.63. Difference: (everolimus vs axitinib) 0.02	Total cost: Everolimus = £24,387 Axitinib = £42,533 Difference: (everolimus vs axitinib) - £18,146	Detailed healthcare resource information is reported. Frequency of GP and nurse visits and blood tests were based on published literature.	Everolimus is dominant.

5.4 Overview and critique of company's economic evaluation

The company submitted a *de novo* economic model to assess the cost effectiveness of lenvatinib in combination with everolimus compared to current NICE approved treatments for previously treated RCC; that is, axitinib, cabozantinib, everolimus monotherapy, and nivolumab.

The company's base case analysis relies on an indirect treatment comparison (ITC) to estimate the relative treatment effectiveness between lenvatinib combination therapy and axitinib, cabozantinib and nivolumab, respectively, due to the absence of direct head-to-head clinical trials. This NMA assumes that hazard rates for PFS and OS between each of the comparator treatments are proportional to each other, which has been demonstrated in previous technology appraisals to be an invalid assumption.[51] This led to the ERG's request during the clarification stage for the company to consider an alternative approach for estimating relative differences in PFS and OS, and the company provided a scenario analysis to incorporate a different approach, which avoided this assumption but did not consider it as their base case analysis. This is discussed in detail in Section 5.4.5.

Another key issue with the methods used by the company is the inconsistency in the treatment effectiveness measures used for the treatments in the HOPE 205 trial and those applied for the additional treatments in the ITC. For both PFS and OS, the company estimated treatment effects for the comparators relative to the lenvatinib combination therapy group. However, for the everolimus group, the KM data are used directly from the trial, which results in curves with a greater hazard rate than if the everolimus HR ratio from the ITC was applied to the lenvatinib combination group curve. This inconsistency leads to an implausible set of survival curves for PFS, in which the risk of progression for nivolumab is at times greater than that for everolimus. This contradicts the results of the CheckMate 025 trial [38]and, therefore, causes the results to be unreliable. For the scenarios based on parametric survival curves, the risk of progression for nivolumab is always greater than for everolimus as the HR between lenvatinib combination and everolimus monotherapy derived from the fitted Weibull model is greater than that derived in the ITC.

The ERG noted a contradiction in the company's submission that stated that treatment was assumed to continue until progression, while stating elsewhere that it was based on time to treatment discontinuation (TTD) from the HOPE 205 trial. The ERG can clarify that the latter was the approach used in the company's submitted base case model. The model also contained an inaccuracy in the calculation of QALYs relating to the use of the TTD data, in that the model applied a pre-progression on-treatment utility (capturing AE differences) for all patients on-treatment, regardless of progression status, and the off-treatment utility is applied to the difference in TTD and PFS. This calculation is correct if treatment is discontinued at or before progression, however, the data used in the model

indicate that a proportion of patients progress before discontinuing treatment. This means the utilities applied in the model are inaccurate. This is discussed in more detail in Section 5.4.4.1.

The remaining sections of this report give a more detailed description and critique of those issues summarised above, as well as additional specific issues relating to each of the key aspects of the economic analysis, starting with a quality assessment in Section 5.4.1 based on the NICE reference case and Philips checklists.[67, 68]

5.4.1 NICE reference case and Philips quality assessment checklists

Table 37 and Table 38 summarise the ERG's quality assessment of the company's economic evaluation. Table 37 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.[32] Table 38 summarises the ERG's appraisal of the quality of the company's de novo economic model using the Philips checklist.[68]

Table 37. Assessment of company's base case against the NICE reference case

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?**
Decision problem	The scope developed by NICE	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. The time horizon was set at 20 years, which was deemed sufficient to capture the lifetime of patients on second line therapy for RCC.
Synthesis of evidence on outcomes	Systematic review	Yes. A systematic review was conducted to identify data sources for outcome measures including disease progression, mortality and quality of life.
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. Utility values were based on EQ-5D scores elicited from patients with RCC in the AXIS trial.[69]
Benefit valuation	Time-trade off or standard gamble	Yes. Time-trade of valuation of the EQ-5D.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes. EQ-5D UK tariff.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

Abbreviations used in the table: EQ-5D, EuroQol-five dimensions questionnaire; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; RCC, renal cell carcinoma.

Table 38. Assessment of company's base case against the Philips checklist.

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated.
S3: Rationale for structure	The model structure is consistent with previously used models in previously treated, advanced RCC.
S4: Structural assumptions	The chosen structure is largely appropriate, although the structure has limitations that are restrictive to assuming primary therapy until progression. However, the marketing authorisations of the comparator treatments allows for treatment beyond progression and the company's data suggest that some patients are treated beyond progression.
S5: Strategies/ comparators	Lenvatinib combination therapy was compared to axitinib, cabozantinib, everolimus and nivolumab.
S6: Model type	A partitioned survival (area under the curve) model was used which the ERG considers to be appropriate.
S7: Time horizon	A time horizon of 20 years was used, which was considered sufficient to capture all the relevant costs and benefits associated for the lifetime of patients with previously treated, advanced RCC.
S8: Disease states/pathways	The model included three health states: progression-free survival on treatment, post-progression survival and death. Treatment duration was captured independently from disease progression. The health states considered are deemed appropriate and sufficient to capture all the outcomes and costs.
S9: Cycle length	A cycle length of 1 month was chosen, which was deemed reasonable by the ERG. A half cycle correction was also applied, which was considered an appropriate adjustment to estimate given the cycle length.
Data	
D1: Data identification	The main source of evidence was the phase II HOPE 205 trial comparing lenvatinib in combination with everolimus against everolimus monotherapy. A systematic literature review was carried out to identify all relevant studies for comparator treatments to inform the NMA, which was performed to estimate relative treatment effects for axitinib, cabozantinib and nivolumab. Resource use data was identified through systematic review and clinical expert opinion.

Dimension of quality	Comments
D2: Pre-model data analysis	Survival analysis was performed for the head-to-head trial data for lenvatinib combination and everolimus monotherapy in order to extrapolate the outcomes of OS and PFS. In the company's base case analysis, the company applies HRs to estimate outcomes for the remaining treatments.
D2a: Baseline data	Baseline data for PFS and OS were informed by the HOPE 205 trial and were considered to be reflective appropriate for the model population.
D2b: Treatment effects	Treatment effectiveness data for lenvatinib combination therapy and everolimus monotherapy was obtained from the HOPE 205 trial. A network meta-analysis was carried out to estimate the survival curves of axitinib, cabozantinib and nivolumab. The company's base case analysis estimated relative treatment effects for OS and PFS in an ITC. This approach requires hazard rates for each outcome in each trial to be approximately proportional, which is not the case for all trials in the network. The ERG requested an alternative approach that did not require this assumption to hold and the company then produced an analysis based around a NMA of survival curves based on fractional polynomial hazard functions. This was presented as a scenario analysis.
D2c: Costs	All costs were clearly stated. Resource use is estimated for the base case analysis mainly based on the feedback from the NICE appraisal committed in TA333 assessing axitinib and were validated by the company's clinical experts. NHS England National Tariffs and PSS costs were used where available, in line with the NICE reference case.
D2d: Quality of life weights (utilities)	The HSUVs for all health states are based on utility values elicited in the AXIS trial, and are applied to each treatment assuming that there is no treatment related differences. These values have been used in three previous technology appraisals and were considered to be reflective of the values of the advanced RCC population encountered in UK clinical practice by the committee. Disutilities associated with AEs were obtained from a range of studies identified through systematic literature review. These additional sources were not considered to be reliable by the ERG, as they were not generalisable to the RCC population. The AEs that were included in the model were those identified by the company's clinical experts as having a significant impact on quality of life or costs. The incidence of AEs were based on the HOPE 205 trial.
D3: Data incorporation	The company chose to use KM data directly to inform the model, with parametric survival curves used only to inform the extrapolation. The ERG considered it preferable to use the parametric curve for the entire time horizon to avoid the need for an adjustment to the extrapolation to fit the tail of the KM curve. The ERG considers this to cause an inconsistency in the assessment of the best fitting parametric curve.
Assessment of uncertainty	
D4a: Methodological D4b: Structural	Methodological and structural uncertainty was adequately explored in the model, for the trial duration. The electronic model allowed provided several options to allow varying methodological and structural assumptions. One limitation was that the model didn't allow for treatment beyond progression.
D4c: Heterogeneity	The economic analysis is based on the ITT populations of all the relevant clinical trials and no subgroup analyses were performed to assess differences in baseline characteristics.
D4d: Parameter	Parametric uncertainty was explored through deterministic sensitivity analyses and a probabilistic sensitivity analysis around the base case. However, some parameters that the ERG considered to be important were not included in these analyses.
Consistency	
C1: Internal consistency	There was an error in the use of treatment unit costs for everolimus monotherapy, which the company corrected following clarification questions, as well as an error in the calculation of QALYs, which led to patients a proportion of patients post progression having a utility relating to pre-progression.

Dimension of quality	Comments
C2: External consistency	The extrapolated clinical outcomes were assessed by clinical experts, who concluded that they were plausible.
Abbreviations used in table: AE, adverse events; ERG, evidence review group; HSUVs, health state utility values; ITC, indirect treatment comparison; ITT, intention to treat; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; QALYs, quality-adjusted life-years; RCC, renal cell carcinoma; TTD, time to discontinuation.	

5.4.2 Population

The company's economic model was based on the population of the HOPE 205 trial, i.e. adults with advanced or metastatic renal cell carcinoma who have had 1 prior vascular endothelial growth factor (VEGF)-targeted therapy, which is in line with the NICE final scope.[31, 32] No subgroups were considered in the economic analysis.

5.4.2.1 ERG critique

The ERG considers the company's analysis to be reflective of the population as outlined in the NICE final scope.

5.4.3 Interventions and comparators

The economic analysis compared lenvatinib in combination with everolimus with axitinib, cabozantinib, everolimus monotherapy and nivolumab. The NICE final scope also included best supportive care (BSC) as a comparator but the company chose to exclude this from the economic analysis following the Committee's decision in the cabozantinib technology appraisal (GID-TA10075).[32, 51]

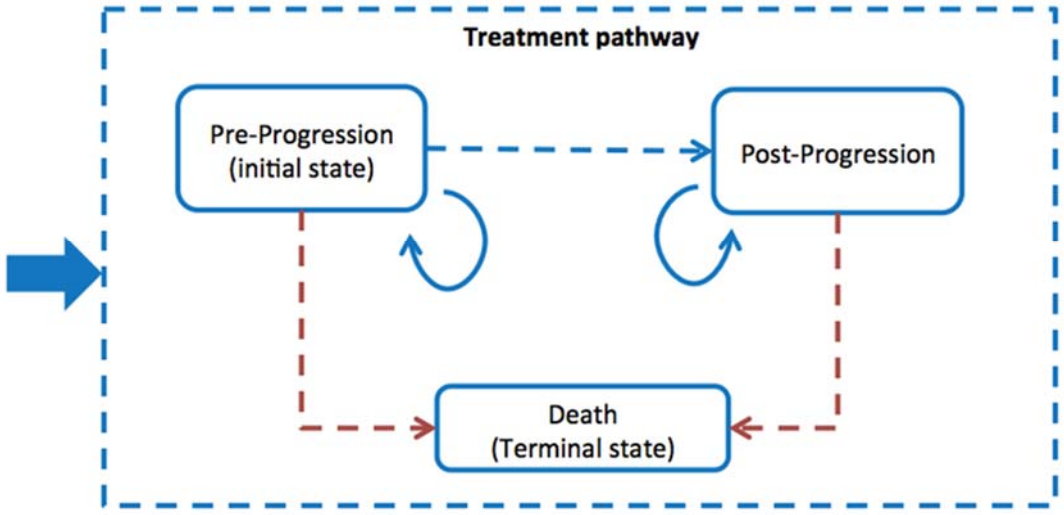
5.4.3.1 ERG critique

The ERG considers the company's analysis to include all relevant comparators.

5.4.4 Modelling approach and model structure

The company developed a *de novo* economic model in Microsoft® Excel using a partitioned survival structure with three health states: progression-free disease, post-progression, and death. A diagram showing the disease pathway is given in Figure 19. PFS data were used to determine the proportion of patients in the progression-free health state at a given time, while OS data were used to determine the proportion of patients who had reached the terminal death state at a given time. The proportion of patients in the post-progression health state at a given time was calculated as the difference between OS and PFS. The proportion of patients in each of these health states was estimated for each of the 240 monthly cycles in the model, giving a time horizon of 20 years. A description and critique of the methods used to estimate PFS and OS is given in Section 5.4.5.

Figure 19. Transition of health states (CS, Figure 56, page 103)



5.4.4.1 ERG critique

The ERG considers the model structure used by the company to be reasonable and includes all relevant health states. The cycle length of 1 month is consistent with the frequency of consultant oncologist visits and is, therefore, likely to be short enough to reflect the key changes in the disease pathway and the treatment pathway. The time horizon of 20 years was justified by the company as representing a lifetime for patients with advanced RCC. The estimated proportions of patients in the death health state reach zero within this time horizon, so the ERG considers this reasonable.

5.4.5 Treatment effectiveness

Two of the key outcomes that impact the quality and length of life for patients with RCC, and therefore the number of QALYs accumulated over their lifetime, are PFS and OS. Hence, a key aspect to developing a partitioned survival model is the accuracy of the estimation and the plausibility of the extrapolation of PFS and OS for each treatment assessed in the model.

PFS and OS Kaplan-Meier (KM) data were available from the HOPE 205 trial and the company used this data directly to determine the probability of remaining in each of the health states for each model cycle.[31] Beyond the trial follow-up period, the company estimated the probabilities based on a Weibull curve that was fitted as a dependent model to the trial data for both PFS and OS, and the resulting relative risks from cycle to cycle were applied to the last available probability of the KM data to estimate the probabilities for each of the remaining cycles. A range of other parametric distributions were considered, including the use of both dependently fitted models and independently fitted models to each treatment group, and the most plausible extrapolation was chosen by the company based on a number of criteria.

The first criterion was to assess the proportionality of the hazards between the two treatment groups using log-cumulative hazard plots against log time, and a global hypothesis test based on residuals. For OS, the global test gave a non-significant result (p = 0.4412), indicating a lack of evidence to reject the null hypothesis of proportional hazards. The company highlighted that the log-cumulative hazard plots crossed within the first 3 months and show a convergence at around 10 months, which may indicate that a PH assumption is not plausible. For PFS, the global test gave a non-significant result (p = 0.5461) indicating a lack of evidence to reject the null hypothesis of proportional hazards. However, the company highlighted that the log-cumulative hazard plots are not parallel and cross within the first month. The company also highlight a convergence in the middle of the curves, and hence, a proportional hazards assumption may not be plausible.

For the second criterion, the company assessed the visual fit of the log-cumulative hazard plots for the observed trial data against the log-cumulative hazard plots for the fitted parametric models, for both dependent and independent models. The company determined that, of the dependent models fitted for OS, the Gamma, Gompertz and Weibull had a better fit than the exponential, log-logistic and log-normal, but none of them had a particularly good fit. The company also concluded that none of the independently fitted models showed a good fit as the curves were either crossing (Gamma and log-normal), almost crossing (Weibull and log-logistic) or were poorly fitting in low log time (exponential and Gompertz). For the dependently fitted models for PFS, the company determined that the Gamma and Weibull curves provided a better fit than the other curves but still did not provide a good fit. For the independently fitted models, the fit was considered by the company to be poor, with the Gamma and Weibull curves providing the best fit.

The third and fourth criteria were an assessment of statistical model fit using the Akaike and Bayesian information criteria (AIC/BIC), and an assessment of the predicted gain (and uncertainty) in PFS/OS for the lenvatinib combination group for the pre-trial cut-off period as well as post-trial cut-off period. The company determined that none of the independent or dependent parametric models show unrealistically high or low extrapolation gain, although there is large uncertainty around the estimate from the exponential curve. They also note that the AIC/BIC statistics were similar for the dependent PH models compared to the corresponding independent models, but the confidence intervals around the extrapolation gain appeared to be larger for the independently fitted models. The company chose to use the KM data with parametric extrapolation as it provided a more modest PFS and OS benefit with narrower confidence intervals.

The fifth criterion was a comparison of the pre-extrapolation survival gain and the post-extrapolation survival gain. The company considers a post-extrapolation survival gain per month greater than the pre-extrapolation survival gain per month to be implausible, and therefore assessed the ratio of the survival gain per month before and after the trial end point. All the estimated gains per month were lower in the

post-extrapolation period compared to the pre-extrapolation period and so this satisfies the company's fifth criterion for all models tested. The ERG notes that the company incorrectly calculated the ratio of these values and therefore the conclusions drawn from these values may not be accurate.

After consideration of all the criteria, the company chose to use the KM data for the pre-extrapolation period and use the dependently fitted Weibull distribution to estimate the extrapolated probabilities beyond the trial follow-up period, for both PFS and OS. To estimate the survival curves for axitinib, cabozantinib and nivolumab, the company applied the HRs derived from the NMA to the lenvatinib combination curves for both PFS and OS. The resulting PFS and OS curves are given in Figure 20 and Figure 21, respectively.

Figure 20. PFS curves used in the company's base case analysis (CS, page 134, Figure 78)

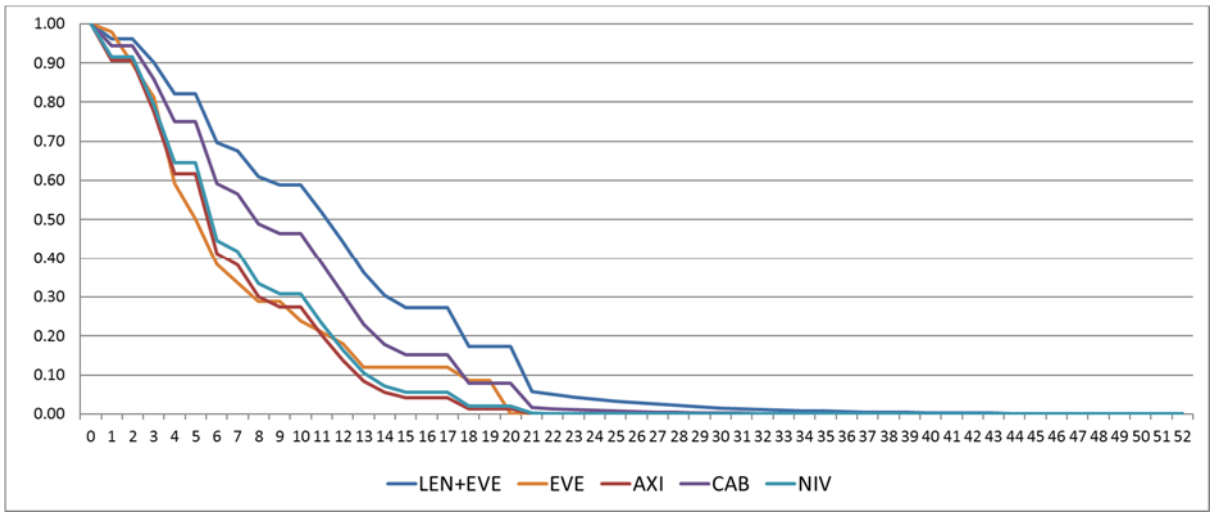
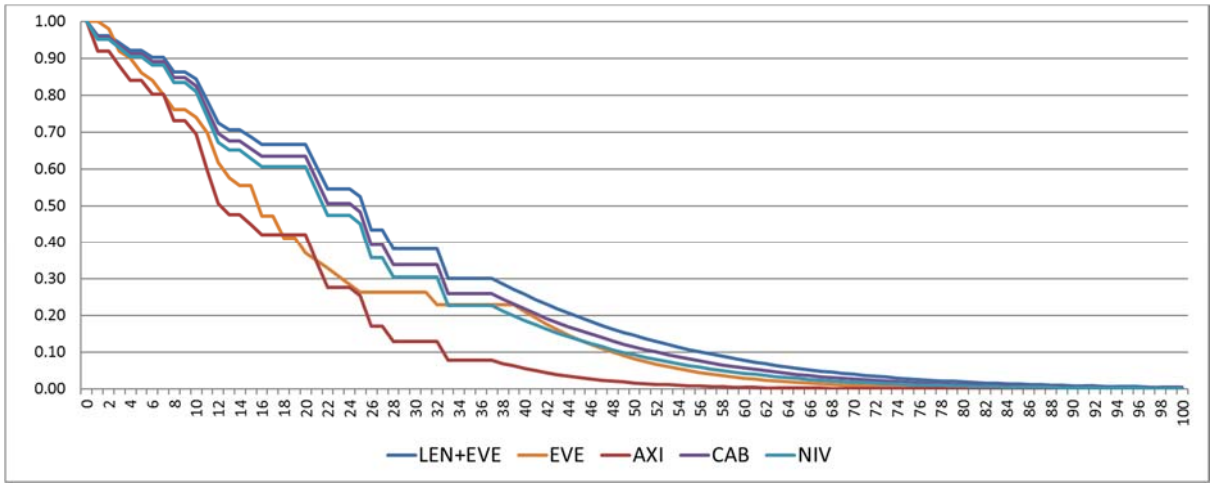


Figure 21. OS curves used in the company's base case analysis (CS, page 135, Figure 79)



5.4.5.1 ERG critique

The ERG considers the methods used for the estimation and extrapolation of PFS and OS to have potentially serious flaws that result in implausible model outcomes and, therefore, potentially unreliable results of cost-effectiveness.

The key issues stem from the assumption that the hazard rates for each treatment are proportional for both PFS and OS. From the on-going cabozantinib STA (GID-TA10075), the ERG considered the TARGET trial, providing a link between axitinib and everolimus in the NMA, to show hazard rates that were not proportional across the entire trial follow-up period for both PFS and OS, and so deriving a HR between the two from the ITC would be flawed, leading to inaccurate PFS and OS estimates.[42, 51] The ERG considers a more appropriate approach to be to assume that axitinib has equal efficacy to everolimus, allowing a simplified network to be used to estimate the remaining HRs, for which a proportional hazards assumption is reasonable. A similar assumption has been made in previous NICE technology appraisals.[70-72]

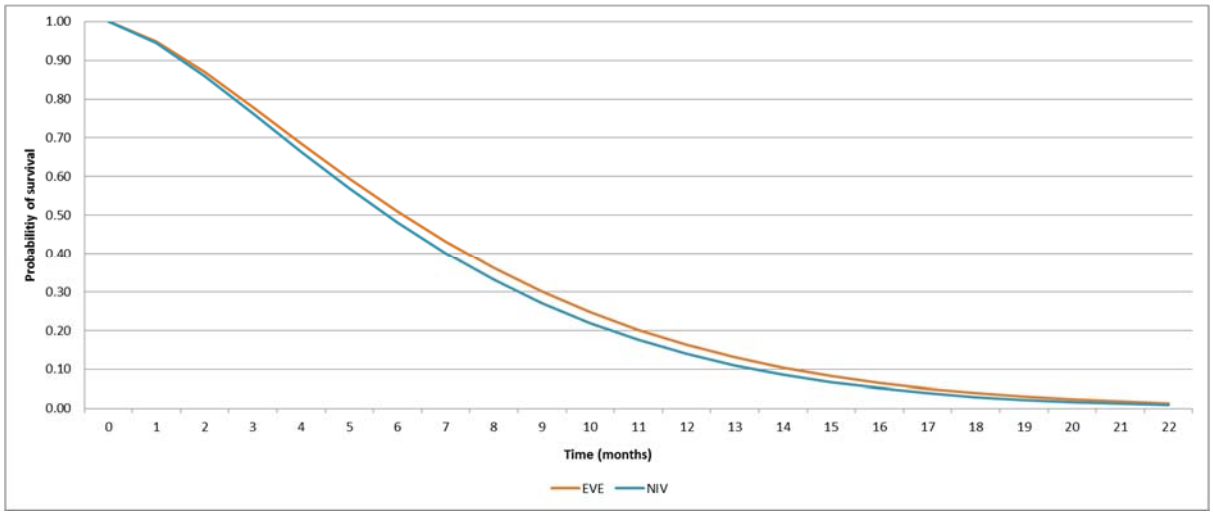
Another issue, which may be caused by the violation of proportional hazards in the network, relates to the inconsistency of the relative treatment effect derived from the fitted dependent Weibull curves for PFS, and the PFS HRs derived from the ITC for the same comparison of lenvatinib combination versus everolimus monotherapy. This results in a fitted everolimus Weibull PFS curve that has a lower hazard rate than the nivolumab Weibull curve generated by applying the ITC-derived PFS HR to the lenvatinib combination Weibull curve. This contradicts the results of the CheckMate 025 trial comparing nivolumab with everolimus, and is therefore implausible.[38] The everolimus monotherapy and nivolumab curves derived by the company based on the dependently fitted Weibull model are shown in Figure 22.

The HRs derived for PFS for lenvatinib combination versus everolimus and nivolumab, respectively, from both the Weibull model and the ITC are given in Table 39, showing the discrepancy caused by combining treatment effects from alternative methods.

Table 39. Comparison of PFS HRs from Weibull model and ITC for lenvatinib combination versus everolimus and nivolumab, respectively.

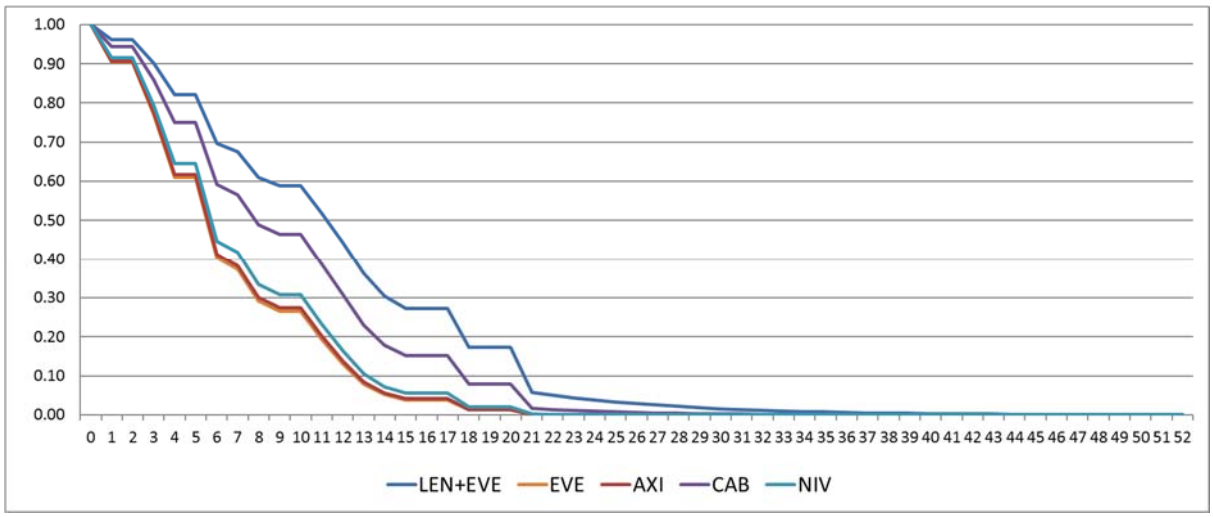
HRs	Weibull	ITC
Everolimus	[redacted]	[redacted]
Nivolumab	-	[redacted]
Abbreviations in table: HR, hazard ratio; ITC, indirect treatment comparison.		

Figure 22. PFS curves for everolimus and nivolumab based on dependent fit.



The impact of this may be small as the company only used the Weibull curves for the extrapolation of the survival curves rather than for the entire time horizon. The PFS KM data used directly in the company's base case show that the everolimus and nivolumab curves are similar and cross over, which may still be implausible, but at least more plausible than the company's Weibull curves appear to be. However, the discrepancy still indicates that the extrapolated curves may be unreliable. The company's PFS base case curves with the ITC HR applied for the everolimus group is shown in Figure 23. A scenario analysis using these curves is presented in Section 6.2.

Figure 23. Company's PFS curves when ITC HR is applied for everolimus



Further to this, the ERG considers the methods used to extrapolate the survival curves, for both PFS and OS, using the fitted parametric functions, to be inconsistent with the assessment of the goodness-of-fit of the parametric curves to the survival data. Given that the company adjusts the Weibull curves to form a continuous extrapolation from the end of the KM data, then, if the extrapolation of the fitted Weibull curve is plausible, the company's adjustment used in the model must be implausible. On the

other hand, if the adjusted curves provide a plausible extrapolation then the fitted Weibull curves implicitly provide an implausible extrapolation and should, therefore, not be used to inform the extrapolation. In either case, the ERG considers the company's piecewise survival curves used for the base case analysis to be flawed. The ERG's preferred approach would be to use a suitably fitting parametric curve for the entire time horizon, with a plausible extrapolation informed either by long term survival data, or, where there is an absence of data, expert clinical opinion.

Given that the company's methods require PH – at least between one of the treatment groups in the HOPE-205 trial and all external comparator treatments included in the ITC – it is appropriate to use a parametric model in which PH can hold, e.g. exponential, Weibull and Gompertz. Within this subset of functions, the ERG considers independently fitted models to be more suitable given that the log-cumulative hazard plots for the HOPE-205 trial suggest a potential deviation from PHs between lenvatinib combination therapy and everolimus monotherapy, for both PFS and OS, indicated by a crossover of the curves and convergence and divergence at various intervals. The ERG notes that the small numbers of patients in the trial make these assessments uncertain and so it may not be such an implausible assumption to make.

Although the ERG considers it more reliable to assess the visual fit using the survival curves themselves as opposed to the log-cumulative hazard plots, it appears from the log-cumulative hazard plots that, for OS, the Gamma, log-logistic and Weibull models have the best fit, with very little to differentiate the three. However, when looking at the survival curves themselves with the KM plots, the log-logistic curves have a notably better fit than the Gamma and Weibull curves. For PFS, the ERG considers the log-logistic to have the best fitting curve based on the log-cumulative hazard plots, with the only notable deviation from the data being in the first month, which also applies to the other models assessed by the company. Comparing the survival curves to the KM data also appears to indicate that the log-logistic is the best fitting model.

It may be suitable to use the log-logistic curves for both PFS and OS for an economic analysis with only the head-to-head comparisons from the HOPE-205 trial, i.e. lenvatinib combination therapy versus everolimus, but it would result in potentially implausible curves for the remaining comparators if HRs were to be applied, as the resulting curves would no longer represent a curve that can be parameterised as a log-logistic curve. To perform a full analysis with all comparators based on the company's base case model, the ERG considers it reasonable to use the Weibull model for both PFS and OS, as the fit was reasonable and it allows PH to apply.

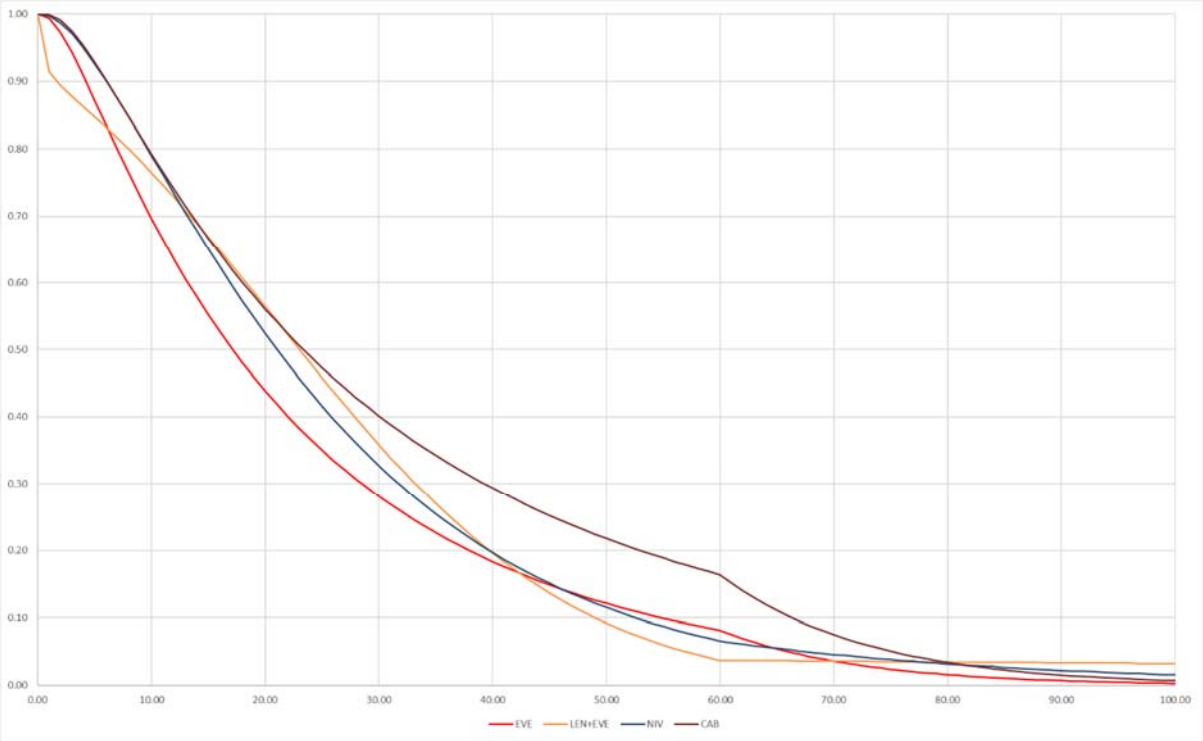
Given the violations of PH across the trials in the ITC as discussed in Section 1.1, the ERG requested that the company use an alternate approach for the ITC as used in the on-going cabozantinib STA (GID-TA10075), which estimates the relative treatment effect on model parameters without requiring an

assumption of PH to hold.[51] Two slightly different approaches were considered in this STA, one by Ouwens *et al.* 2010. based on standard parametric survival models and one by Jansen *et al.* 2011 based on fractional polynomial (FP) based survival models.[53, 73] The key limitation of these two methods is that the goodness-of-fit is measured globally and so the best fitting overall model may not provide individually well-fitted curves. Despite this, the ERG considers these methods to have the potential to provide a more accurate estimation of survival for all comparators and considered it a worthwhile route to explore.

In response to clarification questions, the company provided an alternate approach to estimating PFS and OS for each treatment, which avoided the assumption of PH. The method used was that described by Jansen *et al.* 2011, which estimated treatment effects on each of the parameters of a specified survival function in an NMA performed using WinBUGS.[53] More specifically, the method defines the hazard function as a FP, and a range of variations of the polynomials with different powers were tested for optimal fit. Further detail on the method and the ERG's critique of the company's application of the NMA is given in Section 4.4. The following will discuss the ERG's critique of the company's application of the output of the NMA into the economic model.

The ERG considers the company's application of the FPs in the model to be flawed. The survival curves based on these hazard functions were only generated up to 5 years, beyond which the survival probabilities are estimated by multiplying the previous probability by one minus the hazard rate. The company did not provide a justification for this approach and the ERG considers it to be mathematically incorrect. The incorrect calculation is demonstrated in Figure 24, showing the company's best fitting second order FP curve for OS, and a clearly implausible deviation in the curves at 60 months. The ERG notes that this deviation is not apparent in the first order FPs and therefore may represent a reasonable approximation for the company's base case.

Figure 24. Company's second order fractional polynomial OS curves



Despite the fact the ERG considers the model results provided for the FP scenario to be unreliable, the ERG does prefer the FP approach over the company's base case analysis, which assumes PHs, and considers the FP approach to provide more plausible curve fits. Therefore, the ERG regenerated the FP based curves for the entire time horizon, using R software, based on the parameter values produced from the ERG's output of the NMA. These were then used in the ERG's preferred base case analysis reported in Section 6.3.[74] The survival curves were generated by firstly integrating the FPs up to the time point for each cycle to give the cumulative hazard at each cycle, which was then used to estimate the survival probabilities as the exponential of the negative value of the cumulative hazard up to the time point of each cycle.

The curves generated by the ERG, based on the best fitting FPs as determined by the DIC statistics form the ERG-and company-performed NMA, were largely similar up to the 5-year time point with some slight deviation from the curves provided by the company. These differences are likely to be a result of a different method used to estimate the integral of the hazard function, which was approximated by the company in WinBUGs using monthly intervals. The ERG's approach used the *integrate* command in R to provide a more accurate estimate of the integral of the cumulative hazard up to each cycle, from which the survival probabilities can be calculated up to the entire time horizon of the model.

Some of the FPs defined by the values provided by the company had divergent integrals caused within the first month or so, resulting in an infinite cumulative hazard and, therefore, implausible survival

curves that drop to zero almost immediately. The ERG, therefore, restricted these integrals to remove the small and implausible divergent part of the hazard function, and instead assumed that the cumulative hazard is zero for the initial period. For the base case curves, this slight inaccuracy does not appear to affect the fit of the survival curves to the KM data.

Although the ERG prefers the FP approach to the fitting of survival curves for this particular STA, the ERG would also highlight that caution should be taken in the interpretation of the results based on these curves, as the method is restricted to a particular type of fractional polynomial across all treatment groups, which may not be a good fit for each of them. The goodness-of-fit statistics only indicates the best fitting model as a whole, and doesn't indicate whether a particular treatment has the best fitting curve. However, the ERG ran the NMA to generate the trial specific fitted curves rather than those adjusted to the combined everolimus data. This gives an indication of whether the curves are well fitted to each trial and, therefore, whether the treatment effect measured by the change in the parameter values is reliable. Plots of these are given in Section 1.1, and demonstrate a generally reasonable fit for all treatment groups, with a slight overestimation of PFS for the lenvatinib combination group.

The ERG notes that many of the OS FP curves had a similar DIC to the best fitting curve as determined by the company and, therefore, assessed the visual fit of these curves for comparison. There appeared to be only one other curve that provided a plausible curve and that was the first order FP with P = -0.5, although the ERG notes that this may be a result of the divergent integrals. The FP curve with P = -0.5 was used by the ERG in a scenario analysis around the ERG's preferred base case, which is presented in Section 6.4.1.

5.4.6 Treatment discontinuation

To estimate the proportion of patients who remain on primary treatment at any given cycle, the company used time to treatment discontinuation (TTD) KM data directly from the HOPE 205 trial for both lenvatinib combination and everolimus monotherapy. To estimate proportions of patients on treatment for the remaining comparators, the company calculated the ratio of median treatment duration relative to lenvatinib combination, using data from the respective trials used to estimate treatment effectiveness in the ITC, and applied these ratios as powers to the lenvatinib combination TTD KM data. The relative ratios of treatment durations, and the treatment durations used by the company to calculate them, are presented in Table 40.

Table 40. Treatment durations and relative ratios applied (Adapted from CS, page 108, Figure 58)

Treatment durations	Lenvatinib combination	Everolimus	Axitinib	Cabozantinib	Nivolumab
Median treatment durations in trials (months)	8.0	4.1	8.2	8.3	5.5

Relative ratio applied	-	-	1.025	1.0375	0.724

5.4.6.1 ERG critique

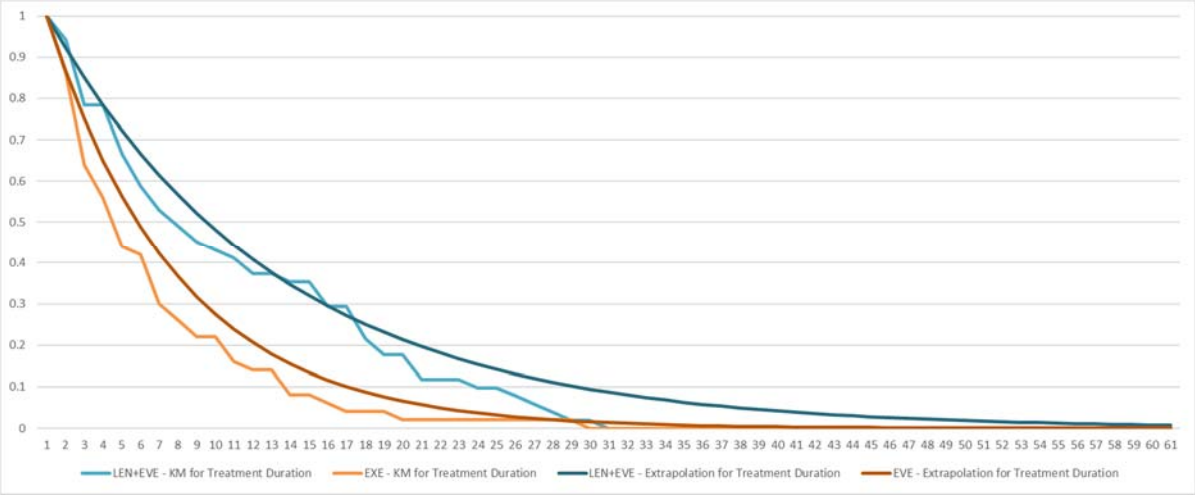
The ERG considers the company's approach to be incorrect in that the method implies an assumption that the ratio of median treatment duration is equivalent to a ratio of the hazard rates for treatment discontinuation for each treatment. This can clearly be shown to be implausible by estimating the median TTD for the for the resulting curves, which differs from those values from which the curves were derived. These values are given in Table 41.

Table 41. Modelled treatment durations in the company's base case

Treatment durations	Lenvatinib combination	Everolimus	Axitinib	Cabozantinib	Nivolumab
Median treatment durations in trials (months)	8.0	4.1	8.2	8.3	5.5
Estimated median treatment durations in company's base case	<7	<4	~7	~7	<5

In response to clarification questions, the company fitted exponential curves to the TTD KM data from the HOPE 205 trial for the lenvatinib combination therapy and everolimus monotherapy, although they found them to be poorly fitting. The company's fitted curves can be seen in Figure 25.

Figure 25. Company's fitted exponential curves to TTD KM data (Clarification response document)



The ERG also requested that the company provide an alternative approach to estimating TTD curves for the remaining comparators in the model, by digitising available published KM plots and fitting survival curves to the data. In response to this request, the company digitised KM TTD plots from the CheckMate 025 trial and the METEOR trial for nivolumab and cabozantinib, respectively.[37, 38] However, the company also chose to digitise the gamma extrapolation that was fitted by another

company for the cabozantinib STA.[51] The extrapolation in the published plot was only given up to 36 months, and so the company used an exponential extrapolation to extend the curve beyond 36 months. The company provided little justification for this approach, and, in particular, the ERG is unclear whether the exponential curve was fitted to the digitisation of the KM and gamma digitisation or if an alternative curve was used, e.g. the curves fitted to the HOPE 205 trial. The ERG considers a better approach to fit models to the digitised KM data alone and use the extrapolation derived from the best fitting curve.

The ERG performed their own digitisation of the TTD plots and used this data to fit survival curves using R.[74] To do this, pseudo individual patient data (IPD) were estimated using the digitised data, which was inputted into the algorithm described by Guyot *et al.*2012, as used by the company.[75] The pseudo-IPD data generated from this algorithm was then used in the *flexsurv* package of R to fit a range of standard parametric survival curves (exponential, Weibull, Gompertz, generalised Gamma, log-logistic, log-normal, generalised F and a range of splines with 1, 2 and 3 knots, respectively).[76] These were assessed for goodness-of-fit using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, as well as assessing the visual fit of the curves.

The ERG considers the log-normal distribution and the 2-knot spline to provide the best fitting curves based on the AIC and BIC statistics in Table 42 and Table 43, and on visual inspection both appear reasonable. The key difference can be seen in

Figure 26, showing that the spline appears to have a better fit to the lenvatinib KM data that the lognormal does. The spline was therefore used in the ERG's preferred base case. The ERG also included a scenario analysis that used the lognormal curve and this is presented in Section 6.4. The lognormal and spline TTD curves for each treatment can be seen in Figure 26 to Figure 29.

Table 42. AIC statistics for TTD curves fits

AIC	Lenvatinib combination	Everolimus	Cabozantinib	Nivolumab
Exponential	338	288	2026	2569
Generalised F	343	290	1988	2527
Generalised gamma	341	288	1988	2525
Gompertz	339	289	2026	2566
Log-logistic	343	287	1989	2534
Log-normal	341	**286**	**1987**	2524
1-knot spline	340	288	1991	2524
2-knot spline	**338**	290	1991	**2521**
3-knot spline	338	292	1990	2523
Weibull	339	290	2025	2570

Table 43. BIC statistics for TTD curves fits

BIC	Lenvatinib combination	Everolimus	Cabozantinib	Nivolumab
Exponential	**340**	**290**	2030	2573
Generalised F	350	297	2003	2543
Generalised gamma	346	293	1999	2537
Gompertz	343	293	2034	2574
Log-logistic	347	291	1997	2542
Log-normal	344	290	**1995**	**2532**
1-knot spline	346	294	2002	2536
2-knot spline	345	297	2006	2537
3-knot spline	348	301	2009	2543
Weibull	343	293	2032	2578

Figure 26. Lenvatinib combination fitted TTD curves

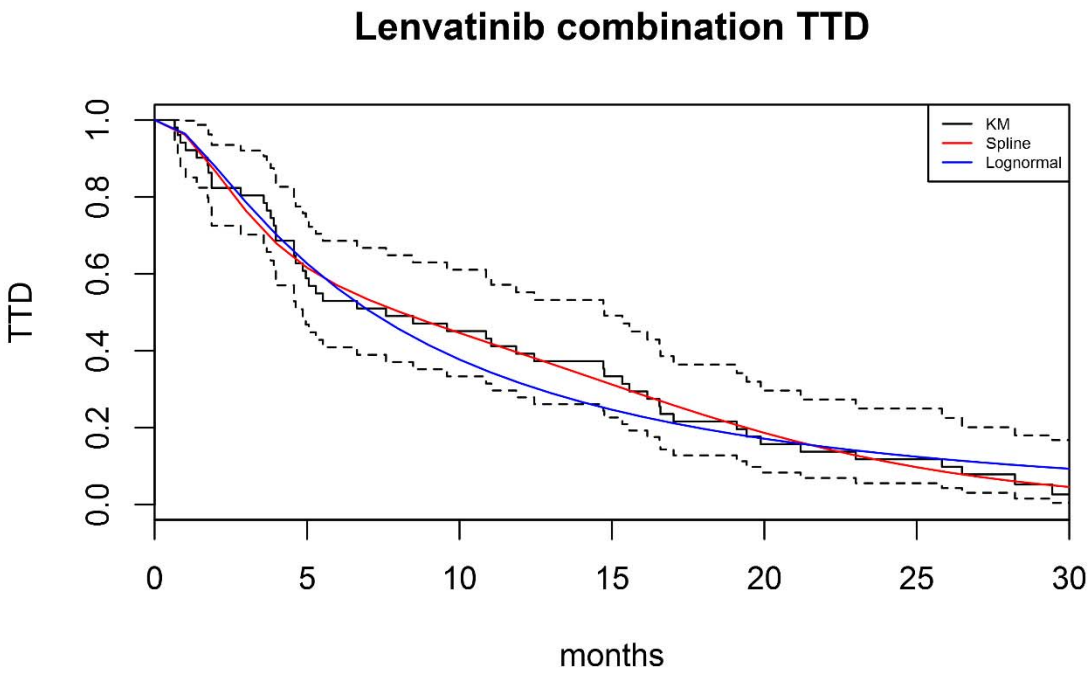


Figure 27. Everolimus fitted TTD curves

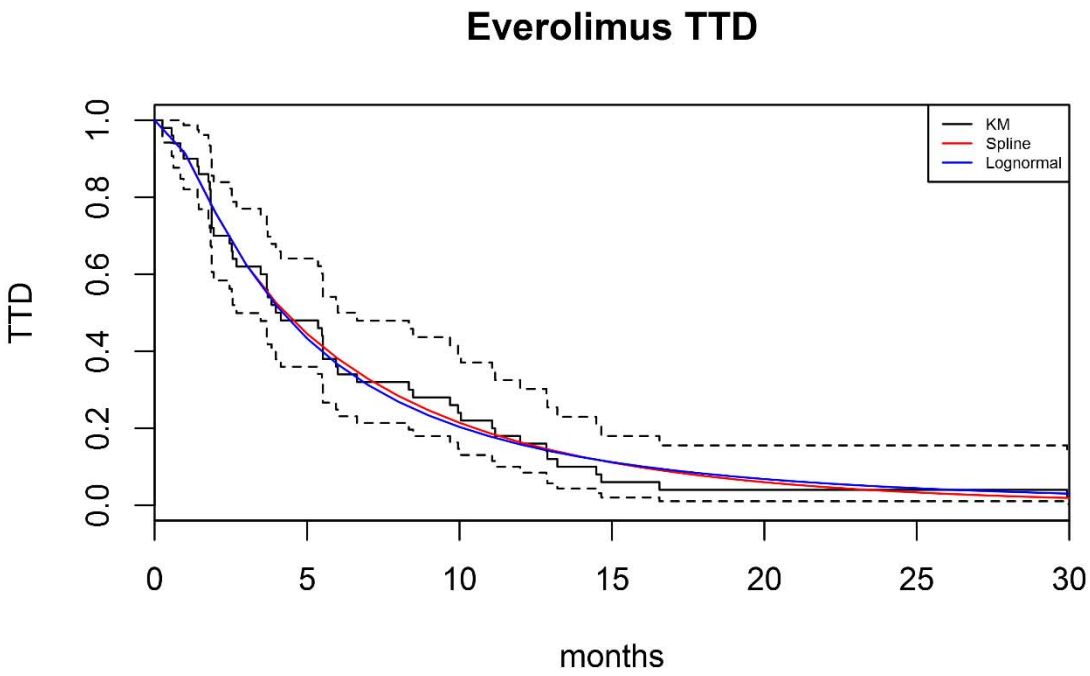


Figure 28. Cabozantinib fitted TTD curves

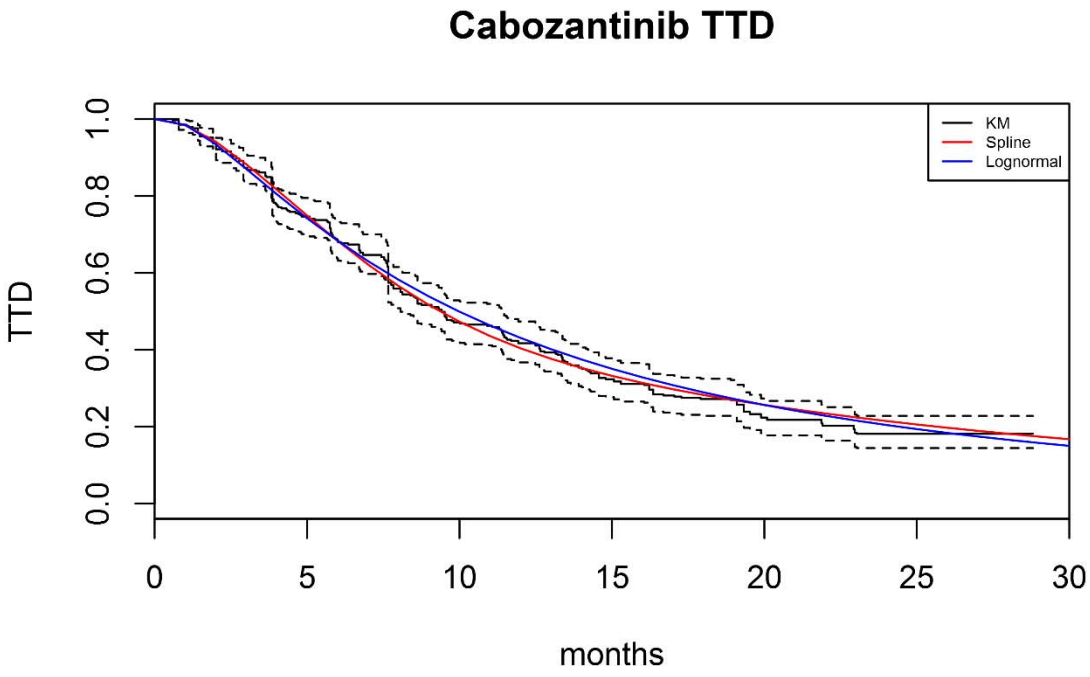
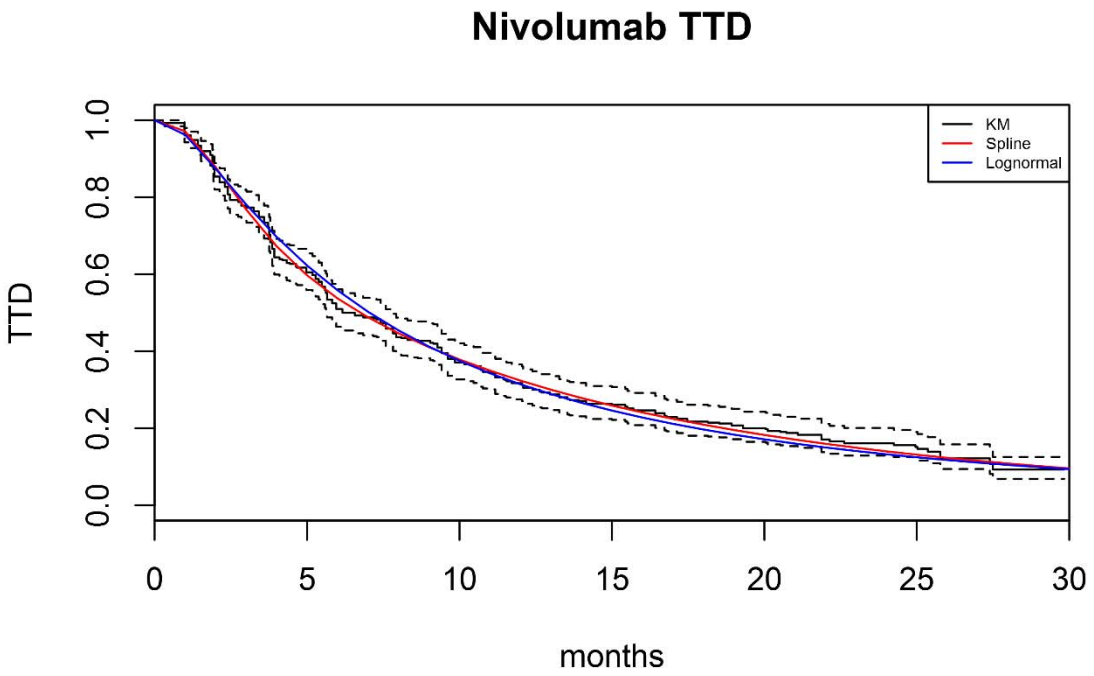


Figure 29. Nivolumab log-normal fitted curve



5.4.7 Adverse events

The company included Grade 3 and higher adverse events that are considered to have an impact on patients' quality of life based on feedback from their clinical experts. The following treatment-related adverse events (TRAEs) are included in the model: diarrhoea, fatigue/asthenia, vomiting, nausea, hypertension, decreased weight, stomatitis and dyspnoea.

The company reports that the rates used in the model are based on the rates observed in the respective trials as summarised in Table 44. The duration of adverse events assumed in the model are reported in Table 45, and are based on the durations observed in the HOPE 205 trial.

Table 44. Rates of adverse events assumed in the model (CS, Figure 89, pg 155)

Adverse events	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%

Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%
Sources: LEN+EVE (Eisai Ltd, 2015), Everolimus (Eisai Ltd, 2015), Axitinib (Motzer *et al.* 2013), Cabozantinib (Choueiri *et al.* 2016), Nivolumab (Motzer *et al.* 2015) Note: The prevalence values reported are treatment-related adverse events, with the exception of cabozantinib for which only treatment-emergent adverse events were available.					

Table 45. Duration of adverse events

Adverse event	Duration in days	Source
Diarrhea	25.51	HOPE 205 trial
Fatigue/Asthenia	49.39	
Vomiting	10.11	
Nausea	34.79	
Hypertension	28.34	
Decreased Weight	49.59	Assumed equal to decreased appetite (NCT01136733)
Stomatitis	37.48	HOPE 205 trial
Dyspnea	33.56	
Abbreviations in table: LEN+EVE, lenvatinib compared to everolimus.		

The costs of managing adverse events were included in the model, and a quality of life decrement was also applied when patients experience adverse events as described in Section 5.4.9.4 and Section 5.4.8, respectively.

5.4.7.1 ERG critique

The ERG considers the company's approach to incorporating the impact of adverse events in the model to be reasonable, and the ERG's clinical experts confirmed that all relevant adverse events have been included. However, there seems to be some confusion about the terms used to describe the adverse events from HOPE 205 trial across the CS, and in the HOPE 205 CSR. The company refers to adverse events the CS as "treatment-emergent", while in the CSR they are described as "treatment-related treatment-emergent adverse events". The company confirmed during the clarification stage that the adverse event rates obtained from the HOPE 205 trial and used in the economic model are indeed TRAEs and not treatment-emergent as reported in the CS.

The ERG identified a discrepancy in the rates Grade 3 or 4 fatigue/asthenia experienced by patients receiving everolimus in the HOPE 205 trial relative to previous trials that included everolimus as a comparator. Patients receiving everolimus in the HOPE 205 trial did not experience Grade 3 or 4 fatigue/asthenia. However, in the RECORD-1 and METEOR trials Grade 3 fatigue/asthenia was observed in 4% and 9% of patients in the everolimus group, respectively.[37] [36] It is unclear to the ERG what would cause this observed difference.

5.4.8 Health-related quality of life

5.4.8.1 Systematic literature review to identify HRQoL studies

The company carried out a systematic literature review to identify relevant health-related quality of life (HRQoL) studies for all the comparators. The search was carried out on the 25th October, 2016 and the following electronic databases were searched: MEDLINE and MEDLINE In-process; Embase; and The Cochrane Library.

In addition to the databases, the company searched the following online sources:

- The International Network of Agencies for Health Technology Assessment (INAHTA);
- Canadian Agency for Drugs and Technologies in Health (CADTH);
- National Institute of Health and Clinical Excellence (NICE);
- Scottish Medicine Consortium (SMC);
- Australian Pharmaceutical Benefits Scheme (PBS);
- New Zealand Pharmaceutical Management Agency (PHARMAC);
- European Society for Medical Oncology (ESMO);
- National Comprehensive Cancer Network (NCCN);
- UK Department of Health;
- UK Office for National Statistics (ONS);
- Cancer Research UK;
- American Cancer Society (ACS).

The inclusion and exclusion criteria applied in the search are summarised in Table 46.

Table 46. Inclusion and exclusion criteria applied in the HRQoL search (CS, pg 137, Figure 80)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	•Lenvatinib •Cabozantinib •Nivolumab •Temsirolimus	•Not second line advanced/metastatic RCC treatment after one prior anti-VEGF therapy

	•Everolimus •Pazopanib •Sunitinib •Sorafenib •Bevacizumab •Axitinib	•Surgical /Radiotherapy /Diagnostic intervention
Outcomes	•Health related quality of life •Utility values •Weightings •Preference •Health Status •Specific quality of life instruments	
Study design	•Systematic reviews •Meta-analysis •Pooled analyses	Reviews, case reports, editorials, letters, notes/comments, errata
Language restrictions	English	Non-English language
Abbreviations: RCC, renal cell carcinoma, VEGF, vascular endothelial growth factor.		

A total of 17 studies were identified by the search, of which, nine studies were HTA submissions and the RCC treatments assessed across the HTAs were axitinib, sorafenib, sunitinib, everolimus and nivolumab. [56-59, 77-79 80, 81] Eight studies were quality of life studies, and the treatments assessed across the studies were nivolumab, axitinib, everolimus, and sorafenib.[82 9, 63, 65, 69, 83-85]The EuroQol five dimensions questionnaire (EQ-5D) was the instrument used to elicit health-state utility values (HSUVs) in 10 of the studies,[9, 56, 58, 66, 69, 77, 79, 80, 82, 85] while three studies used disease-specific instruments only,[78, 83, 84] and four studies did not report the instrument used.[59, 63, 65, 81] The studies are summarised in Table 47.

Table 47. Summary of studies identified in search for HRQoL studies (CS, pg 140-148, Figure 82)

General data						Patient Characteristics	Results	Utility Instrument
Author (year)	**Study design**	**Country**	**Patient Number**	**Follow-up/ Observation period**	**Intervention(s)**	**Details**	**QoL Results**	**All HRQoL scales reported**
NICE appraisal committee (includes additional detail from Thompson *et al.* 2010) (2009)[56]	HTA appraisal based on a CUA and evidence from a phase 3 RCT (sorafenib) or a single arm phase 2 trial (sunitinib) and a pooled analysis of a review and Medicare data (BSC).	UK	NA	NA	Sorafenib or sunitinib	Patients with advanced RCC in whom immunotherapy has failed.	Sorafenib utility (from unpublished survey of physicians) Manufacturer; Same for sorafenib and BSC: Progression-free survival 0.737 Progressed disease 0.548 Sunitinib utility (EQ-5D from single arm Phase 2 trial) Manufactuer; Progression-free survival; sunitinib 0.803 vs BSC 0.758 Progressed disease; sunitinib 0.758 vs BSC 0.683 ERG re-analysis (trial data and UK EQ-5D tariffs); Same for all treatments: Progression-free survival 0.76 Progressed disease 0.68 No disutility Sorafenib FACT-G and FKSI There was no significant difference between the placebo and sorafenib groups over the first 32 weeks of treatment.	FACT-G, FKSI, EQ-5D

General data						Patient Characteristics	Results	Utility Instrument
NICE appraisal committee (includes additional detail from Pitt et al, 2009) (2011)[77]	HTA appraisal based on a CUA and evidence from a phase 3 RCT	UK	NA	NA	Everolimus plus BSC	Adults aged ≥ 18 years with aRCC whose cancer had progressed on or within 6 months of receiving VEGF-targeted therapy (sunitinib, sorafenib, and/or bevacizumab)	Utility (trial data and UK EQ-5D tariffs) Same for everolimus and BSC: Stable disease without AEs 0.76 Stable disease with AEs 0.71 Progressed disease 0.68 Death 0 Disutility for AE -0.05 EORTC, FKSI-DRS Time to deterioration in functioning/symptoms was delayed with everolimus plus BSC by 3.5 months.	EORTC QLQ-C30, FKSI-DRS, EQ-5D
NICE appraisal committee (includes additional detail from Riemsma *et al.* 2012) (2015)	HTA appraisal based on a CUA and evidence from an RCT (AXIS), with additional studies for an indirect comparison of axitinib with BSC.	UK	NA	NA	Axitinib	Patients with aRCC in whom treatment with sunitinib or cytokines has failed.	Utility (AXIS) Same for axitinib and BSC Manufacturer; Progression-free 0.69 (average on-treatment) Progressed disease 0.61 (average end of treatment) ERG re-analysis; Progression-free 0.73 (average on-treatment) Progressed disease 0.61 (average end of treatment) No disutility FSKI-15, EQ-5D and FKSI-DRS Mean scores were similar between axitinib and sorafenib until EOT.	FKSI-15, FKSI-DRS, EQ-5D

NICE appraisal committee Papers (2016)[58]	HTA evaluation	UK	NA	NA	Nivolumab	Patients with previously treated advanced or mRCC.	Utility: Manufacturer, ERG re-analysis, additional analysis for ACM respectively (data from CheckMate 025, AXIS, TA333, oncologist and'best available evidence for AE) Pre-progression, nivolumab 0.80, 0.80, 0.73 Post-progression, nivolumab 0.73, 0.73, 0.64 Pre-progression, everolimus 0.76, 0.76, 0.69 Post-progression, everolimus 0.70, 0.70, 0.61 Pre-progression, axitinib 0.69, 0.76, 0.69 Post-progression, axitinib 0.61, 0.70, 0.61 Pre-progression, BSC 0.69, 0.76, 0.69 Post-progression, BSC 0.61, 0.70, 0.61 No disutility for base-case. In SA - pneumonitis -0.15, diarrhoea -0.1, anaemia -0.081, pneumonia -0.13 EQ-5D (from CheckMate 025 trial) Median change in utility from baseline showed a statistically significant benefit of nivolumab compared with everolimus for weeks 8-12, 24-44, 52-68 and 80. 53% of patients treated with nivolumab experienced meaningful EQ-5D VAS improvement compared with 39% of patients treated with everolimus (p=0.005). FKSI-DRS 55% of patients in the nivolumab group experienced 'meaningful' FKSI-DRS improvement compared with 37% of patients in the everolimus group at week 104 (p<0.001).	EQ-5D, FKSI-DRS

General data						Patient Characteristics	Results	Utility Instrument
Scottish Medicines Consortium (SMC 595/10) (2014)[78]	HTA evaluation	Scotland	NA	NA	Everolimus	Advanced mRCC after failure of VEGF treatment.	Utility (based on UK TTO, adjusted for AEs based on RECORD-1 trial) Stable disease without AEs 0.795 Stable disease with AEs everolimus 0.610 (-0.185 disutility) Stable disease with AEs axitinib 0.575 (-0.22 disutility) Disease progression 0.355 FKSI-DRSI and EORTC QLQ-C30 (based on trial data) Similar HRQoL for everolimus and BSC.	EORTC QLQ-C30, FKSI-DRSI, TTO
Scottish Medicines Consortium (SMC 855/13) (2013)[59]	HTA evaluation	Scotland	NA	NA	Axitinib	Patients with a RCC whose cancer had progressed after first line therapy with either sunitinib or a cytokine.	Utility (EQ-5D; based on AXIS trial) Same for axitinib and BSC Progression free survival 0.69 Progressed disease 0.61 No disutility	Not reported

General data						Patient Characteristics	Results	Utility Instrument
Scottish Medicines Consortium (SMC 1188/16)[79]	HTA evaluation	Scotland	NA	NA	Nivolumab	Patients with aRCC after prior therapy in adults.	Utility (EQ-5D; based on CheckMate 025 trial and weighted values from AXIS trial) Progression-free nivolumab 0.80 Progression-free everolimus 0.76 Progression-free axitinib 0.69 Post-progression nivolumab 0.73 Post-progression everolimus 0.70 Post-progression axitinib 0.61 FKSI-DRSI A meaningful symptom improvement occurred in 55% of patients in the nivolumab group compared to 37% of patients in the everolimus group. EQ-5D VAS A meaningful symptom improvement occurred in 53% of patients in the nivolumab group compared to 39% of patients in the everolimus group.	EQ-5D, EQ-5D VAS, FSKI-DRS

General data						Patient Characteristics	Results	Utility Instrument
pan-Canadian Oncology Drug Review (2016)[80]	HTA evaluation	Canada	NA	NA	Nivolumab	Patients with locally advanced or mRCC who have received at least one prior anti-angiogenic therapy.	Manufactuter submission Utility (EQ-5D: based on Checkmate 025 trial) Progression free with response 0.887 Progression free no response 0.835 Progressed disease 0.806 EGP re-analysis Progression free with response 0.69-0.887 Progression free no response 0.69-0.835 Progressed disease 0.61-0.806 No disutility FSKI-DRS (based on Checkmate 025) The median changes from baseline were statistically better in the nivolumab group, compared with everolimus ($p<0.05$).	EQ-5D, FSKI-DRS
PBAC (2012)[81]	HTA evaluation	Australia	NA	NA	Sorafenib	Patients with stage IV clear cell renal carcinoma who have failed therapy with first line treatment.	Utility weights were literature-based, with the utility difference between sorafenib and placebo being the midpoint of calculated utility values for progressed and non-progressed patients (values not reported).	Not reported

General data						Patient Characteristics	Results	Utility Instrument
Cella D et al. (2016)[82]	Phase 3 OL RCT (CHECKMATE-025; NCT01668784)	International (24 countries across North America, Europe, Australia, South America, Asia)	706/821 patients had baseline HRQoL data (86%) Nivolumab: 362 Everolimus 344	Study stopped early as it met its primary objective. Minimum follow-up time was 14 months, median follow-up for survival was nivolumab 18.3 months and everolimus 17.2 months.	Nivolumab: 3mg/kg every 2 weeks (28-day cycle) Everolimus: 10mg once per day (28-day cycle)	Patients aged ≥ 18 years, with aRCC, measurable disease, Karnofsky PS ≥70 and had received one or two anti-angiogenic therapies for advanced RCC (no more than 3 prior systemic therapies in total (including cytokines and cytotoxic chemotherapy).	Utility (EQ-5D) Baseline, mean (SD) Nivolumab 0.78 (0.24) vs everolimus 0.78 (0.21) Average (on-treatment), LSM; Difference: 0.04 95% CI 0.02 to 0.07; p=0.003 FKSI-DRS Nivolumab patients had an improvement from baseline. Everolimus patients had a deterioration from baseline.	FKSI-DRS, EQ-5D index and VAS
Cella D et al. (2013)[69]	Phase 3 OL RCT (AXIS; NCT00678392)	Not reported	723 patients Axitinib: 361 Sorafenib: 362	Treated until progression, toxicity, withdrawal or death.	Axitinib: 5mg b.i.d. increased to 7mg b.i.d. and again to 10mg b.i.d. if tolerated Sorafenib: 400mg b.i.d. reduced to 400mg q.d. or EOD if not tolerated	Patients aged ≥ 18 years, with aRCC after failure of one first-line systemic regimen, evidence of measurable disease and ECOG PS of 0 or 1.	Utility (EQ-5D), mean (SD) Baseline: not reported Average "post-treatment" Axitinib 0.71 vs Sorafenib 0.69 Difference 0.02; 95% CI -0.01 to 0.05; p=0.193 Observed EQ-5D means were similar until EOT, after which there was a drop when patients typically experienced disease progression. FKSI-15 and FKSI-DRS Mean scores were similar between axitinib and sorafenib until EOT.	FKSI-15, FKSI-DRS, EQ-5D index

General data						Patient Characteristics	Results	Utility Instrument
Beaumont JL et al. (2011)[83]	Phase 3, DB, placebo controlled RCT (RECORD-1; NCT00410124)	Not reported	Everolimus: 277 patients enrolled, 242 analysed Placebo, 139 patients enrolled, 128 analysed	All of the longitudinal models were performed using only the first 8 months of follow-up.	Everolimus	Adults aged ≥ 18 years with mRCC that showed a clear-cell component and had progressed on or were within 6 months of stopping treatment with sunitinib and/or sorafenib.	There was little difference between everolimus and placebo in global quality of life trends.	EORTC QLQ-C30, FKSI-DRS
Trask *et al.* 2011[84]	Phase 3, OL, MC, single arm trial	USA	62 patients enrolled	Median of 6.3 months of treatment; range 0.2-33.6 months)	Axitinib	Adults aged ≥ 18 years with mRCC, prior nephrectomy, ECOG PS ≤ 1, and prior failed treatment with sorafenib.	Longer PFS and OS were associated with higher (more favorable) baseline FKSI-15 and FKSI-DRS.	FKSI-15, FSKI-DRS
Karakiewicz *et al.* 2016[9]	OL, single arm, MC trial (NCT01473043)	Canada and Australia	15 patients enrolled	Median time on axitinib was 118.0 days (range: 3.5-645,0 days)	Axitinib	Adults aged ≥ 18 years with mRCC with a component of clear-cell subtype who failed a prior single line of therapy with any of: interleukin-2, interferon, bevacizumab, sunitinib, pazopanib, tivozanib, temsirolimus, or everolimus.	Utility (EQ-5D), mean Baseline: 0.7947 EOT: 0.711 EuroQol VAS mean Baseline: 73.3 EOT: 66.8	EQ-5D, Euro-Qol VAS

General data						Patient Characteristics	Results	Utility Instrument
Thompson *et al.*2008[65]	Systematic review and economic evaluation	UK	NA	NA	Sorafenib	Patients with RCC as a second line treatment and unsuitable for IFN	Utility (SE) (derived from Pfizer submission) Progression free survival 0.76 (0.03) Progressed disease 0.68 (0.04) No disutility	Not reported
Chandiwana *et al.* 2014[63]	Economic evaluation	UK	NA	NA	Everolimus Axitinib	Patients with advanced mRCC who had failed previous therapy with sunitinib.	Utility (TTO; calculated based on Swinburn et al, 2010) Same for everolimus and axitinib Stable disease 0.795 Stable disease with AEs (everolimus) 0.610 (-0.185 disutiliy) Stable disease with AEs (axitibnib) 0.575 (-0.22 disutility) Progressed disease 0.355 Death 0.00	TTO
Ozono *et al.* 2014[85]	Phase 2 OL MC single-arm trial (UMIN000004742)	Japan	57 patients enrolled, 49 patients analysed	Interim analysis (49 patients with median of 4.4 months of treatment)	Everolimus	RCC with clear cell component, patients who received one TKI as first line therapy, did not receive cytokine and chemotherapy and ECOG PS 0-1	EORTC QLQ-C30, FKSI-DRS All QOL scores were not changed at 2 months, while dyspnea and global health scores were worsened at 4 months.	EORTC QLQ-C30, FKSI-DRS, EQ-5D

Abbreviations in table: ACM, Appraisal Committee Meeting; AE, adverse events; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technology in Health; CUA, cost utility analysis; ECOG, Eastern Cooperative Oncology Group; EGP, Economic Guidance Panel; EORTC, European Organisation for Research and Treatment; EOT, end of treatment; EQ-5D, Euroqol - 5 dimension; ERG, Evidence Review Group; FKSI, Functional Assessment of Cancer Therapy-Kidney Symptom Index; FACT-G, Functional Assessment of Cancer Therapy: General; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index - Disease Related Symptoms; HRQoL, Health-related quality of life; HTA, Health Technology Assessment; IFN, interferon; MC, multi-centre; mRCC, metastatic renal cell carcinoma; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; OL, open-label; ORR, overall response rate; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; PS, performance status; QLQ-C30, Quality of Life Questionnaire-C30; QOL, quality of life; RCC, renal cell carcinoma; SA, Scenario analysis; SE, standard error; SMC, Scottish Medicines Consortium; TKI, tyrosine kinase inhibitor; TTO, time trade off; UK, United Kingdom; VEGF, Vascular Endothelial Growth Factor.

5.4.8.2 Health state utility values used in the model

The company assumes that the quality of life of patients changes according to progression status and whether or not patients experience adverse events. The company reports that the HSUVs used in the base case analysis are based on EQ-5D data collected in the AXIS trial as reported in the CS for the technology appraisal of axitinib as a second-line treatment for RCC (TA333).[57]

EQ-5D data in the AXIS trial was collected at screening, and then every 4 weeks of therapy, at the end of study treatment, and at follow-up (28 days after end of treatment). For the progression-free health state, the mean of the utility estimates at each time point of the trial were weighted by the number of patients still on treatment at that time point, while for progressed disease it was the weighted average of the mean utility at the end of treatment. The mean utility values estimated for the progression-free and the progressed health states in TA333 were 0.69 and 0.61, respectively.[57]

Patients across the treatment arms in the model are assumed to have a utility value of 0.69, when they have stable disease and are not experiencing adverse events. A utility decrement is then deducted from this for patients experiencing Grade 3 or higher adverse events, in order to reflect the impact of the different safety profiles of each treatment on quality of life. The utility decrements assumed for the adverse events are summarised in Table 48, while the rates of adverse events for each treatment and the total disutility are presented in Table 49. The company reports that the rates used are based on the respective clinical trials, as described in Section 5.4.7.

Table 48. Utility decrements assumed for adverse events

Health state	Mean utility	Disutility of AEs	Source of disutility
Stable with no AE	0.692	NA	N/A
Progressive	0.610	NA	
Stable with diarrhoea Grade III+	0.465	-0.227	Swinburn 2010[86]
Stable with fatigue Grade III+	0.514	-0.178	
Vomiting Grade III+	NR	-0.030	Shiroiwa 2009[87]
Stable with nausea Grade III+	0.470	-0.222	Swinburn 2010[86]
Stable with hypertension Grade III+	0.559	-0.133	
Decreased Weight Grade III+	NR	-0.038	Hudgens 2014 (Using decreased appetite as a proxy)[88]
Stomatitis Grade III+	NR	-0.040	Shiroiwa 2009[87]

Abbreviations in table: AE, adverse event; NA, not applicable; NR, not reported.
Note: Cited as Shabaruddin, n.d. in the CS, which is a systematic literature review and the original source of these values is Shiroiwa 2009.

Table 49. Total disutility estimation (CS, pg 152, Figure 85)

Adverse event	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Adverse events prevalence					
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%
Disutility	**-0.013**	**-0.003**	**-0.010**	**-0.011**	**-0.002**
Abbreviations in table: LEN+EVE, lenvatinib in combination with everolimus.					

Table 50. HSUVs used in base case analysis (CS, pg 152, Figure 86)

HSUVs	Lenvatinib combination	Everolimus	Axitinib	Cabozantinib	Everolimus	Nivolumab
Stable disease state with treatment	0.68	0.69	0.68	0.68	0.69	0.69
Stable disease state without treatment	0.69	0.69	0.69	0.69	0.69	0.69
Progressive state	0.61	0.61	0.61	0.61	0.61	0.61
Abbreviations in table: LEN+EVE, lenvatinib in combination with everolimus.						

The company also carried out a scenario analysis using HSUVs from a vignette study by Swinburn *et al*. 2010 and the results of the analysis are reported in Section 5.5.[86]

5.4.8.3 ERG critique

The company's utilities in the base case analysis for stable disease without adverse events, and progressed disease are based on values from the AXIS trial, that were used in the axitinib Single Technology Appraisal (TA 333) and in subsequent submissions to NICE. The ERG considers this approach to be reasonable as based on previous evaluations the population in the AXIS trial is considered to be reflective of the patient population encountered in UK clinical practice.

The company goes on to assume a utility decrement for patients when they experience adverse events. The ERG notes that the utility value of 0.69 already includes the impact of adverse events on quality of life and, therefore, there is going to be double counting in terms of decrements, for axitinib at least. However, the company's approach in assuming that all patients start with a value of 0.69, and using the

proportions of adverse events experienced in the trials is fair and should reflect the difference in safety profiles across the treatments.

The utility decrements for adverse events used by the company were obtained from the company's submission for TA333 and two published quality of life studies. [57, 87, 88] The company cites the systematic literature review by Shabaruddin *et al*. as the source of utility decrements used for vomiting and stomatitis in the model. The original source of the decrements reported in Shabaruddin *et al.* is a vignette study carried out in a Japanese population by Shiroiwa *et al*. to estimate HSUVs for patients with colorectal cancer. The ERG disagrees with the use of values elicited Shiroiwa *et al.* for more than one reason. The values in Shiroiwa *et al*. are based on data collected from members of the general population and not from patients experiencing the health state as stipulated by the NICE Reference Case.[89] Furthermore, the estimates were elicited for patients with colorectal cancer and not renal cancer which may not be generalisable to patients with RCC. The ERG explores the impact of removing utility decrements due to adverse events in a scenario analysis, and the results of this scenario are reported in Section 6.2.

The ERG identified an error in terms of the QALY calculations, which the company corrected during the clarification stage. A proportion of patients can continue to receive treatment beyond progression. However, the utility value of 'stable disease on treatment' was applied to all patients on treatment instead of the value for 'progressed patients. The ERG corrected this as described in Section 6.1.

5.4.9 Resources and costs

The company reviewed the studies identified by the systematic literature described and critiqued in Section 5.3 for estimates of resource use and costs in for the management of advanced RCC following one prior VEGF-targeted therapy: The studies presented in Table 51 are studies considered by the company to include relevant data on resource use and costs. The studies have been summarised previously in Table 36 of Section 5.3.

Table 51. Studies identified by systematic literature review that include resource use estimates and costs (CS, pg 157, Figure 91)

	Studies
1	NICE (2011). "Everolimus for the second-line treatment of advanced RCC (TA219)". HTA submission. https://www.nice.org.uk/guidance/ta219.
2	Review of NICE TA219: Pitt, M, Crathorne, L, Moxham, T, Bond, M and Hyde, C (2010) "Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis (Structured abstract)." Health Technology Assessment Database(3): 41.
3	NICE (2015). "Axitinib for treating advanced RCC after failure of prior systemic treatment (TA333)". HTA submission. https://www.nice.org.uk/guidance/ta333.
4	Riemsma R, Al M, Corro Ramos I, Deshpande S et al. (2012). "Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment: a Single Technology Appraisal." York:Kleijnen Systematic Reviews Ltd (October 2012)

5	NICE (2016). “Nivolumab for treated or metastatic renal cell carcinoma [ID853]”. HTA submission. https://www.nice.org.uk/guidance/gid-ta10037/consultation/html-content
6	SMC (2013). “Axitinib (Inlyta) resubmission 855/13 SMC Advice. http://www.scottishmedicines.org.uk/SMC_Advice/Advice/855_13_axitinib_Inlyta/axitinib_Inlyta_Resubmission
7	SMC (2007). “Sunitinib 50mg capsule (Sutent) 343/07 SMC advice” https://www.scottishmedicines.org.uk/files/sunitinib_Sutent_MRCC_343_07.pdf
Abbreviations:	

5.4.9.1 Pharmacological costs

The pharmacological costs considered in the model are drug acquisition and administration costs. In order to estimate drug acquisition costs for lenvatinib combination and everolimus monotherapy the company used TTD data from the HOPE 205 trial to determine the proportion of patients on treatment in each cycle of the model. The proportions of patients per cycle receiving treatment in the axitinib, cabozantinib and everolimus groups, were estimated by calculating a “relative treatment duration” and applying this estimate to the proportion of patients in the lenvatinib combination treatment group. The relative treatment durations were estimated by dividing the median duration of treatment with lenvatinib combination in the HOPE 205 trial (i.e. 8 months) by the median duration of treatment of the comparator treatment that was observed in its respective trial. The company’s approach for applying TTD in the model was previously described in detail and critiqued in Section 5.4.6. The drug acquisition costs assumed in the model are summarised in Table 52.

Table 52. Drug acqusition unit costs assumed in the model (CS, pg 159, Figure 93)

Treatment	Dose per unit	Units per pack	Cost per pack (£)[90]	Price per unit (£)
Lenvatinib	4mg 10mg	30 30	1,437 1,437	47.90
Everolimus (combined with lenvatinib)	5mg	30	2,250	75.00
Everolimus	10mg	30	2,673	89.10
Axitinib	5mg	56	3,517	62.80
Cabozantinib	20mg/40mg/60mg	30	5,143	171.43
Nivolumab	100mg	1	1,097	1,097.00
Abbreviations in table: mg, milligramme.				

The drug doses assumed in the model are summarised in Table 53. The dose of nivolumab administered to patients is determined based on weight and is calculated as 3mg/kg. The company used the mean weight of patients in the HOPE 205 trial of 80.8 kg to estimate a dose of 244 mg of nivolumab which is applied in the model. The company accounted for dose reductions relative to intended doses when estimating acquisition costs in the model. The dose reductions assumed in the model are based on the actual doses received in the HOPE 205, AXIS, CheckMate 025, and METEOR trials. During the

clarification stage, the company provided the ERG with additional information on how dose reductions were estimated in the model, which is presented in Table 53.

Table 53. Dosage assumptions in the model (CS, pg 160, Figure 94)

Therapy	Intended dose (mg)	Frequency	Dose reduction	Number of tabs/vials needed	Final dose (mg)
Lenvatinib	18	Daily	[redacted]	–	[redacted]
Everolimus (combined with lenvatinib)	5	Daily	[redacted]	–	[redacted]
Axitinib	10	Daily	[redacted]	2.00	[redacted]
Cabozantinib	60	Daily	[redacted]	1.00	[redacted]
Nivolumab	244*	Every 2 weeks	[redacted]	3.00	[redacted]
Everolimus (monotherapy)	10	Daily	[redacted]	2.00	[redacted]

Abbreviations in table: mg, milligramme; tab, tablet.
*The dose of nivolumab is 3mg/kg, and assuming a mean patient weight of 80.8 kg this is equal to 244 mg.

Box 14. Dose reductions applied in the model (company's response to ERG's clarification question B22)

the dose reduction percentages reported for lenvatinib and everolimus were taken directly from the mean doses reported in the HOPE 205 study ie 13.3mg/18mg = 73.9% for lenvatinib and 4.4mg/5mg = 88% for everolimus 5mg.

To ensure that all dosing costs were applied consistently to cabozantinib, axitinib and nivolumab and in the absence of patient level data, a similar approach was taken to calculate the dose reductions required for these comparators.

In the cabozantinib Phase III trial (Choueiri 2016), only the median daily dose of 43mg was reported which is [redacted] of the required dose of 60mg, as reported in the dose reduction column of Figure 94. In the axitinib phase III trial (Rini 2011), the mean relative dose intensity (defined as the actual total dose / intended total dose × 100) was 99% in the axitinib group, as reported in the dose reduction column of Figure 94. In the nivolumab phase III trial (Motzer 2015), dose reductions were not allowed and therefore equal to 100% of the required dose, as reported in the dose reduction column of Figure 94.

Abbreviations in table: mg, milligramme.

The company originally included an administration cost for all treatments in the model. However, when asked by the ERG at clarification stage to justify assuming an administration costs of £183.50 per model cycle for oral treatments, which patients took at home, the company decided to only include an administration cost for nivolumab which is administered intravenously in its base case analysis. The administration cost assumed for nivolumab in the model is presented in Table 54. The monthly treatment-related costs are summarised in Table 55.

Table 54. Administration cost assumed for nivolumab in the model (CS, page 160, Figure 95)

Administration costs	HRG code	Mean cost	Reference
Simple parenteral chemotherapy (first attendance)	SB12Z	236.19	NHS ref costs 2015-16[91]
Abbreviations in table: HRG, Healthcare Resource Group; NHS, National Health Service. *The dose of nivolumab is 3mg/kg, and assuming a mean patient weight of 80.8 kg this is equal to 244 mg.			

Table 55. Monthly treatment-related costs (Adapted from CS, page 161, Figure 96)

Comparator	Drug acquisition cost per dose (£)	Administration route	Admin. cost per cycle (£)	Total Cost per month* (£)
Lenvatinib combination therapy	[redacted]	N/A	-	[redacted]
Axitinib	[redacted]	N/A	-	[redacted]
Cabozantinib	[redacted]	N/A	-	[redacted]
Nivolumab	[redacted]	IV	472.38	[redacted]
Everolimus	[redacted]	N/A	-	[redacted]
*These costs are from the company's updated model, in which administration costs were removed and the correct cost was used for everolimus monotherapy.				

5.4.9.2 Health state unit costs and resource use

The company estimated resource use for disease management for stable disease and progressive disease separately. Resource use assumptions were mainly based on feedback from the NICE committee on estimates reported in the NICE TA of axitinib (TA333), that were also used in the technology appraisals for nivolumab and cabozantinib.[92] The company validated the resource use assumptions by consulting with eight clinical experts currently practicing in the NHS in England and Wales.

Prior to progression, patients are assumed to require monthly oncologist visits and blood tests, in addition to computerised tomography (CT) scans every 3 months. After patients progress, they continue to have monthly oncologists visits in addition to monthly GP visits, a mean of 1.5 specialist nurse visits a month and pain medication for 28 days per month. Resource use assumed in the model is summarised in Table 56.

In the company's base case analysis, patients are assumed to receive best supportive care once they progress, with only disease management costs being applied in the model.

Table 56. Resource use for disease management in the model (CS, pg 163, Figure 97)

Cost Item	**Price per Item Unit (£)**	**DDD/Frequency per cycle**	**Proportion of Patients %**	Cost per cycle (£)	**Source of unit costs**
Stable Disease Health Care Resource Use Costs					
Oncologist Examination	162.84	1.00	100.00%	162.84	Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (Source NHS Reference costs 2015/16)
CT Scan	140.11	0.30	100.00%	42.03	RD27Z Computerised Tomography Scan of more than three areas (Source: NHS Reference costs 2015/16)
Blood Test	3.00	1.00	100.00%	3.00	DAPS05 NHS Reference costs 2015/16
Total Stable Disease Costs				207.87	
Progressive Disease Health Care Resource Use Costs					
Oncologist Examination	162.84	1.00	100.00%	162.84	Cost of Consultant Medical oncology visit (Source NHS Reference costs 2015/16)
GP visit	36.00	1.00	100.00%	36.00	PSSRU 2016 Section10.3b page 145 GP unit cost Per surgery consultation lasting 9.22 minutes, including direct staff costs, with qualification costs
Specialist community nurse visit	43.00	1.50	100.00%	64.50	PSSRU 2016 Section10.2 page 143 Nurse (GP practice), unit costs, including qualifications
Pain medication	5.36	28.00	100.00%	150.08	TA333 (BNS Section 4.7.2 Opioid analgesics (morphine sulphate 1mg/ml, net price 50ml vial = £5.00 using NHS reference costs 2010/11), adjusted to 2015/16 prices using PSSRU 2016 Section 16.3 page 196, The HCHS index
Total Progressive Disease Costs				413.42	
Source: TA333 (Axitinib NICE guidance, company submission pages 161-163) and Nivolumab NICE company submission (page 178) and ERG report (pg 123) and cabozantinib ACD (pg 16)					

5.4.9.3 End of life costs

The company assumed a cost of £7,450 attributed to end-of-life care in the model. This cost for end-of-was obtained from a paper published by the Nuffield Trust estimating costs associated with end of life care in the UK.[93] A summary of the cost components considered in the paper for end-of-life care is presented in Table 57. The cost was inflated to 2016 values using the PSSRU inflation index. This cost is applied to all patients who die in the model. The total costs attributed to deaths for each treatment arm in the model were calculated as the sum of the cost per death (i.e. £7,450) multiplied by (1-proportion of patients surviving at each cycle).

Table 57. Costs of end-of-life care (CS, pg 164, Figure 98)

Mortality costs	Cost component	Costs reported in 2013 cost year
Secondary (acute hospital care)	Cost of emergency inpatient admissions	4,071
	Cost of non-emergency inpatient admissions	1,360
	Cost of outpatient visits	378
	Cost of A&E visits	80
	Cost of all hospital contacts	5,890
Local authority funded social care	Cost of local authority-funded social care	444
District nursing	Cost of district nursing care	588
GP contacts	Cost of GP visits	365
Total used in the model (Inflation-adjusted for 2016)		7,450
Abbreviations in table: A&E, Accident and Emergency; GP, general practitioner. Source: Nuffield Trust. (2014). Exploring the cost of care at the end of life. (Georghiou, 2014) http://www.nuffieldtrust.org.uk/sites/files/nuffield/publication/end_of_life_care.pdf		

5.4.9.4 Adverse event costs

The company included the costs of managing Grade 3/4 adverse events that have an impact on quality of life in the model. The proportions of patients experiencing each adverse event in the model used to estimate costs are those reported in Table 49

Table 49 of Section 5.4.7. The prevalence of adverse events were adjusted in order to obtain the prevalence/frequency of each adverse event per model cycle (i.e. per month). The following formula was used to estimate the monthly frequency of adverse events:

$$Monthly\ frequency\ of\ adverse\ event = (median\ duration\ of\ AE \div median\ treatment\ duration)\ x\ (prevalence\ of\ adverse\ event\ in\ trial)$$

The median duration of AEs used were the durations observed for lenvatinib combination in the HOPE 205 trial and are presented in Table 58. The costs of adverse event episodes assumed in the model are

based on feedback from the company's clinical experts and are summarised in Table 59. The estimated monthly cost of adverse events for each treatment arm in the model are presented in Table 60.

Table 58. Duration of adverse events assumed in the model (CS, pg 166, Figure 100)

Adverse event	Duration in days	Source
Diarrhoea	25.51	HOPE 205 trial.[31]
Fatigue/Asthenia	49.39	
Vomiting	10.11	
Nausea	34.79	
Hypertension	28.34	
Stomatitis	37.477	
Dyspnoea	33.56	
Decreased Weight	49.59	Assumed equal to decreased appetite

Table 59. Costs of managing adverse events applied in the model (CS, pg 165, Figure 99)

Adverse event	HRG Cost (£)	Source[91]
Diarrhoea	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Fatigue/Asthenia	658.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of F2F community nurse contact of £43 (Source: PSSRU 2016)
Vomiting	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Nausea	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Hypertension	850.67	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (£162.84) (Source NHS Reference costs 2015/16) + 2 follow up GP visits (£36) Source: PSSRU 2016
Decreased Weight	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Stomatitis	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Abbreviations in table: CC, complication or comorbidity; HRG, Healthcare Resource Group; NHS, National Health Service.		

Table 60. Monthly costs of adverse events in the model (CS, pg 167, Figure 100)

Adverse event	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Diarrhoea	152	15	85	101	10
Fatigue/Asthenia	65	0	66	72	16
Vomiting	60	0	8	15	0
Nausea	46	0	15	39	2
Hypertension	117	17	145	128	0

Decreased Weight	12	0	18	18	0
Stomatitis	0	12	6	12	0
Dyspnoea	12	49	0	18	5
Total	**464**	**94**	**344**	**404**	**32**
Abbreviations in table: LEN+EVE, lenvatinib combined with everolimus.					

5.4.9.5 ERG critique

The ERG found the formulae in the model to be generally sound, with prices inflated correctly to 2015/2016 rates when necessary. Unit costs are based on NHS Reference Costs and PSSRU costs, as specified in the NICE Reference Case.[89]

The ERG identified a few key issues in the approach taken by the company to estimate pharmacological costs in the model, which could cause erroneous cost effectiveness results.

In order to estimate the final dose received by patients after accounting for dose reductions that occurred in trials, the company applied the dose reduction factor to the intended dose and then rounded it to the nearest tablet or vial to calculate the dose received per patient. The ERG considers this method to be potentially overestimating or underestimating the costs for some treatments as the reduction factors estimated by the company were based on the mean doses received across the whole trial population, and not per patient. Therefore, applying the reduction factor to the total cost of the intended dose may be a better approach than that taken by the company. The dose reduction factors assumed for nivolumab and axitinib, are [redacted], and [redacted] of doses, respectively so this does not impact estimated costs for nivolumab while having a minimal impact on axitinib costs. However, although reduction factor of [redacted] and [redacted] are applied for everolimus when used in combination with lenvatinib and as monotherapy, respectively, patients are still assumed to receive the full dose of 5 mg and 10mg. respectively a day after the doses are rounded. A reduction factor of [redacted] is applied for cabozantinib, but when rounded to the nearest tablet patients are still assumed to receive their full 60 mg dose.

The dose reductions assumed by the company for nivolumab and axitinib are not consistent with the reductions reported and applied in the NICE appraisals of axitinib, nivolumab, and cabozantinib.[70, 92, 94] The preferred relative dose intensity assumed for nivolumab was 97.5 % in the cabozantinib STA to reflect the ERG's recommendation in the nivolumab STA, while for axitinib in all three appraisals it was 102%.[57, 58, 95]

The company did not include subsequent therapies in its base case analysis, and therefore, the ERG asked the company to carry out a scenario analysis using the proportions of subsequent treatments received in the respective trials for all the treatments arms. The company did not provide this and instead chose to estimate a cost based on the UK market share of the drugs received as subsequent therapies

across the lenvatinib combination and everolimus groups of the HOPE 205 trial and apply this cost to all the treatment groups. The justification provided by this company for using this approach is presented in Box 15.

Box 15. Subsequent therapy analysis carried out by the company (Clarification response document)

The data were not based on respective clinical trial data for the comparators for the following reasons: (1) data are not available for all drugs, including LEN+EVE in the respective clinical trials, and (2) the difference in cost could be related to an expensive secondary therapy and would bias the ICER, (3) the secondary therapy would be significantly biased by the availability of drugs at the end of the trial, and not based on clinical practice. Using real world evidence is more robust than using trial data, mainly because the trials were not performed at the same time, and many comparators were not available when these trials were performed. Therefore, a more realistic approach is to use a similar secondary therapy for each model arm.
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LEN+EVE, levatinib combined with everolimus.

The ERG disagrees with the justification put forward by the company, and the approach taken in this analysis. A proportion of patients in the HOPE 205, METEOR, CheckMate 025, and AXIS trials received a further line of therapy after discontinuing treatment. Therefore, the effectiveness estimates obtained from all these trials implicitly included any potential benefits that the patients received from these subsequent treatments that are not attributed to the initial drugs received in the trials. In order to assign a cost to this additional benefit received by patients, it is more accurate to use the actual proportion of treatments received in the trials in a manner reflective of what is available in the UK. The ERG carried out a scenario analysis for trial based subsequent treatment costs, which is presented in Section 6.2.

The ERG considers the resource use assumptions made by the company to be generally reasonable, and the ERG's clinical experts confirmed that the assumptions made for disease, adverse events management and end-of-life care are broadly in line with UK clinical practice. However, according to the lenvatinib SmPC, patients receiving lenvatinib require a liver function test every 2 weeks for the first 2 months and then monthly thereafter for the duration of treatment. The company's assumption in the model is that patients have monthly blood tests, which means that the costs for the lenvatinib combination therapy group are underestimated by 2 additional blood tests. This is unlikely to have an impact on the overall ICERs as the cost of each blood test is small (£3).

The ERG identified an error in how the costs of everolimus were originally estimated for patients in the everolimus group of the model. The cost of a 5mg tablet was used and multiplied by two to calculate the cost of the daily 10mg dose instead of applying the cost of a 10mg tablet which is less expensive. The company corrected this during clarification stage.

5.5 Results included in company's submission

5.5.1 Base case results

The results of the company's base case analysis are presented in Table 61. According to the company's analysis, lenvatinib combination is expected to extend patients' lives by around 11 months, 6 months, 4 months, and 2 months compared to axitinib, everolimus, nivolumab, and cabozantinib, respectively. This translates to an incremental average QALY gain of 0.57, 0.35, 0.20, and 0.11 QALYs for patients receiving lenvatinib combination compared axitinib, everolimus, nivolumab, and cabozantinib, respectively.

Table 61. Results of company's base case analysis (Clarification responses document)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
LEN+EVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,971
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,167
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,299
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,404

5.5.2 Sensitivity analysis

The company carried out one-way sensitivity and scenario analyses exploring the impact of changing assumptions surrounding the following parameters:

- Treatment duration;
- Discount rates;
- Clinical inputs;
    - Parametric distributions for: TTD, PFS, and OS
    - Nivolumab mortality
- Health state utilities;
- Subsequent therapy.

The results of the company's deterministic sensitivity analyses are presented in 5.5. The ICERs for lenvatinib combination compared to nivolumab, axitinib and cabozantinib seem to be particularly sensitive to assumptions surrounding treatment duration with the greatest impact being on the results of lenvatinib combination compared to cabozantinib. Assuming that treatment duration is equal to PFS in the model increases the ICER of lenvatinib combination compared to cabozantinib 54-fold to £118,341 per QALY, while using the digitised TTD KM curve makes lenvatinib combination dominate.

Assuming the upper and lower limits of the 95% CIs of lenvatinib OS HRs had a large impact on the ICER for lenvatinib combination compared to everolimus, with lenvatinib combination going from being dominated to having an ICER of £54,276 per QALY when the lower and upper limits were applied, respectively. Varying other parameters in the model seem to have less of an impact on the cost-effectiveness results.

Table 62. Deterministic sensitivity analysis results (company's clarification responses document)

Scenario		LEN+EVE vs Nivolumab ICER(£)	LEN+EVE vs Axitinib ICER(£)	LEN+EVE vs Cabozantinib ICER(£)	LEN+EVE vs Everolimus ICER(£)
Base case		**7,299**	**32,971**	**2,167**	**122,404**
Treatment duration - switching at progression		55,258	70,023	118,341	133,776
Treatment duration - extrapolation		65,388	52,929	103,016	143,891
Treatment duration - Digitisation		Dominant	55,782	Dominant	122,404
Extreme discounting values (0% Ben and costs)		8,819	31,674	2,811	115,781
Extreme discounting values (5% Ben and costs)		6,614	33,530	1,901	125,209
LEN+EVE OS CI+ (based on trial HR CIs)		7,394	26,959	3,382	54,276
LEN+EVE OS CI- (based on trial HR CIs)		7,174	41,088	649	Dominated
LEN+EVE PFS CI+ (based on trial HR CIs)		14,095	33,557	5,426	123,108
LEN+EVE PFS CI- (based on trial HR CI's)		1,551	32,492	Dominant	121,378
Overall survival	Piecewise - Gompertz (second best)	7,199	37,382	798	142,150
	Parametric - Gompertz (Best fitting)	7,175	38,940	502	133,712
	Parametric - Weibull (second best)	7,285	34,051	1,994	108,868
	Individual - Weibull (Best fitting)	7,272	34,744	1,817	103,221
	Individual - Gompertz (second best)	7,088	43,506	Dominant	135,817
Progression free survival	Piecewise - Gompertz (second best)	7,136	32,962	1,887	122,659
	Parametric - Weibull (Best fitting)	7,354	32,946	2,937	122,428
	Individual - Gompertz (Best fitting)	7,007	32,960	1,604	123,558
	Individual - Weibull (second best)	7,410	32,980	2,292	122,882
Additional set of utility (vignette study)		5,732	38,811	1,790	124,685

Additional set of utility (TA417) option	-55,957	32,971	2,167	204,579
Evorolimus Generic price (capecitabine price as a proxy)	6,416	34,624	2,505	123,303
Secondary therapy included	95,972*	95,972*	95,972*	95,972*
Natural mortality for NIV after 60 months	7,670	32,971	2,167	122,404

Abbreviations in table: CI; confidence interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN+EVE, lenvatinib combined with everolimus; TA, technology appraisal.
*There seems to be an error in the model in this additional scenario that the company carried during clarification stage as the model gives identical ICERs for LEN+EVE against all the comparators. The ERG did not explore this further as this scenario was not carried in line with what the ERG requested as explained in Section 5.4.9.5, and is of limited value.

5.5.2.1 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results across a 1,000 iterations. The mean probabilistic ICERS are presented in Table 63, and are not in line with deterministic ICERs with the greatest discrepancies observed for cabozantinib and nivolumab, where the probabilistic ICERs are 129 times and four times higher than the deterministic ICERs, respectively. The resultant scatterplots and cost-effectiveness acceptability curves (CEACs) from the PSA are presented in Figure 30 and Figure 31, respectively. Figure 5 confirms that there is a great deal of uncertainty surrounding the results of the comparison of lenvatinib combination compared to cabozantinib and nivolumab with simulations falling in all four quadrants.

The probability of lenvatinib combination therapy being cost-effective compared to everolimus, axitinib, cabozantinib, and nivolumab is 10.7%, 71.5%, 9.2%, and 8.6%, respectively at a willingness-to-pay (WTP) threshold of £20,000 per QALY. At a WTP threshold of £30,000 per QALY, the probability of lenvatinib combination being cost-effective compared to everolimus, axitinib, cabozantinib, and nivolumab is 22.2%, 46.2%, 17.6%, and 14.0%, respectively.

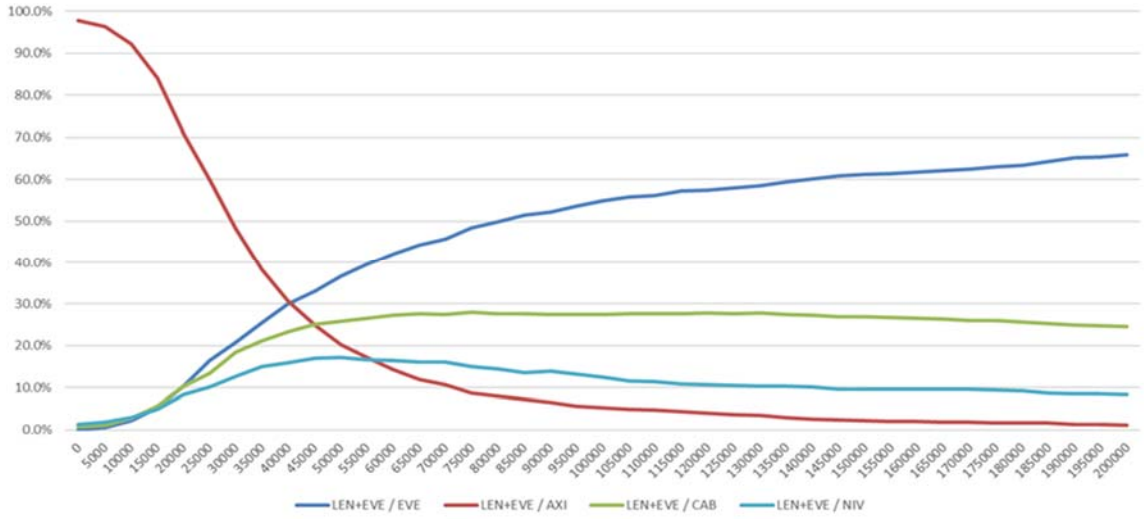
Table 63. Mean probabilistic ICERs (company's clarification responses document)

Treatment	LEN+EVE vs Axitinib	LEN+EVE vs Cabozantinib	LEN+EVE vs Nivolumab	LEN+EVE vs Everolimus
Deterministic ICER (£)	32,971	2,167	7,299	122,404
Mean probabilistic ICER (£)*	47,343	279,561	29,567	154,941

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LEN+EVE, lenvatinib combined with everolimus.
*The ERG was unable to obtain mean ICERs similar to those reported by the company.

Figure 30. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for LEN+EVE versus comparators (company's clarification responses document)

Figure 31. Cost-effectiveness acceptabilty curves (company's clarification responses document)



5.5.3 Model validation

The ERG performed a thorough validation of the company's economic model to identify discrepancies with between the CS and the model, and to identify any calculation errors that could impact the company's results. The ERG found a few potentially serious errors but these have been corrected in Section 6.1.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG identified the following errors in the company's base case model:

1. The first error was an inconsistent application of the half cycle correction for costs and QALYs, which led to an overestimation of QALYs for all treatments, favouring those with the greatest survival benefit, i.e. lenvatinib combination. The QALY value for the first cycle was incorrectly added to the sum of the half cycle values. For costs, only the half cycle values were included in the sum. The ERG corrected this so that the QALY calculation was in line with the calculation used for costs.

2. The second error was in the calculation of QALYs, which applied a utility associated with pre-progression to all patients who were on treatment, and therefore, did not account for patients who progressed but remained on treatment.

The results of the company's corrected base case are presented in Table 64 as a pairwise analysis, and in Table 65 as an incremental analysis.

Table 64. Results of company's corrected base case analysis (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,068
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,185
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,295
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,233

Table 65. Results of company's corrected base case analysis (Incremental)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extended dominance
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extended dominance
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£122,233

6.2 ERG scenario analysis

6.2.1 Trial based subsequent treatments

The ERG conducted a scenario analysis around the company's corrected base case to include the costs of the subsequent treatments that patients received in their respective trials. This contrasts with the company's scenario analysis, which based subsequent treatment costs on an estimated market share and applied the same cost to each treatment group. The ERG considers the trial based approach more appropriate as the treatment effectiveness is partly driven by the subsequent treatments received in the trials, and hence, the costs should reflect that. The results of this scenario are given in Table 66.

Table 66. Results of trial based subsequent treatments scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,550
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,266
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,100

6.2.2 ITC based HR applied for everolimus PFS and OS

The ERG conducted a scenario around the company's corrected base case, which estimates PFS and OS for the everolimus group by applying the HR from the ITC to the lenvatinib combination piecewise curve that was used in the company's base case. This scenario avoids the implausible outcome of nivolumab becoming less effective than everolimus in terms of PFS, as described in Section 5.4.5. The results are given in Table 67.

Table 67. Results of everolimus ITC HR scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,068
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,185
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,295
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	121,024

6.2.3 Utilities based on TA417

The ERG conducted a scenario using the company's option in the economic model to apply utilities from TA417. The results are presented in Table 68.

Table 68. Results of TA417 utility scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,068
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,185
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	204,377

6.2.4 General population mortality for 50% of nivolumab patients

The ERG conducted a scenario using the company's option in the economic model to apply the general population mortality to 50% of patients who are progression-free after 5 years. The results are given in Table 69.

Table 69. Results of TA417 mortality scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	33,068
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,185
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,674
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,233

6.3 ERG preferred base case

The ERG's preferred base case incorporates changes to the survival modelling that was used by the company, by using the fractional polynomial based curves for PFS and OS that were considered the best fitting by both the ERG and the company; that is, the first order polynomial with P = -1 for OS, and the second order polynomial with P1 and P2 = - 2 for PFS. The ERG's fitted 2-knot splines were used for to estimate TTD, and subsequent treatment costs were based on the treatments received in each of the respective trials. The results of the ERG's preferred base case are summarised in Table 70, which shows the cumulative effect on the results by including each change, as well as showing the ICER for each single change compared to the company's corrected base case.

Table 70. Results of the ERG preferred base case (Pairwise)

Results per patient	Lenvatinib comb. (1)	Axitinib (2)	Cabozantinib (3)	Everolimus (4)	Nivolumab (5)	Incremental values			
						(1-2)	(1-3)	(1-4)	(1-5)
Company's corrected base case									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER						33,068	2,185	122,233	7,295
ERG's preferred survival curves: Best fitting fractional polynomials for OS and PFS, and 2-knot spline for TTD									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**63,208**	**Dominated**	**84,440**	**Dominated**
ICER with all changes incorporated						**63,208**	**Dominated**	**84,440**	**Dominated**
Subsequent treatment costs based on trials									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**32,550**	**Dominated**	**122,100**	**4,266**
ICER with all changes incorporated						**62,496**	**Dominated**	**84,311**	**Dominated**
ERG's preferred base case ICER						**62,496**	**Dominated**	**84,311**	**Dominated**
Abbreviations in the table: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year									

Table 71. Results of the ERG preferred base case (Incremental)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,311
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

6.4 ERG scenario analyses

6.4.1 Alternate first order OS fractional polynomial (P = -0.5)

The ERG conducted a scenario analysis around the ERG's preferred base case that uses an alternate OS fractional polynomial based curve with a similar goodness-of-fit but showing a lesser treatment effect for lenvatinib combination, cabozantinib and nivolumab in comparison to everolimus monotherapy. Further detail on these curves is given in Section 5.4.5. The results of this scenario are given in Table 72.

Table 72. Results of alternative OS curve scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	65,379
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	88,358

6.4.2 Alternate TTD curve (Lognormal)

The ERG conducted a scenario that uses the lognormal curve for TTD that was fitted by the ERG as discussed in Section 5.4.6.1. The results of this scenario are given in Table 73.

Table 73. Results of alternative TTD curve scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,968

Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95,217

6.4.3 Utilities based on TA417

The ERG conducted a scenario using the company's option in the economic model to apply utilities from TA417. The results are presented in Table 74.

Table 74. Results of TA417 utility scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,496
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	116,458

6.4.4 General population mortality for 50% of nivolumab patients

The ERG conducted a scenario using the company's option in the economic model to apply the general population mortality to 50% of patients who are progression-free after 5 years. The results are given in Table 75.

Table 75. Results of TA417 mortality scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,496
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84,311

7 END OF LIFE

Patients treated with axitinib and everolimus, as modelled, are expected to have a mean lifetime of less than 2 years. However, the newer treatments of cabozantinib and nivolumab show an expected lifetime of greater than 2 years, so there is some uncertainty as to whether the life expectancy is short enough to fulfil the first of the end of life criteria.

In terms of an extension to life, lenvatinib has a modelled increase in life expectancy of greater than 3 months when compared to the next most effective treatment, cabozanitnib. The increase is greater still for the remaining treatments.

The ERG notes that end of life criteria have been applied in previous NICE technology appraisals for patients with previously treated renal cell carcinoma.

8 OVERALL CONCLUSIONS

The clinical evidence presented in the company's submission (CS) for lenvatinib plus everolimus combination therapy is derived from HOPE 205, an open label, phase II, international, multicentre trial.

The main objective of HOPE 205 was to compare PFS of lenvatinib combination therapy versus everolimus monotherapy in adults diagnosed with unresectable or advanced, predominantly clear cell RCC, whose disease had progressed on or within nine months of stopping prior therapy with one prior VEGF-targeted therapy. HOPE 205 is a well conducted trial, with appropriate statistical analyses and a trial population largely generalizable to patients in UK clinical practice; a third of patients were recruited from the UK and the baseline characteristics of the full trial population were similar to the UK subgroup. Although, as in many clinical trials, patients in HOPE 205 were younger and healthier (>50% of patients had an ECOG performance status of 0) than what would be expected in UK clinical practice.

The sample size of the study was small, with around 50 patients randomised to each treatment arm, which introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy. The patient's baseline characteristics appear relatively well balanced between the trial arms, though some differences (a larger proportion of patients with more than one metastasis, a slightly shorter duration of prior VEGF-targeted therapy, and fewer patients with complete or partial response to first-line VEGF-targeted therapy in the everolimus group) potentially indicate a poorer prognosis for the everolimus group compared with patients randomised to lenvatinib combination therapy. However, the ERG notes that due to the small sample size the potential impact of the differences should be interpreted with caution. In addition, the open label design and the lack of blinded outcomes assessment of PFS and tumour response is concerning. An independent radiology review (IRR) of PFS and tumour response was done retrospectively on the request of EMA/FDA. HRQoL, one of the outcomes of interest listed in the scope, was not captured in HOPE 205.

HOPE 205 showed that patients treated with lenvatinib combination therapy had significantly longer PFS (HR 0.40, 95% CI: 0.24 to 0.68) and OS (HR 0.59, 95% CI: 0.36 to 0.97) than patients treated with everolimus monotherapy. More patients treated with lenvatinib combination therapy also achieved a complete or partial response than patients treated with everolimus monotherapy (RR 7.2, 95% CI: 2.3 to 22.5). However, more patients had serious adverse events in the combination group than in the everolimus group.

No head-to-head trials comparing lenvatinib combination therapy with nivolumab, cabozantinib, axitinib, and BSC (placebo) were identified and therefore the company conducted indirect treatment comparisons (ITC). Five trials comparing treatments for patients with advanced RCC who had failed at least one prior VEGF-targeted therapy were identified. TARGET (sorafenib versus placebo), which

only enrolled patients who had not had prior anti-VEGF targeted therapy, was also included to form a connected network. The trials differed in terms of number and type of prior therapies, subsequent therapies, and outcome assessment.

The relative efficacy of lenvatinib combination therapy versus each comparator was initially estimated using the Bucher method for all outcomes. The analyses of OS and PFS was based on HRs, which are conditional on the proportional hazard (PH) assumption being fulfilled. However, the PH assumption does not hold for PFS and OS in several of the trials in the network and hence no meaningful interpretation of the resulting HRs from these analyses can be made. Therefore, the company assessed PFS and OS in a survival curve-based NMA using fractional polynomials, which does not rely on the PH assumption being fulfilled. Based on the difference in prior therapy in TARGET and confounding of OS due to cross-over, which couldn't be adequately adjusted for, axitinib and everolimus were assumed to have similar efficacy for the NMA of PFS and OS.

[redacted] The ERG assessed how well the best fitting NMA models the input data as FP curves, which showed a good statistical fit for both trial arms in CheckMate 025 and HOPE 205 for OS. For PFS the best fitting model showed a good fit for CheckMate 025, and the everolimus group in HOPE 205, but the lenvatinib combination therapy group in HOPE 205 was potentially overestimated. There were also several first and second order curves with a similarly good fit for OS. The ERG's inspection of the different curves shows that only one other fractional polynomial provides plausible curves.

The indirect comparisons for ORR and safety, which were estimated using risk ratios and the Bucher method, encompassed the full original network, in which the comparison with axitinib is reliant on the link via the TARGET trial. The comparison with axitinib is therefore potentially flawed based on difference in the trial populations in terms of type of prior therapy. The ORR was higher for patients treated with lenvatinib combination therapy compared with nivolumab, cabozantinib, axitinib, everolimus and placebo, although only the difference to the last two were statistically significant.

The company's primary analysis for each outcome were based on the full population and the primary analysis of each trials, that is, irrespective of differences between the trials in number and type of prior therapy, and investigator or independent outcome assessment.

The company submitted a *de novo* economic model with some potentially serious methodological flaws that led to unreliable estimates of treatment effectiveness and time to treatment discontinuation, and therefore unreliable estimates of cost effectiveness.

The key flaw in the company's methodology that impacted the economic model was the company's consideration that a proportional hazards assumption was robust enough to provide reliable treatment effectiveness estimates of progression-free survival and overall survival. Previous STAs in renal cell carcinoma have shown that this is not the case and that an alternative approach where this assumption is not required is likely to provide more reliable estimates of these key outcomes, which are very influential on the estimates of the mean QALYs expected to be accrued by patients, and therefore on the cost effectiveness results.

In attempting to account for this issue the company provided results of an alternative approach, which was found by the ERG to produce reasonably well fitting survival curves for OS and PFS. However, the economic analysis base on these curves submitted by the company was found to be implemented with errors, and hence, the ERG considered the results to be unreliable. The ERG did, however, use the company's submission to implement the survival curves correctly into the ERG's preferred base case, to provide a more reliable cost effectiveness analysis.

The ERG also considered the company's estimates of time to treatment discontinuation to be flawed, although this led to underestimated treatment duration for some of the comparators, in particular cabozantinib and nivolumab. The ERG fitted survival curves to KM data from the respective trials for each comparator and included the best fitting curve (2-knot spline) into the ERG's preferred base case.

Although quality of life data was not captured in the company's trial, the use of EQ-5D data from the AXIS trial in the same disease area was considered to be reasonable by the company, and was considered by clinical experts to be reflective of the population of previously treated patients with renal cell carcinoma.

The key sources of uncertainty that remain in the company's base case lie in the estimation of survival curves. The fractional polynomial method used to estimate PFS and OS survival curves, is limited by fitting a particular type of polynomial for each trial included in the NMA. This means that the goodness-of-fit is measured to the network as a whole and may result in individual poor fitting curves. The ERG generally considered the curves to fit the trial data well. However, there was some overestimation of PFS for the lenvatinib group which may underestimate the ICERs in the ERG's preferred base case.

8.1 Implications for research

BSC is a comparator of limited importance as there are now several active second-line treatment options for patients with advanced RCC and patients well enough to receive active treatment are unlikely to receive BSC. Axitinib has been the main second-line line treatment option in the UK since it was recommended by NICE in February 2015. Nivolumab was recommended by NICE in November 2016 and it is likely to supersede axitinib as the mainstay of second-line treatment. Cabozantinib, which is subject to ongoing NICE appraisal (GID-TA10075), is also expected to be used more than axitinib if recommended by NICE. Although everolimus has been available via the CDF for patients unable to take axitinib and in Feb 2017 recommended by NICE for routine commissioning, it is unlikely to gain usage over the other available treatment options. The only direct evidence for lenvatinib combination therapy is from HOPE 205 where it is compared to everolimus monotherapy. Robust direct evidence of lenvatinib combination therapy compared with the more relevant comparators, nivolumab and potentially cabozantinib, is therefore needed to reduce the uncertainty of the indirect comparisons presented in this report.

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10 APPENDICES

10.1 Baseline characteristics HOPE 205

Table 76. Baseline demographic and disease characteristics of ITT population and UK participants in study E7080-G000-205 (Clarification response A6)

Baseline characteristic	**ITT Population**			**UK Patients**		
	Lenvatinib combination therapy (n=51)	**Lenvatinib monotherapy (n=52)**	**Everolimus monotherapy (n=50)**	**Lenvatinib combination therapy (n=17)**	**Lenvatinib monotherapy (n=15)**	**Everolimus monotherapy (n=18)**
Country UK Czech Republic Poland Spain United States	 17 (33.3%) 13 (25.5%) 8 (15.7%) 8 (15.7%) 5 (9.8%)	 15 (28.8%) 5 (9.6%) 9 (17.3%) 6 (11.5%) 17 (32.7%)	 18 (36.0%) 5 (10.0%) 9 (18.0%) 4 (8.0%) 14 (28%)	N/A	N/A	N/A
Age (years)	61 (44–79)	64 (41–79)	59 (37–77)	66 (54- 74)	61 (41-76)	60 (39, 75)
Sex						
Men	35 (69%)	39 (75%)	38 (76%)	11 (65%)	10 (67%)	12 (67%)
Women	16 (31%)	13 (25%)	12 (24%)	6 (35%)	5 (33%)	6 (33%)
ECOG Performance status						
0	27 (53%)	29 (56%)	28 (56%)	10 (59%)	7 (47%)	10 (56%)
1	24 (47%)	23 (44%)	22 (44%)	7 (41%)	8 (53%)	8 (44%)
MSKCC risk group						
Favourable	12 (24%)	11 (21%)	12 (24%)	3 (18%)	1 (7%)	3 (17%)
Intermediate	19 (37%)	18 (35%)	19 (38%)	7 (41%)	4 (27%)	8 (44%)
Poor	20 (39%)	23 (44%)	19 (38%)	7 (41%)	10 (67%)	7 (39%)
Heng risk group*						
Favourable	8 (16%)	7 (14%)	9 (18%)	2 (12%)	1 (7%)	1 (6%)
Intermediate	32 (64%)	33 (64%)	29 (58%)	12 (71%)	10 (67%)	13 (72%)
Poor	10 (20%)	12 (23%)	12 (24%)	3 (18%)	4 (27%)	4 (22%)
Haemoglobin, n (%)						
≤130 g/L (men) or ≤115 g/L (women)	33 (65%)	36 (69%)	31 (62%)	13 (77%)	13 (87%)	11 (61%)
>130 g/L (men) or >115 g/L (women)	18 (35%)	16 (31%)	19 (38%)	4 (24%)	2 (13%)	7 (39%)
Corrected serum calcium, n (%)						
≥2・5 mmol/L	6 (12%)	8 (15%)	8 (16%)	2 (12%)	5 (33%)	4 (22%)
<2・5 mmol/L	45 (88%)	44 (85%)	42 (84%)	15 (88%)	10 (67%)	14 (78%)
Number of metastases						

1	18 (35%)	9 (17%)	5 (10%)	8 (47%)	4 (27%)	2 (11%)
2	15 (29%)	15 (29%)	15 (30%)	5 (29%)	5 (33%)	7 (39%)
≥3	18 (35%)	28 (54%)	30 (60%)	4 (24%)	6 (40%)	9 (50%)
Sites of metastasis						
Bone	12 (24%)	13 (25%)	16 (32%)	4 (24%)	4 (27%)	7 (39%)
Liver	10 (20%)	14 (27%)	13 (26%)	5 (29%)	2 (13%)	4 (22%)
Lung	27 (53%)	35 (67%)	35 (70%)	8 (47%)	9 (60%)	11 (61%)
Lymph nodes	25 (49%)	31 (60%)	33 (66%)	7 (41%)	9 (60%)	9 (50%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Centre
Data are number of patients (%), or median (range). * One patient in the lenvatinib plus everolimus group was excluded because of missing baseline laboratory values.

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/108/10

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
5	The sentence "Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy ([redacted]) and placebo ([redacted]) in favour of lenvatinib combination." has been changed to "Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy (relative risk [RR] 7.2; 95% CI: 2.3 to 22.5, direct comparison HOPE 205) and placebo ([redacted]) in favour of lenvatinib combination."
8	Results in Table A have been corrected.
9	Results in Table B have been corrected.
45	In flow diagram "Discontinued intervention (n=29)" has been changed to "Discontinued intervention (n=45)"
51	The sentence "At the pre-specified update analysis in December 2014 this had increased slightly as 66% of patients had progressed and 47% had died in the two treatment groups of interest to this appraisal." Has been changed to " At the pre-specified update analysis in December 2014 this had increased slightly as 56% of patients had progressed and 47% had died in the two treatment groups of interest to this appraisal."
69	The % of patients in the everolimus arm of REORD-1 with a poor MSKCC has been changed from 15 to 14
76	The sentence "The ITC, which informed the company base case showed [redacted] between lenvatinib combination therapy and everolimus ([redacted]), nivolumab ([redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy." has been changed to "The ITC, which informed the company base case showed [redacted] between lenvatinib combination therapy and everolimus (HR 0.40; 95% CI: 0.24 to 0.68, direct comparison HOPE 205), nivolumab ([redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy."
80	The sentence "The difference in OS was [redacted] between lenvatinib combination therapy and everolimus ([redacted]) and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1." has been changed to "The difference in OS was [redacted] between lenvatinib combination therapy and everolimus (HR 0.59; 95% CI: 0.36 to 0.97, direct comparison HOPE 205) and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1.
87	The sentence "However, the results of the ITC, using the Bucher method, [redacted] between lenvatinib combination therapy and axitinib [redacted], everolimus [redacted], nivolumab [redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy." has been changed to "However, the results of the ITC, using the Bucher method, [redacted] between lenvatinib combination therapy and axitinib [redacted]), everolimus (HR 0.40; 95% CI: 0.24 to 0.68, direct comparison HOPE 205), nivolumab ([redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy." And the sentence "The difference in OS was [redacted] between lenvatinib combination therapy and everolimus ([redacted] and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1." has been changed to "The difference in OS was [redacted] between lenvatinib combination therapy and everolimus (HR 0.59; 95% CI: 0.36 to 0.97, direct comparison HOPE 205) and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1."

88	The duplicate sentence “However, there are several first and second order curves with a similar DIC for OS.” Has been removed The sentence “Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy ([redacted]) and placebo ([redacted]) in favour of lenvatinib combination.” has been changed to “Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy (relative risk [RR] 7.2; 95% CI: 2.3 to 22.5, direct comparison HOPE 205) and placebo ([redacted]) in favour of lenvatinib combination.”
93	Table 32 updated with correct key sections of the CS.
96	Text amended to acknowledge the company’s clarification of the cost-effectiveness literature search.
102	Text added to highlight that the comparison of lenvatinib combination with everolimus in the ITC is a direct comparison.
105	Typographical error corrected.
110	Text added to highlight that the comparison of lenvatinib combination with everolimus in the ITC is a direct comparison.
117	ERG updated the AIC statistics in Table 42, following the correction to the TTD data for cabozantinib.
118	ERG updated the BIC statistics in Table 43, following the correction to the TTD data for cabozantinib.
119	ERG updated Figure 28, following the correction to the TTD data for cabozantinib.
120	Text amended to reflect the company’s clarification that the adverse events included in the model were treatment-emergent rather than treatment-related.
121	The footnote in Table 44 has been amended to reflect the adverse events included in the model, as clarified by the company. The text in Section 5.4.7.1 has also been amended to reflect the corrections.
133	Dyspnoea has been added to Table 48,
134	The duplicate of the everolimus column in Table 50 has been removed.
135-136	Hoyle et al. and Chandiwana et al studies have been added to Table 51.
141-142	The costs of adverse events in Table 60 have been corrected by the ERG to reflect the company’s described methods.
144	The total life-years have been corrected in Table 61.
147	The ICERs for the company’s scenario for the “generic everolimus cost” have been corrected to be in line with those presented by the company. A note has also been added to highlight that the results appear to be erroneous though.
148	ERG added extra detail to highlight errors with the company’s PSA results.
151-156	ERG’s results updated following corrections to the duration adjustment to adverse events as well as the TTD data for cabozantinib.
159	The sentence “The ORR was higher for patients treated with lenvatinib combination therapy compared with nivolumab, cabozantinib, axitinib, everolimus and placebo, although only the difference to the last two were statistically significant.” has been changed to “The ORR was

	higher for patients treated with lenvatinib combination therapy compared with everolimus (direct comparison HOPE 205), nivolumab, cabozantinib, axitinib and placebo, although only the difference to the last two were statistically significant.”

[redacted]

Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy (relative risk [RR] 7.2; 95% CI: 2.3 to 22.5, direct comparison HOPE 205) and placebo [redacted] in favour of lenvatinib combination. The difference between lenvatinib combination therapy and nivolumab [redacted], cabozantinib [redacted] and axitinib [redacted] also favoured lenvatinib combination therapy, [redacted].

There was [redacted] in the proportion of patients experiencing at least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib based on the ITC [redacted]. A higher proportion of patients experienced at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted]. There was [redacted] in discontinuation due to AEs between lenvatinib combination therapy and cabozantinib ([redacted]), but [redacted] patients discontinuing treatment due to AE with the lenvatinib combination therapy compared with nivolumab ([redacted]) and placebo ([redacted]).

1.3 Summary of cost effectiveness evidence submitted by the company

The company submitted a *de novo* economic model to assess the cost effectiveness of lenvatinib in combination with everolimus compared to everolimus monotherapy, axitinib, cabozantinib and

Table A. Results of the ERG preferred base case (Pairwise)

Results per patient	Lenvatinib comb. (1)	Axitinib (2)	Cabozantinib (3)	Everolimus (4)	Nivolumab (5)	Incremental values			
						(1-2)	(1-3)	(1-4)	(1-5)
Company's corrected base case									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER						28,433	Dominated	110,355	Dominated
ERG's preferred survival curves: Best fitting fractional polynomials for OS and PFS, and 2-knot spline for TTD									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**56,063**	**Dominated**	**74,239**	**Dominated**
ICER with all changes incorporated						**56,063**	**Dominated**	**74,239**	**Dominated**
Subsequent treatment costs based on trials									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**27,915**	**Dominated**	**110,223**	**Dominated**
ICER with all changes incorporated						**55,351**	**Dominated**	**74,110**	**Dominated**
ERG's preferred base case ICER						**55,351**	**Dominated**	**74,110**	**Dominated**
Abbreviations in the table: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year									

Table B. Results of the ERG preferred base case (Incremental)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,110
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The ERG considers the systematic review methods used by the company to be appropriate, suitable eligibility criteria were applied by the company and all relevant clinical efficacy studies relating to lenvatinib and the comparators listed in the NICE final scope are likely to have been identified.

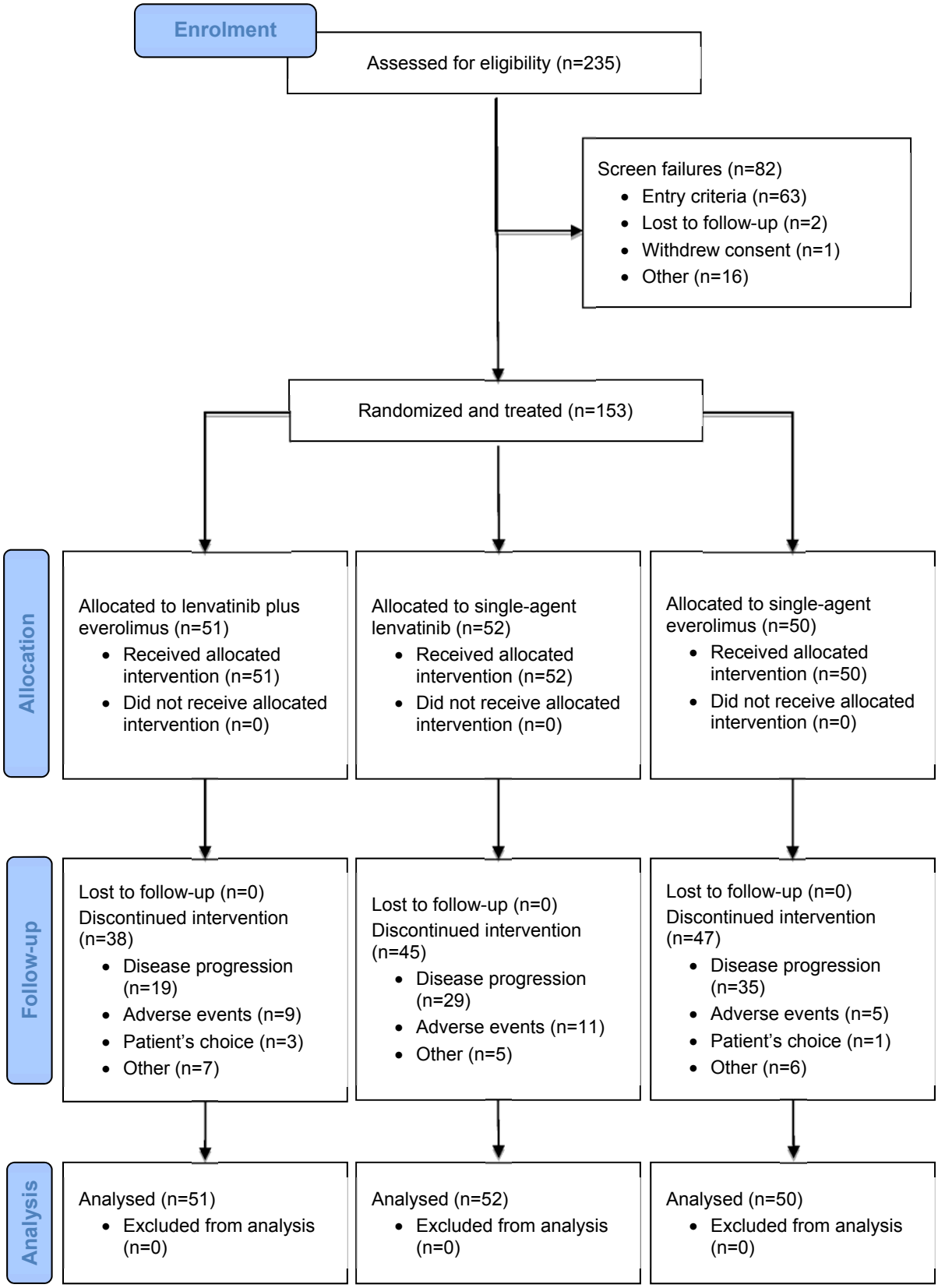
Overall, the ERG considers the trial, HOPE 205, to be largely well conducted and the statistical analyses to be appropriate. A third of the trial population was recruited from the UK and the baseline characteristics of the UK patients were similar to the full trial population, which the ERG and its clinical experts consider to be representative of patients in UK clinical practice eligible for treatment with lenvatinib combination therapy, although, as in trials in general, they represent the slightly younger and fitter proportion of patients found in clinical practice.

All relevant comparators as specified in the NICE final scope for this STA were considered within the CS.

Economic

The economic analysis performed by the company was reasonably well presented in the CS. The economic model design was sound and the ERG did not have any major difficulty in validating the model. A few errors were identified but the company clarified and corrected these issues.

Figure 6. CONSORT Flow diagram HOPE 205 (CS, clarification response C6)



All outcomes were investigator assessed although the regulatory agencies EMA and FDA requested *post-hoc* IRR of PFS and response data. The patient's baseline characteristics appear relatively well balanced between the trial arms, though some differences potentially indicate a poorer prognosis for the everolimus group compared with patients randomised to lenvatinib combination therapy. However, the number of patients are very small and the potential impact of the differences should be interpreted with caution. A third of the trial population was recruited from the UK and the baseline characteristics of the UK patients are similar to the full trial population. Based on the baseline characteristics, the full trial population is representative of patients in UK clinical practice, although they represent the slightly younger and fitter proportion of patients found in clinical practice. The primary outcome in HOPE 205 was PFS; other outcomes assessed in the trial included OS, tumour response, and safety. ITT analyses were performed for all efficacy outcomes and adverse events were analysed using the Safety Analysis Set.

Overall, the ERG considers the trial to be largely well conducted and the statistical analyses to be appropriate. However, the ERG is concerned about the small sample size of the study, which introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy. In addition, the ERG is concerned about the open label design and the lack of blinded outcomes assessment of PFS and tumour response, which was only done retrospectively on the request of EMA/FDA. The ERG also notes that HRQoL, one of the outcomes of interest listed in the scope, was not captured in HOPE 205.

Clinical effectiveness results HOPE 205

This section describes the results of HOPE 205, the only trial identified by the company that provides direct evidence of the clinical effectiveness of lenvatinib combination therapy.

Data in HOPE 205 were analysed at several different time points, summarised in Table 12. The ERG notes that the primary analysis took place June 2014, the same time as recruitment closed, and hence minimum follow up was close to none. At this time point 62% of patients had progressed and 45% had died in the combination and everolimus monotherapy groups. At the pre-specified update analysis in December 2014 this had increased slightly as 56% of patients had progressed and 47% had died in the two treatment groups of interest to this appraisal. At the OS analysis in July 2015, requested by the EMA and FDA, 68% had died and minimum follow up was around 12 months. The difference between the EMA and FDA analyses of PFS (investigator assessed, data cut June 2014) and OS (data cut July 2015) lies in the use of different stratification variables: the IVRS (interactive voice recording system) dataset was used for the FDA while CRF (case report form) data was used for the EMA. At the clarification stage the company provided more details about the impact of the different analyses: "The FDA requested that, for the calculation of the HRs (hazard ratios) of PFS and OS, the stratification

Table 26. Summary of baseline characteristics in trials included in the network (adapted from CS, Appendix 8.5, Table 3.1.1)

Study	Treatments	Age, median	Male %	Ethnicity white %	ECOG/Karnofsky performance status[a] %			MSKCC %		
					0/90-100	1/70-80	2/<70	Favourable	Intermediate	Poor
AXIS	Axitinib	61	73	77	54	45	<1	28	37	33
	Sorafenib	62	71	74	55	44	0	28	36	33
CheckMate 025	Nivolumab	62	77	86	68	32	<1	35	49	16
	Everolimus	62	74	89	65	35	<1	36	49	15
HOPE 205	Lenvatinib combination therapy	61	69	NR	53	47	-	24	37	39
	Everolimus	59	76	NR	56	44	-	24	38	38
METEOR	Cabozantinib	63	77	82	68	32	-	45	42	12
	Everolimus	62	73	80	66	34	-	46	41	13
RECORD-1	Everolimus	61	78	NR	63	36	-	29	56	14
	Placebo	60	76	NR	68	33	-	28	57	15
TARGET	Sorafenib	58	70	NR	49	49	2	52	48	-
	Placebo	59	75	NR	46	52	1	51	49	-

Abbreviations: NR, not reported; MSKCC, Memorial Sloane Kettering Cancer Center Risk Score

For all outcomes the latest data cut reported for each study was used in the ITC.

For the fractional polynomial NMA the company digitalised the published KM curves for OS and PFS for CheckMate 025 and METEOR and used individual patient data (IPD) for HOPE 205.

4.4.4 Results

4.4.4.1 PFS

ITC - Bucher method

The company acknowledges that number and type of prior therapy, as well as independent or investigator assessment of response may impact PFS, but conducted the ITC of lenvatinib combination therapy versus the other treatments despite these differences as they did not substantially modify the HRs within the everolimus trials (HOPE 205, CheckMate 025, METEOR, RECORD-1). The ERG notes that the PHs assumption does not hold for all trials in the network, and as no meaningful conclusions can be drawn from the HRs from these trials, using the Bucher method will only propagates this flaw into the ITC results and it is therefore inappropriate.

The ITC, which informed the company base case showed [redacted] between lenvatinib combination therapy and everolimus (HR 0.40; 95% CI: 0.24 to 0.68, direct comparison HOPE 205), nivolumab [redacted]), and placebo ([redacted]) favouring lenvatinib combination therapy. There was [redacted] in PFS between lenvatinib combination therapy and cabozantinib ([redacted]). Based on this analysis lenvatinib combination therapy may also be superior to axitinib, but the company highlights that this result should be interpreted with caution due the prior therapy for patients in TARGET being primarily cytokines rather than one prior VEGF-targeted therapy. The ERG highlights that the assumption of PHs is not fulfilled for PFS in CheckMate 025, TARGET, and potentially METEOR and so no meaningful conclusions can be made including these trials in an analysis based on PHs. However, if the PHs assumption would have been fulfilled for all comparisons within the network, the ERG's preferred analysis would have been independent assessment for all trials and one prior VEGF-targeted therapy where possible, the exclusion of TARGET, and hence axitinib, from the network due to the lack of prior VEGF-targeted therapies and insufficient crossover adjustment.

Table 28. Indirect treatment comparisons of progression-free survival: hazard ratio (95% CI) for lenvatinib combination therapy versus other treatments (CS, page 72, Figure 39)

Treatment	Main analysis as reported by trial[a,b]	Independent assessment[b]	One prior VEGF[a]	Prior sunitinib[a]
Everolimus [c]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

4.4.4.2 OS

ITC - Bucher method

The ITC, based on the Bucher method and the assumption of PHs, which informed the company base case showed [redacted] between lenvatinib combination therapy and nivolumab ([redacted]), cabozantinib ([redacted]) or axitinib ([redacted]) based on the primary analyses using full trial populations (variety of prior therapies) and ITT analysis (ignoring crossover). The difference in OS was [redacted] between lenvatinib combination therapy and everolimus ([redacted], direct comparison HOPE 205) and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1. The company points out that the results for the multi-step indirect comparison of lenvatinib combination therapy and axitinib should be interpreted with caution. The ERG highlights that the assumption of PHs is not fulfilled for OS in CheckMate 025 and TARGET and hence no meaningful interpretation of HRs can be made between lenvatinib combination therapy and nivolumab or axitinib. However, if the PHs assumption would have been fulfilled for all comparisons within the network, the ERG's preferred analysis would have been one prior VEGF-targeted therapy where possible, and the exclusion of TARGET, and so axitinib, from the network due to the lack of prior VEGF-targeted therapies and insufficient crossover adjustment. The ERG notes that the company's primary analysis ignores crossover but that crossover adjusted data for RECORD-1 (everolimus versus placebo) and TARGET (sorafenib versus placebo) are reported by the company in the footnote of Table 29.

being fulfilled. However, the PHs assumption does not hold for PFS in CheckMate 025, METEOR and TARGET, and for OS in CheckMate 025 and TARGET. Therefore, the company re-assessed PFS and OS in a Bayesian NMA using fractional polynomials, which does not rely on the PHs assumption being fulfilled. For the NMA the company assumed that axitinib and everolimus monotherapy have similar efficacy.

- The company's primary analyses were based on the full populations and the primary analysis for all trials irrespective of number and type of prior therapy, and investigator or independent outcome assessment.

- The ERG highlights that no meaningful interpretation of the resulting HRs and 95% CIs for PFS can be made between lenvatinib combination therapy and nivolumab or axitinib as the PHs assumption does not hold. However, the results of the ITC, using the Bucher method, [redacted] between lenvatinib combination therapy and axitinib [redacted], everolimus (HR 0.40; 95% CI: 0.24 to 0.68, direct comparison HOPE 205), nivolumab [redacted], and placebo ([redacted]) favouring lenvatinib combination therapy. There was [redacted] in PFS between lenvatinib combination therapy and cabozantinib.

- The ERG tested how well the model captures the underlying PFS KM data as a FP curve, which showed a good fit for both trial arms in CheckMate 025 and the everolimus group in HOPE 205, but potentially an overestimate of PFS in the lenvatinib combination group in the same trial.

- [redacted] The ITC, based on the Bucher method, showed [redacted] in OS between lenvatinib combination therapy and nivolumab ([redacted]), cabozantinib ([redacted]) or axitinib ([redacted]) based on the full trial populations (variety of prior therapies) and ITT analysis (ignoring cross-over). The difference in OS was [redacted] between lenvatinib combination therapy and everolimus (HR 0.59; 95% CI: 0.36 to 0.97, direct comparison HOPE 205) and placebo ([redacted]) based on the ITT analysis (ignoring crossover) of RECORD-1.

- [redacted]The ERG tested how well the model captures the underlying OS KM data, which showed a good fit for both trial arms in both CheckMate 025 and HOPE 205. However, there are several first and second order curves with a similar DIC for OS. The ERG's inspection of the different curves shows that only one other fractional polynomial provides plausible curves.

- Based on the indirect treatment comparison (ITC) using the Bucher method, there was [redacted] in ORR between lenvatinib combination therapy and everolimus monotherapy (relative risk [RR] 7.2; 95% CI: 2.3 to 22.5, direct comparison HOPE 205) and placebo [redacted] in favour of lenvatinib combination. The difference between lenvatinib combination therapy and nivolumab [redacted], cabozantinib [redacted] and axitinib [redacted] also favoured lenvatinib combination therapy, [redacted].

- There was [redacted] in the proportion of patients experiencing at least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib based on the ITC [redacted]. A higher proportion of patients experienced at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted]. There was [redacted] difference in discontinuation due to AEs between lenvatinib combination therapy and cabozantinib ([redacted]), but [redacted] patients discontinuing treatment due to AE with the lenvatinib combination therapy compared with nivolumab ([redacted]) and placebo ([redacted]).

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft® Excel based economic model. Table 32 summarises the location of the key economic information within the company's submission (CS).

Table 32. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.1
Population	5.2
Interventions and comparators	5.2
Model approach and model structure	5.2
Treatment duration	5.2
Treatment effectiveness	5.3
Health-related quality of life	5.4
Adverse events	5.4
Resource use and costs	5.5
Summary of base case inputs	5.6
Base case results	5.7
Sensitivity analyses	5.8
Scenario analyses	5.8
Subgroup analyses	5.9
Validation	5.10
Interpretation and conclusions	5.11
Abbreviations used in table: CS, company's submission.	

5.2 Summary of the company's key results

The company's deterministic base case results are given in Table 33 and the results of the probabilistic sensitivity analysis are given in Table 34.

Table 33. Results of company's base case analysis (Clarification responses document)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
LEN+EVE	[redacted]	[redacted]	[redacted]	–	–	–	–
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,971
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,167
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,299
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,404

approved by the European Medicines Agency in July 2006, this restriction was considered appropriate and sufficient to capture all the relevant cost-effectiveness studies within this patient population." The ERG considers this to be reasonable. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

Initially, the ERG identified some economic evaluation studies in non-UK settings that had been captured by the company's literature search for randomised clinical trials described in Section 4.1.1, yet had not been captured in the search for cost-effectiveness studies. In response to clarification questions, the company identified that part of the SLR Appendix had inadvertently not initially been sent and then provided this information which showed that the studies identified by the ERG had indeed been captured in the search for cost effectiveness studies.

5.4 Overview and critique of company's economic evaluation

The company submitted a *de novo* economic model to assess the cost effectiveness of lenvatinib in combination with everolimus compared to current NICE approved treatments for previously treated RCC; that is, axitinib, cabozantinib, everolimus monotherapy, and nivolumab.

The company's base case analysis relies on an indirect treatment comparison (ITC) to estimate the relative treatment effectiveness between lenvatinib combination therapy and axitinib, cabozantinib and nivolumab, respectively, due to the absence of direct head-to-head clinical trials. This NMA assumes that hazard rates for PFS and OS between each of the comparator treatments are proportional to each other, which has been demonstrated in previous technology appraisals to be an invalid assumption.[51] This led to the ERG's request during the clarification stage for the company to consider an alternative approach for estimating relative differences in PFS and OS, and the company provided a scenario analysis to incorporate a different approach, which avoided this assumption but did not consider it as their base case analysis. This is discussed in detail in Section 5.4.5.

Another key issue with the methods used by the company is the inconsistency in the treatment effectiveness measures used for the treatments in the HOPE 205 trial and those applied for the additional treatments in the ITC. For both PFS and OS, the company estimated treatment effects for the comparators relative to the lenvatinib combination therapy group. However, for the everolimus group, the KM data are used directly from the trial, which results in curves with a greater hazard rate than if the everolimus HR ratio from the ITC was applied to the lenvatinib combination group curve. This inconsistency leads to an implausible set of survival curves for PFS, in which the risk of progression for nivolumab is at times greater than that for everolimus. This contradicts the results of the CheckMate 025 trial [38]and, therefore, causes the results to be unreliable. For the scenarios based on parametric survival curves, the risk of progression for nivolumab is always greater than for everolimus as the HR between lenvatinib combination and everolimus monotherapy derived from the fitted Weibull model is greater than that derived in the ITC (direct comparison, HOPE 205).

The ERG noted a contradiction in the company's submission that stated that treatment was assumed to continue until progression, while stating elsewhere that it was based on time to treatment discontinuation (TTD) from the HOPE 205 trial. The ERG can clarify that the latter was the approach used in the company's submitted base case model. The model also contained an inaccuracy in the calculation of QALYs relating to the use of the TTD data, in that the model applied a pre-progression on-treatment utility (capturing AE differences) for all patients on-treatment, regardless of progression status, and the off-treatment utility is applied to the difference in TTD and PFS. This calculation is correct if treatment is discontinued at or before progression, however, the data used in the model

Dimension of quality	Comments
D2: Pre-model data analysis	Survival analysis was performed for the head-to-head trial data for lenvatinib combination and everolimus monotherapy in order to extrapolate the outcomes of OS and PFS. In the company's base case analysis, the company applies HRs to estimate outcomes for the remaining treatments.
D2a: Baseline data	Baseline data for PFS and OS were informed by the HOPE 205 trial and were considered to be reflective and appropriate for the model population.
D2b: Treatment effects	Treatment effectiveness data for lenvatinib combination therapy and everolimus monotherapy was obtained from the HOPE 205 trial. A network meta-analysis was carried out to estimate the survival curves of axitinib, cabozantinib and nivolumab. The company's base case analysis estimated relative treatment effects for OS and PFS in an ITC. This approach requires hazard rates for each outcome in each trial to be approximately proportional, which is not the case for all trials in the network. The ERG requested an alternative approach that did not require this assumption to hold and the company then produced an analysis based around a NMA of survival curves based on fractional polynomial hazard functions. This was presented as a scenario analysis.
D2c: Costs	All costs were clearly stated. Resource use is estimated for the base case analysis mainly based on the feedback from the NICE appraisal committed in TA333 assessing axitinib and were validated by the company's clinical experts. NHS England National Tariffs and PSS costs were used where available, in line with the NICE reference case.
D2d: Quality of life weights (utilities)	The HSUVs for all health states are based on utility values elicited in the AXIS trial, and are applied to each treatment assuming that there is no treatment related differences. These values have been used in three previous technology appraisals and were considered to be reflective of the values of the advanced RCC population encountered in UK clinical practice by the committee. Disutilities associated with AEs were obtained from a range of studies identified through systematic literature review. These additional sources were not considered to be reliable by the ERG, as they were not generalisable to the RCC population. The AEs that were included in the model were those identified by the company's clinical experts as having a significant impact on quality of life or costs. The incidence of AEs were based on the HOPE 205 trial.
D3: Data incorporation	The company chose to use KM data directly to inform the model, with parametric survival curves used only to inform the extrapolation. The ERG considered it preferable to use the parametric curve for the entire time horizon to avoid the need for an adjustment to the extrapolation to fit the tail of the KM curve. The ERG considers this to cause an inconsistency in the assessment of the best fitting parametric curve.
Assessment of uncertainty	
D4a: Methodological D4b: Structural	Methodological and structural uncertainty was adequately explored in the model, for the trial duration. The electronic model allowed provided several options to allow varying methodological and structural assumptions. One limitation was that the model didn't allow for treatment beyond progression.
D4c: Heterogeneity	The economic analysis is based on the ITT populations of all the relevant clinical trials and no subgroup analyses were performed to assess differences in baseline characteristics.
D4d: Parameter	Parametric uncertainty was explored through deterministic sensitivity analyses and a probabilistic sensitivity analysis around the base case. However, some parameters that the ERG considered to be important were not included in these analyses.
Consistency	
C1: Internal consistency	There was an error in the use of treatment unit costs for everolimus monotherapy, which the company corrected following clarification questions, as well as an error in the calculation of QALYs, which led to a proportion of patients post progression having a utility relating to pre-progression.

5.4.5.1 ERG critique

The ERG considers the methods used for the estimation and extrapolation of PFS and OS to have potentially serious flaws that result in implausible model outcomes and, therefore, potentially unreliable results of cost-effectiveness.

The key issues stem from the assumption that the hazard rates for each treatment are proportional for both PFS and OS. From the on-going cabozantinib STA (GID-TA10075), the ERG considered the TARGET trial, providing a link between axitinib and everolimus in the NMA, to show hazard rates that were not proportional across the entire trial follow-up period for both PFS and OS, and so deriving a HR between the two from the ITC would be flawed, leading to inaccurate PFS and OS estimates.[42, 51] The ERG considers a more appropriate approach to be to assume that axitinib has equal efficacy to everolimus, allowing a simplified network to be used to estimate the remaining HRs, for which a proportional hazards assumption is reasonable. A similar assumption has been made in previous NICE technology appraisals.[70-72]

Another issue, which may be caused by the violation of proportional hazards in the network, relates to the inconsistency of the relative treatment effect derived from the fitted dependent Weibull curves for PFS, and the PFS HRs derived from the ITC for the same comparison of lenvatinib combination versus everolimus monotherapy (direct comparison, HOPE 205). This results in a fitted everolimus Weibull PFS curve that has a lower hazard rate than the nivolumab Weibull curve generated by applying the ITC-derived PFS HR to the lenvatinib combination Weibull curve. This contradicts the results of the CheckMate 025 trial comparing nivolumab with everolimus, and is therefore implausible.[38] he everolimus monotherapy and nivolumab curves derived by the company based on the dependently fitted Weibull model are shown in Figure 22.

The HRs derived for PFS for lenvatinib combination versus everolimus and nivolumab, respectively, from both the Weibull model and the ITC are given in Table 39, showing the discrepancy caused by combining treatment effects from alternative methods.

Table 39. Comparison of PFS HRs from Weibull model and ITC for lenvatinib combination versus everolimus and nivolumab, respectively.

HRs	Weibull	ITC
Everolimus	[redacted]	[redacted]
Nivolumab	-	[redacted]
Abbreviations in table: HR, hazard ratio; ITC, indirect treatment comparison.		

company for the cabozantinib STA.[51] The extrapolation in the published plot was only given up to 36 months, and so the company used an exponential extrapolation to extend the curve beyond 36 months. The company provided little justification for this approach, and, in particular, the ERG is unclear whether the exponential curve was fitted to the digitisation of the KM and gamma digitisation or if an alternative curve was used, e.g. the curves fitted to the HOPE 205 trial. The ERG considers a better approach to fit models to the digitised KM data alone and use the extrapolation derived from the best fitting curve.

The ERG performed their own digitisation of the TTD plots and used this data to fit survival curves using R.[74] To do this, pseudo individual patient data (IPD) were estimated using the digitised data, which was inputted into the algorithm described by Guyot *et al.*2012, as used by the company.[75] The pseudo-IPD data generated from this algorithm was then used in the *flexsurv* package of R to fit a range of standard parametric survival curves (exponential, Weibull, Gompertz, generalised Gamma, log-logistic, log-normal, generalised F and a range of splines with 1, 2 and 3 knots, respectively).[76] These were assessed for goodness-of-fit using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, as well as assessing the visual fit of the curves.

The ERG considers the log-normal distribution and the 2-knot spline to provide the best fitting curves based on the AIC and BIC statistics in Table 42 and Table 43, and on visual inspection both appear reasonable. The key difference can be seen in

Figure 26, showing that the spline appears to have a better fit to the lenvatinib KM data that the lognormal does. The spline was therefore used in the ERG's preferred base case. The ERG also included a scenario analysis that used the lognormal curve and this is presented in Section 6.4. The lognormal and spline TTD curves for each treatment can be seen in Figure 26 to Figure 29.

Table 42. AIC statistics for TTD curves fits

AIC	Lenvatinib combination	Everolimus	Cabozantinib	Nivolumab
Exponential	338	288	2052	2569
Generalised F	343	290	2014	2527
Generalised gamma	341	288	2014	2525
Gompertz	339	289	2053	2566
Log-logistic	343	287	2013	2534
Log-normal	341	**286**	**2013**	2524
1-knot spline	340	288	2017	2524
2-knot spline	**338**	290	2017	**2521**
3-knot spline	338	292	2017	2523
Weibull	339	290	2045	2570

Table 43. BIC statistics for TTD curves fits

BIC	Lenvatinib combination	Everolimus	Cabozantinib	Nivolumab
Exponential	**340**	**290**	2056	2573
Generalised F	350	297	2029	2543
Generalised gamma	346	293	2026	2537
Gompertz	343	293	2061	2574
Log-logistic	347	291	2020	2542
Log-normal	344	290	**2020**	**2532**
1-knot spline	346	294	2029	2536
2-knot spline	345	297	2033	2537
3-knot spline	348	301	2036	2543
Weibull	343	293	2054	2578

Figure 26. Lenvatinib combination fitted TTD curves

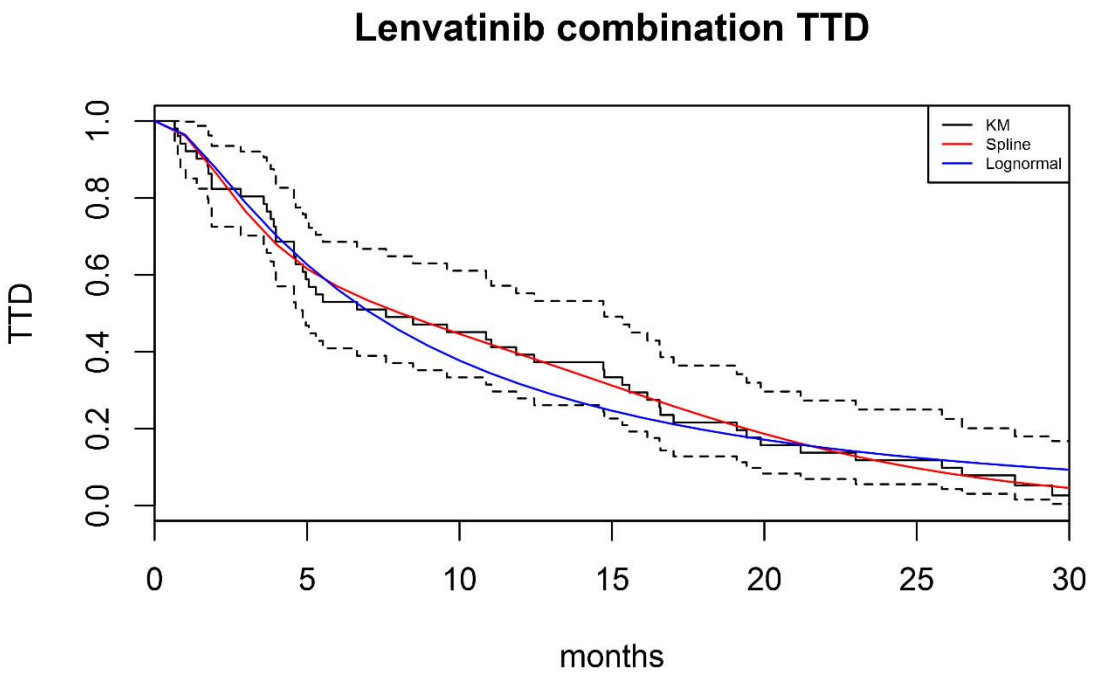


Figure 27. Everolimus fitted TTD curves

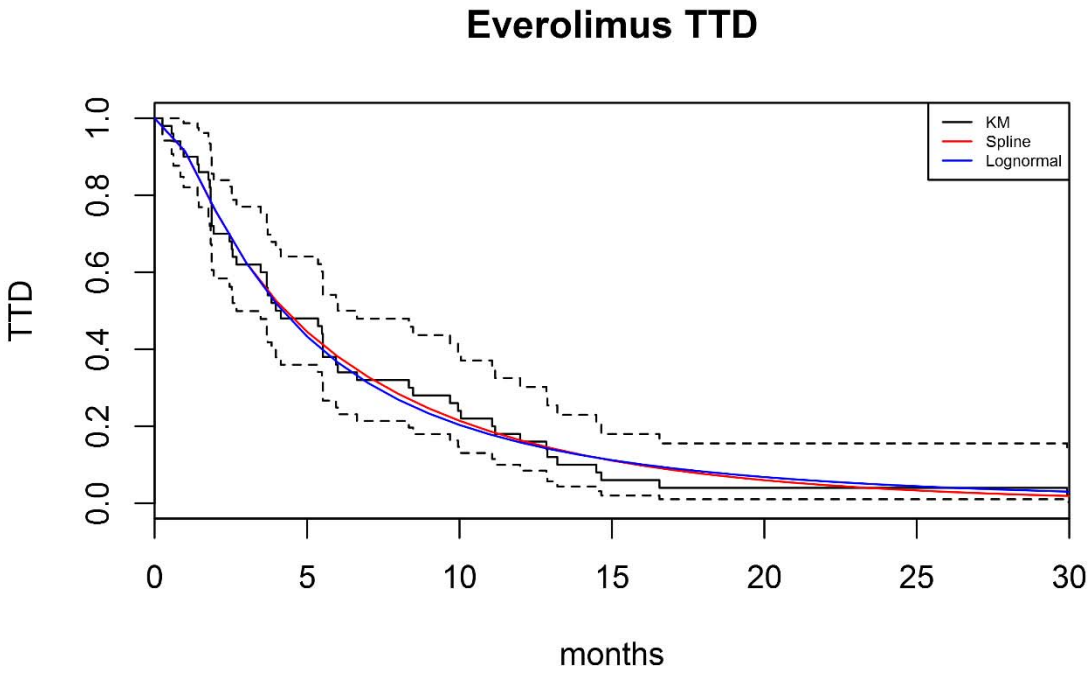


Figure 28. Cabozantinib fitted TTD curves

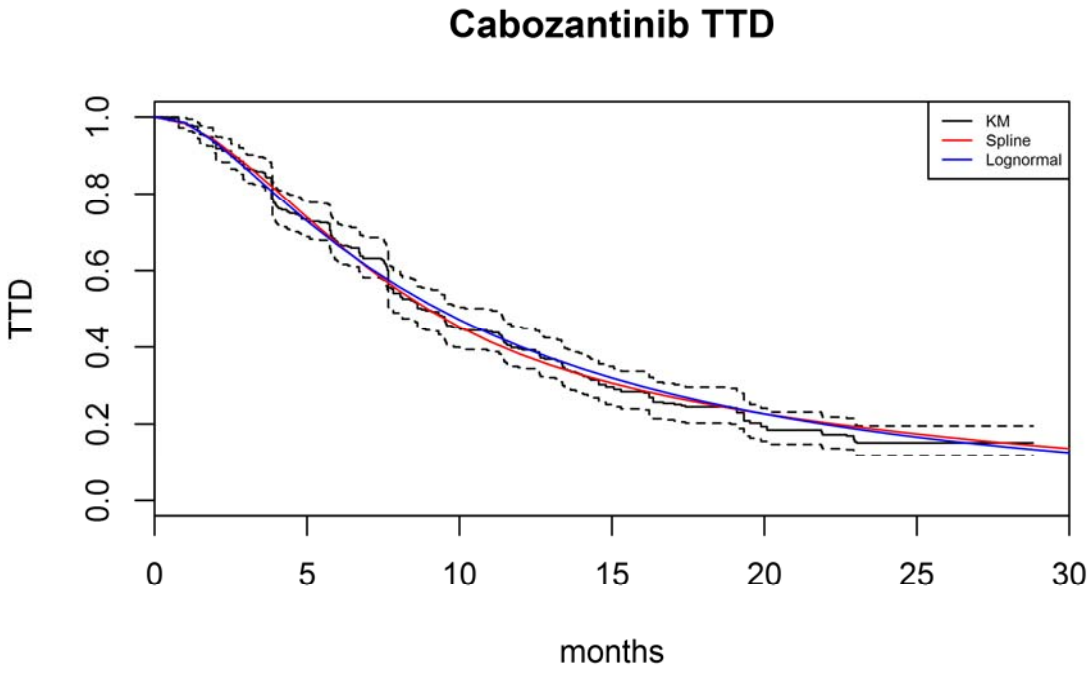
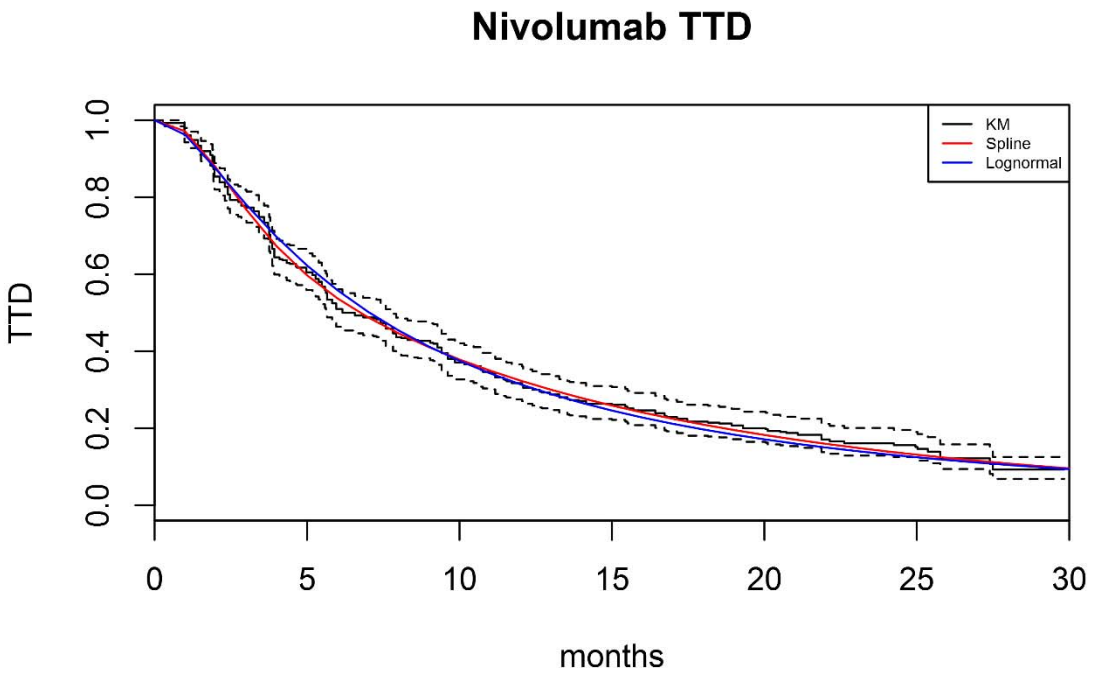


Figure 29. Nivolumab log-normal fitted curve



5.4.7 Adverse events

The company included Grade 3 and higher adverse events that are considered to have an impact on patients' quality of life based on feedback from their clinical experts. The following treatment-emergent adverse events (TEAEs) are included in the model: diarrhoea, fatigue/asthenia, vomiting, nausea, hypertension, decreased weight, stomatitis and dyspnoea.

The company reports that the rates used in the model are based on the rates observed in the respective trials as summarised in Table 44. The duration of adverse events assumed in the model are reported in Table 45, and are based on the durations observed in the HOPE 205 trial.

Table 44. Rates of adverse events assumed in the model (CS, Figure 89, pg 155)

Adverse events	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%

Sources: LEN+EVE (Eisai Ltd, 2015), Everolimus (Eisai Ltd, 2015), Axitinib (Motzer *et al.* 2013), Cabozantinib (Choueiri *et al.* 2016), Nivolumab (Motzer *et al.* 2015)
Note: All prevalence values reported are for treatment emergent adverse events, except for axitinib and nivolumab which are treatment-related adverse events.

Table 45. Duration of adverse events

Adverse event	Duration in days	Source
Diarrhoea	25.51	HOPE 205 trial
Fatigue/Asthenia	49.39	
Vomiting	10.11	
Nausea	34.79	
Hypertension	28.34	
Decreased Weight	49.59	Assumed equal to decreased appetite (NCT01136733)
Stomatitis	37.48	HOPE 205 trial
Dyspnoea	33.56	

The costs of managing adverse events were included in the model, and a quality of life decrement was also applied when patients experience adverse events as described in Section 5.4.9.4 and Section 5.4.8, respectively.

5.4.7.1 ERG critique

The ERG considers the company's approach to incorporating the impact of adverse events in the model to be reasonable, and the ERG's clinical experts confirmed that all relevant adverse events have been included. The ERG identified a discrepancy in the rates of Grade 3 or 4 fatigue/asthenia experienced by patients receiving everolimus in the HOPE 205 trial relative to previous trials that included everolimus as a comparator. Patients receiving everolimus in the HOPE 205 trial did not experience Grade 3 or 4 fatigue/asthenia, but in the RECORD-1 and METEOR trials, Grade 3 fatigue/asthenia was observed in 4% and 9% of patients in the everolimus group, respectively.[37] [36] It is unclear to the ERG what would cause this observed difference

5.4.8.2 Health state utility values used in the model

The company assumes that the quality of life of patients changes according to progression status and whether or not patients experience adverse events. The company reports that the HSUVs used in the base case analysis are based on EQ-5D data collected in the AXIS trial as reported in the CS for the technology appraisal of axitinib as a second-line treatment for RCC (TA333).[57]

EQ-5D data in the AXIS trial was collected at screening, and then every 4 weeks of therapy, at the end of study treatment, and at follow-up (28 days after end of treatment). For the progression-free health state, the mean of the utility estimates at each time point of the trial were weighted by the number of patients still on treatment at that time point, while for progressed disease it was the weighted average of the mean utility at the end of treatment. The mean utility values estimated for the progression-free and the progressed health states in TA333 were 0.69 and 0.61, respectively.[57]

Patients across the treatment arms in the model are assumed to have a utility value of 0.69, when they have stable disease and are not experiencing adverse events. A utility decrement is then deducted from this for patients experiencing Grade 3 or higher adverse events, in order to reflect the impact of the different safety profiles of each treatment on quality of life. The utility decrements assumed for the adverse events are summarised in Table 48, while the rates of adverse events for each treatment and the total disutility are presented in Table 49. The company reports that the rates used are based on the respective clinical trials, as described in Section 5.4.7.

Table 48. Utility decrements assumed for adverse events

Health state	Mean utility	Disutility of AEs	Source of disutility
Stable with no AE	0.692	NA	N/A
Progressive	0.610	NA	
Stable with diarrhoea Grade III+	0.465	-0.227	Swinburn 2010[86]
Stable with fatigue Grade III+	0.514	-0.178	
Vomiting Grade III+	NR	-0.030	Shiroiwa 2009[87]
Stable with nausea Grade III+	0.470	-0.222	Swinburn 2010[86]
Stable with hypertension Grade III+	0.559	-0.133	
Decreased Weight Grade III+	NR	-0.038	Hudgens 2014 (Using decreased appetite as a proxy)[88]
Stomatitis Grade III+	NR	-0.040	Shiroiwa 2009[87]
Dyspnoea	NR	-0.050	Doyle 2008

Abbreviations in table: AE, adverse event; NA, not applicable; NR, not reported.
Note: Cited as Shabaruddin, n.d. in the CS, which is a systematic literature review and the original source of these values is Shiroiwa 2009.

Table 49. Total disutility estimation (CS, pg 152, Figure 85)

Adverse event	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Adverse events prevalence					
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%
Disutility	**-0.013**	**-0.003**	**-0.010**	**-0.011**	**-0.002**
Abbreviations in table: LEN+EVE, lenvatinib in combination with everolimus.					

Table 50. HSUVs used in base case analysis (CS, pg 152, Figure 86)

HSUVs	Lenvatinib combination	Everolimus	Axitinib	Cabozantinib	Nivolumab
Stable disease state with treatment	0.68	0.69	0.68	0.68	0.69
Stable disease state without treatment	0.69	0.69	0.69	0.69	0.69
Progressive state	0.61	0.61	0.61	0.61	0.61
Abbreviations in table: LEN+EVE, lenvatinib in combination with everolimus.					

The company also carried out a scenario analysis using HSUVs from a vignette study by Swinburn *et al*. 2010 and the results of the analysis are reported in Section 5.5.[86]

5.4.8.3 ERG critique

The company's utilities in the base case analysis for stable disease without adverse events, and progressed disease are based on values from the AXIS trial, that were used in the axitinib Single Technology Appraisal (TA 333) and in subsequent submissions to NICE. The ERG considers this approach to be reasonable as based on previous evaluations the population in the AXIS trial is considered to be reflective of the patient population encountered in UK clinical practice.

The company goes on to assume a utility decrement for patients when they experience adverse events. The ERG notes that the utility value of 0.69 already includes the impact of adverse events on quality of life and, therefore, there is going to be double counting in terms of decrements, for axitinib at least. However, the company's approach in assuming that all patients start with a value of 0.69, and using the proportions of adverse events experienced in the trials is fair and should reflect the difference in safety profiles across the treatments.

The utility decrements for adverse events used by the company were obtained from the company's submission for TA333 and two published quality of life studies. [57, 87, 88] The company cites the systematic literature review by Shabaruddin *et al*. as the source of utility decrements used for vomiting and stomatitis in the model. The original source of the decrements reported in Shabaruddin *et al.* is a vignette study carried out in a Japanese population by Shiroiwa *et al*. to estimate HSUVs for patients with colorectal cancer. The ERG disagrees with the use of values elicited Shiroiwa *et al.* for more than one reason. The values in Shiroiwa *et al*. are based on data collected from members of the general population and not from patients experiencing the health state as stipulated by the NICE Reference Case.[89] Furthermore, the estimates were elicited for patients with colorectal cancer and not renal cancer which may not be generalisable to patients with RCC. The ERG explores the impact of removing utility decrements due to adverse events in a scenario analysis, and the results of this scenario are reported in Section 6.2.

The ERG identified an error in terms of the QALY calculations, which the company corrected during the clarification stage. A proportion of patients can continue to receive treatment beyond progression. However, the utility value of 'stable disease on treatment' was applied to all patients on treatment instead of the value for 'progressed patients. The ERG corrected this as described in Section 6.1.

5.4.9 Resources and costs

The company reviewed the studies identified by the systematic literature described and critiqued in Section 5.3 for estimates of resource use and costs in for the management of advanced RCC following one prior VEGF-targeted therapy: The studies presented in Table 51 are studies considered by the company to include relevant data on resource use and costs. The studies have been summarised previously in Table 36 of Section 5.3.

Table 51. Studies identified by systematic literature review that include resource use estimates and costs (adapted from CS, pg 157, Figure 91)

	Studies
1	NICE (2011). "Everolimus for the second-line treatment of advanced RCC (TA219)". HTA submission. https://www.nice.org.uk/guidance/ta219.
2	Review of NICE TA219: Pitt, M, Crathorne, L, Moxham, T, Bond, M and Hyde, C (2010) "Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: a critique of the submission from Novartis (Structured abstract)." Health Technology Assessment Database(3): 41.
3	NICE (2015). "Axitinib for treating advanced RCC after failure of prior systemic treatment (TA333)". HTA submission. https://www.nice.org.uk/guidance/ta333.
4	Riemsma R, Al M, Corro Ramos I, Deshpande S et al. (2012). "Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment: a Single Technology Appraisal." York:Kleijnen Systematic Reviews Ltd (October 2012)
5	NICE (2016). "Nivolumab for treated or metastatic renal cell carcinoma [ID853]". HTA submission. https://www.nice.org.uk/guidance/gid-ta10037/consultation/html-content
6	SMC (2013). "Axitinib (Inlyta) resubmission 855/13 SMC Advice. http://www.scottishmedicines.org.uk/SMC_Advice/Advice/855_13_axitinib_Inlyta/axitinib_Inlyta_Resubmission

7	SMC (2007). “Sunitinib 50mg capsule (Sutent) 343/07 SMC advice” https://www.scottishmedicines.org.uk/files/sunitinib_Sutent_MRCC_343_07.pdf
8	Hoyle, M, Green, C, Thompson-Coon, J, Liu, Z, Welch, K, Moxham, T, et al. (2010). "Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma." Value in Health 13(1): 55-60.
9	Chandiwana, D, Perrin, A and Sherman, S (2014). "A cost effectiveness analysis of everolimus compared with axitinib in the treatment of metastatic renal cell carcinoma in the United Kingdom." Value in Health 17(7): A640.

5.4.9.1 Pharmacological costs

The pharmacological costs considered in the model are drug acquisition and administration costs. In order to estimate drug acquisition costs for lenvatinib combination and everolimus monotherapy the company used TTD data from the HOPE 205 trial to determine the proportion of patients on treatment in each cycle of the model. The proportions of patients per cycle receiving treatment in the axitinib, cabozantinib and everolimus groups, were estimated by calculating a “relative treatment duration” and applying this estimate to the proportion of patients in the lenvatinib combination treatment group. The relative treatment durations were estimated by dividing the median duration of treatment with lenvatinib combination in the HOPE 205 trial (i.e. 8 months) by the median duration of treatment of the comparator treatment that was observed in its respective trial. The company’s approach for applying TTD in the model was previously described in detail and critiqued in Section 5.4.6. The drug acquisition costs assumed in the model are summarised in Table 52.

Table 52. Drug acqusition unit costs assumed in the model (CS, pg 159, Figure 93)

Treatment	Dose per unit	Units per pack	Cost per pack (£)[90]	Price per unit (£)
Lenvatinib	4mg 10mg	30 30	1,437 1,437	47.90
Everolimus (combined with lenvatinib)	5mg	30	2,250	75.00
Everolimus	10mg	30	2,673	89.10
Axitinib	5mg	56	3,517	62.80
Cabozantinib	20mg/40mg/60mg	30	5,143	171.43
Nivolumab	100mg	1	1,097	1,097.00
Abbreviations in table: mg, milligramme.				

The drug doses assumed in the model are summarised in Table 53. The dose of nivolumab administered to patients is determined based on weight and is calculated as 3mg/kg. The company used the mean weight of patients in the HOPE 205 trial of 80.8 kg to estimate a dose of 244 mg of nivolumab which is applied in the model. The company accounted for dose reductions relative to intended doses when estimating acquisition costs in the model. The dose reductions assumed in the model are based on the actual doses received in the HOPE 205, AXIS, CheckMate 025, and METEOR trials. During the

based on feedback from the company's clinical experts and are summarised in Table 59. The estimated monthly cost of adverse events for each treatment arm in the model are presented in Table 60.

Table 58. Duration of adverse events assumed in the model (CS, pg 166, Figure 100)

Adverse event	Duration in days	Source
Diarrhoea	25.51	HOPE 205 trial.[31]
Fatigue/Asthenia	49.39	
Vomiting	10.11	
Nausea	34.79	
Hypertension	28.34	
Stomatitis	37.477	
Dyspnoea	33.56	
Decreased Weight	49.59	Assumed equal to decreased appetite

Table 59. Costs of managing adverse events applied in the model (CS, pg 165, Figure 99)

Adverse event	HRG Cost (£)	Source[91]
Diarrhoea	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Fatigue/Asthenia	658.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of F2F community nurse contact of £43 (Source: PSSRU 2016)
Vomiting	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Nausea	774.43	FZ91F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Hypertension	850.67	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (£162.84) (Source NHS Reference costs 2015/16) + 2 follow up GP visits (£36) Source: PSSRU 2016
Decreased Weight	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Stomatitis	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Abbreviations in table: CC, complication or comorbidity; HRG, Healthcare Resource Group; NHS, National Health Service.		

Table 60. Monthly costs of adverse events in the model

Adverse event	LEN+EVE	Everolimus	Axitinib	Cabozantinib	Nivolumab
Diarrhoea	16	3	9	3	10
Fatigue/Asthenia	13	0	13	2	14
Vomiting	3	0	0	0	1
Nausea	7	0	2	1	5

Hypertension	14	4	16	1	14
Decreased Weight	3	0	4	1	4
Stomatitis	0	4	1	0	2
Dyspnoea	2	13	0	1	2
Total	56	24	45	10	53
Abbreviations in table: LEN+EVE, lenvatinib combined with everolimus.					

5.2.1.1 ERG critique

The ERG found the formulae in the model to be generally sound, with prices inflated correctly to 2015/2016 rates when necessary. Unit costs are based on NHS Reference Costs and PSSRU costs, as specified in the NICE Reference Case.[89]

The ERG identified a few key issues in the approach taken by the company to estimate pharmacological costs in the model, which could cause erroneous cost effectiveness results.

In order to estimate the final dose received by patients after accounting for dose reductions that occurred in trials, the company applied the dose reduction factor to the intended dose and then rounded it to the nearest tablet or vial to calculate the dose received per patient. The ERG considers this method to be potentially overestimating or underestimating the costs for some treatments as the reduction factors estimated by the company were based on the mean doses received across the whole trial population, and not per patient. Therefore, applying the reduction factor to the total cost of the intended dose may be a better approach than that taken by the company. The dose reduction factors assumed for nivolumab and axitinib, are [redacted], and [redacted] of doses, respectively so this does not impact estimated costs for nivolumab while having a minimal impact on axitinib costs. However, although reduction factor of [redacted] and [redacted] are applied for everolimus when used in combination with lenvatinib and as monotherapy, respectively, patients are still assumed to receive the full dose of 5 mg and 10mg. respectively a day after the doses are rounded. A reduction factor of [redacted] is applied for cabozantinib, but when rounded to the nearest tablet patients are still assumed to receive their full [redacted] dose.

The dose reductions assumed by the company for nivolumab and axitinib are not consistent with the reductions reported and applied in the NICE appraisals of axitinib, nivolumab, and cabozantinib.[70, 92, 94] The preferred relative dose intensity assumed for nivolumab was 97.5% in the cabozantinib STA to reflect the ERG's recommendation in the nivolumab STA, while for axitinib in all three appraisals it was 102%.[57, 58, 95]

The company did not include subsequent therapies in its base case analysis, and therefore, the ERG asked the company to carry out a scenario analysis using the proportions of subsequent treatments received in the respective trials for all the treatments arms. The company did not provide this and instead chose to estimate a cost based on the UK market share of the drugs received as subsequent therapies

5.5 Results included in company's submission

5.5.1 Base case results

The results of the company's base case analysis are presented in Table 61. According to the company's analysis, lenvatinib combination is expected to extend patients' lives by around 11 months, 6 months, 4 months, and 2 months compared to axitinib, everolimus, nivolumab, and cabozantinib, respectively. This translates to an incremental average QALY gain of [redacted], and [redacted] QALYs for patients receiving lenvatinib combination compared axitinib, everolimus, nivolumab, and cabozantinib, respectively.

Table 61. Results of company's base case analysis (Clarification responses document)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
LEN+EVE	[redacted]	[redacted]	[redacted]	–	–	–	–
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,971
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,167
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,299
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	122,404

Additional set of utility (TA417) option	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus generic price (capecitabine price as a proxy)†	[redacted]	[redacted]	[redacted]	[redacted]
Secondary therapy included*	[redacted]	[redacted]	[redacted]	[redacted]
Natural mortality for NIV after 60 months	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: CI; confidence interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN+EVE, lenvatinib combined with everolimus; TA, technology appraisal.
†The results of this analysis appear to be erroneous as the total treatment costs for LEN+EVE increase with the lower everolimus cost. The ERG did not consider this further as the ERG does not consider the scenario relevant to the decision problem.
* There seems to be an error in the model in this additional scenario that the company carried during clarification stage as the model gives identical ICERs for LEN+EVE against all the comparators. The ERG did not explore this further as this scenario was not carried in line with what the ERG requested as explained in Section 5.4.9.5, and is of limited value.

5.5.1.1 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results across 1,000 iterations. The mean probabilistic ICERs are presented in Table 63, and are not in line with deterministic ICERs with the greatest discrepancies observed for cabozantinib and nivolumab. However, the ERG notes that the company's probabilistic ICERs are the mean of the 1,000 sampled ICERs, rather than being calculated from the mean costs and QALYs from the samples. The ERG's corrected calculations are also included in Table 63. The resultant scatterplots and cost-effectiveness acceptability curves (CEACs) from the PSA are presented in Figure 30 and Figure 31, respectively. Figure 5 confirms that there is a great deal of uncertainty surrounding the results of the comparison of lenvatinib combination compared to cabozantinib and nivolumab with simulations falling in all four quadrants.

The probability of lenvatinib combination therapy being cost-effective compared to everolimus, axitinib, cabozantinib, and nivolumab is 10.7%, 71.5%, 9.2%, and 8.6%, respectively, at a willingness-to-pay (WTP) threshold of £20,000 per QALY. At a WTP threshold of £30,000 per QALY, the probability of lenvatinib combination being cost-effective compared to everolimus, axitinib, cabozantinib, and nivolumab is 22.2%, 46.2%, 17.6%, and 14.0%, respectively.

Table 63. Mean probabilistic ICERs (adapted from the company's clarification responses document)

Treatment	LEN+EVE vs Axitinib	LEN+EVE vs Cabozantinib	LEN+EVE vs Nivolumab	LEN+EVE vs Everolimus
Deterministic ICER (£)	32,971	2,167	7,299	122,404
Mean probabilistic ICER (£)	47,343	279,561	29,567	154,941
ERG's re-calculated ICERs (£)	38,412	40,090	28,723	129,953

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LEN+EVE, lenvatinib combined with everolimus.

The ERG considers the probabilistic analysis performed by the company to be flawed due to implausible unconstrained normal distributions for HRs and a lack of correlation between treatments for the sampled HRs.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.4 Model corrections

The ERG identified the following errors in the company's base case model:

1. The first error was an inconsistent application of the half cycle correction for costs and QALYs, which led to an overestimation of QALYs for all treatments, favouring those with the greatest survival benefit, i.e. lenvatinib combination. The QALY value for the first cycle was incorrectly added to the sum of the half cycle values. For costs, only the half cycle values were included in the sum. The ERG corrected this so that the QALY calculation was in line with the calculation used for costs.

2. The second error was in the calculation of QALYs, which applied a utility associated with pre-progression to all patients who were on treatment, and therefore, did not account for patients who progressed but remained on treatment.

3. The adverse event costs were not adjusted for treatment duration as described by the company.

The results of the company's corrected base case are presented in Table 64 as a pairwise analysis, and in Table 65 as an incremental analysis.

Table 64. Results of company's corrected base case analysis (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,433
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	110,355

Table 65. Results of company's corrected base case analysis (Incremental)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	110,355
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

6.5 ERG scenario analysis

6.5.1 Trial based subsequent treatments

The ERG conducted a scenario analysis around the company's corrected base case to include the costs of the subsequent treatments that patients received in their respective trials. This contrasts with the company's scenario analysis, which based subsequent treatment costs on an estimated market share and applied the same cost to each treatment group. The ERG considers the trial based approach more appropriate as the treatment effectiveness is partly driven by the subsequent treatments received in the trials, and hence, the costs should reflect that. The results of this scenario are given in Table 66.

Table 66. Results of trial based subsequent treatments scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,915
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	110,223

6.5.2 ITC based HR applied for everolimus PFS

The ERG conducted a scenario around the company's corrected base case, which estimates PFS for the everolimus group by applying the HR from the ITC to the lenvatinib combination piecewise curve that was used in the company's base case. This scenario avoids the implausible outcome of nivolumab becoming less effective than everolimus in terms of PFS, as described in Section 5.4.5. The results are given in Table 67.

Table 67. Results of everolimus ITC HR scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,433
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	109,160

6.5.3 Utilities based on TA417

The ERG conducted a scenario using the company's option in the economic model to apply utilities from TA417. The results are presented in Table 68.

Table 68. Results of TA417 utility scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,433
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	115,520*
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	184,517
* This ICER represents the comparison of nivolumab relative to lenvatinib combination, as nivolumab becomes more expensive and more effective.							

6.5.4 General population mortality for 50% of nivolumab patients

The ERG conducted a scenario using the company's option in the economic model to apply the general population mortality to 50% of patients who are progression-free after 5 years. The results are given in Table 69.

Table 69. Results of TA417 mortality scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,433
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	110,355

6.6 ERG preferred base case

The ERG's preferred base case incorporates changes to the survival modelling that was used by the company, by using the fractional polynomial based curves for PFS and OS that were considered the best fitting by both the ERG and the company; that is, the first order polynomial with P = -1 for OS, and the second order polynomial with P1 and P2 = - 2 for PFS. The ERG's fitted 2-knot splines were used for to estimate TTD, and subsequent treatment costs were based on the treatments received in each of the respective trials. The results of the ERG's preferred base case are summarised in Table 70, which shows the cumulative effect on the results by including each change, as well as showing the ICER for each single change compared to the company's corrected base case.

Table 70. Results of the ERG preferred base case (Pairwise)

Results per patient	Lenvatinib comb. (1)	Axitinib (2)	Cabozantinib (3)	Everolimus (4)	Nivolumab (5)	Incremental values			
						(1-2)	(1-3)	(1-4)	(1-5)
Company's corrected base case									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER						28,433	Dominated	110,355	Dominated
ERG's preferred survival curves: Best fitting fractional polynomials for OS and PFS, and 2-knot spline for TTD									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**56,063**	**Dominated**	**74,239**	**Dominated**
ICER with all changes incorporated						**56,063**	**Dominated**	**74,239**	**Dominated**
Subsequent treatment costs based on trials									
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (compared with base case)						**27,915**	**Dominated**	**110,223**	**Dominated**
ICER with all changes incorporated						**55,351**	**Dominated**	**74,110**	**Dominated**
ERG's preferred base case ICER						**55,351**	**Dominated**	**74,110**	**Dominated**

Abbreviations in the table: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year

Table 71. Results of the ERG preferred base case (Incremental)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,110
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

6.7 ERG scenario analyses

6.7.1 Alternate first order OS fractional polynomial (P = -0.5)

The ERG conducted a scenario analysis around the ERG's preferred base case that uses an alternate OS fractional polynomial based curve with a similar goodness-of-fit but showing a lesser treatment effect for lenvatinib combination, cabozantinib and nivolumab in comparison to everolimus monotherapy. Further detail on these curves is given in Section 5.4.5. The results of this scenario are given in Table 72.

Table 72. Results of alternative OS curve scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,849
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77,610

6.7.2 Alternate TTD curve (Lognormal)

The ERG conducted a scenario that uses the lognormal curve for TTD that was fitted by the ERG as discussed in Section 5.4.6.1. The results of this scenario are given in Table 73.

Table 73. Results of alternative TTD curve scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,815

Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	85,003

6.7.3 Utilities based on TA417

The ERG conducted a scenario using the company's option in the economic model to apply utilities from TA417. The results are presented in Table 74.

Table 74. Results of TA417 utility scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,351
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	102,367

6.7.4 General population mortality for 50% of nivolumab patients

The ERG conducted a scenario using the company's option in the economic model to apply the general population mortality to 50% of patients who are progression-free after 5 years. The results are given in Table 75.

Table 75. Results of TA417 mortality scenario (Pairwise)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Lenvatinib combination	[redacted]	[redacted]	[redacted]	-	-	-	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,351
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,110

only enrolled patients who had not had prior anti-VEGF targeted therapy, was also included to form a connected network. The trials differed in terms of number and type of prior therapies, subsequent therapies, and outcome assessment.

The relative efficacy of lenvatinib combination therapy versus each comparator was initially estimated using the Bucher method for all outcomes. The analyses of OS and PFS was based on HRs, which are conditional on the proportional hazard (PH) assumption being fulfilled. However, the PH assumption does not hold for PFS and OS in several of the trials in the network and hence no meaningful interpretation of the resulting HRs from these analyses can be made. Therefore, the company assessed PFS and OS in a survival curve-based NMA using fractional polynomials, which does not rely on the PH assumption being fulfilled. Based on the difference in prior therapy in TARGET and confounding of OS due to cross-over, which couldn't be adequately adjusted for, axitinib and everolimus were assumed to have similar efficacy for the NMA of PFS and OS.

[redacted] The ERG assessed how well the best fitting NMA models the input data as FP curves, which showed a good statistical fit for both trial arms in CheckMate 025 and HOPE 205 for OS. For PFS the best fitting model showed a good fit for CheckMate 025, and the everolimus group in HOPE 205, but the lenvatinib combination therapy group in HOPE 205 was potentially overestimated. There were also several first and second order curves with a similarly good fit for OS. The ERG's inspection of the different curves shows that only one other fractional polynomial provides plausible curves.

The indirect comparisons for ORR and safety, which were estimated using risk ratios and the Bucher method, encompassed the full original network, in which the comparison with axitinib is reliant on the link via the TARGET trial. The comparison with axitinib is therefore potentially flawed based on difference in the trial populations in terms of type of prior therapy. The ORR was higher for patients treated with lenvatinib combination therapy compared with everolimus (direct comparison HOPE 205), nivolumab, cabozantinib, axitinib and placebo, although only the difference to the last two were statistically significant.

The company's primary analysis for each outcome were based on the full population and the primary analysis of each trials, that is, irrespective of differences between the trials in number and type of prior therapy, and investigator or independent outcome assessment.

The company submitted a *de novo* economic model with some potentially serious methodological flaws that led to unreliable estimates of treatment effectiveness and time to treatment discontinuation, and therefore unreliable estimates of cost effectiveness.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

You are asked to check the ERG report from BMJ Technology Assessment Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of **30 June** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Description of ORR results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 5, Section 1.2 The ERG report states: "Based on the indirect treatment comparison (ITC) using the Bucher method, there was a statistically significant different in ORR between lenvatinib combination therapy and everolimus monotherapy…" Page 88, Section 4.4.5, Second full bullet point This bullet points summarise the ORR results of the ITC. Page 159, Section 8, fourth paragraph. The wording in this paragraph refers to the indirect comparison for ORR and states that "The ORR was higher for patients treated with lenvatinib combination therapy compared with nivolumab, cabozantinib, axitinib, everolimus	Page 5 Section 1.2 Proposed wording is as follows: "Results from HOPE 205 show that there was a statistically significant difference in ORR between lenvatinib combination therapy and everolimus monotherapy... Based on the indirect treatment comparison (ITC) using the Bucher method, there was a statistically significant different in ORR between lenvatinib combination therapy and placebo in favour of lenvatinib combination..." Page 88, Section 4.4.5, Second full bullet point Please could the following sentence be added after the current wording: "Please note that the comparison between lenvatinib combination therapy and everolimus is a direct comparison based on the HOPE 205 study." Page 159, Section 8, fourth paragraph. Please could the following sentence be added after the current wording: "Please note that the comparison between lenvatinib combination therapy and everolimus is a direct comparison based on the HOPE 205	This is a factual inaccuracy as it implies that the ORR results for lenvatinib combination therapy vs everolimus are based on an indirect treatment comparison. As indicated in the notes underneath Table 3.4.2 on page 15 of the Indirect Treatment Comparison report (Appendix 8.5), the indirect estimates ie vs nivolumab, cabozantinib, placebo and axitinib are presented in italics. For clarity, the lenvatinib plus everolimus vs everolimus comparison is a direct comparison based on the HOPE 205 study.	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.

and placebo, although only the difference to the last two were statistically significant.”	study.”		

Issue 2 Inconsistent QALY and ICER values in ERG report for Company’s corrected base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, Table A Nivolumab reported QALY is different from those reported in Tables 64 and 65 (page 151), Table 66 and 67 (page 152), and Table 70 (page 154). All reported incremental ICERs are different from those reported in Tables 64 and 65 (page 151) and Table 70 (page 154)	Propose to update tables with correct values throughout the ERG report.	The same values should be used throughout the report.	The ERG thanks the company for highlighting this inaccuracy. The values in Table A have been updated. All other tables are correct.

Issue 3 Inconsistent QALY and ICER values in ERG report for ERG’s preferred survival curves

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, Table A Axitinib and nivolumab QALYs, incremental QALYs for everolimus and nivolumab and ICERs are different from those reported in Table 70 (page 154) and Table 71 (page 155)	Propose to update tables with correct values throughout the ERG report.	The same values should be used throughout the report.	The ERG thanks the company for highlighting this inaccuracy. The values in Table A have been updated. All other tables are correct.

Issue 4 Inconsistent QALY and ICER values in ERG report for Subsequent treatment costs based on trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, Table A Axitinib and nivolumab QALYs, incremental QALYs for everolimus and nivolumab and ICERs are different from those reported in Table 70 (page 154)	Propose to update tables with correct values throughout the ERG report.	The same values should be used throughout the report.	The ERG thanks the company for highlighting this inaccuracy. The values in Table A have been updated. All other tables are correct.

Issue 5 Inconsistent QALY and ICER values in ERG report for ERG's preferred base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8, Table A and Page 41, Table B Axitinib and everolimus ICERs, axitinib and nivolumab QALYs and incremental QALYs for lenvatinib combination and nivolumab are different from those reported in Table 70 (page 154) and Table 71 (page 155)	Propose to update tables with correct values throughout the ERG report.	The same values should be used throughout the report.	The ERG thanks the company for highlighting this inaccuracy. The values in Table A and Table B have been updated. All other tables are correct.

Issue 6 Incorrect patient numbers in CONSORT Flow diagram

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45, Figure 6, Follow up box,	Please amend this number to be n=45.	The information in the figure is	The ERG thanks the company

single-agent lenvatinib arm The figure quotes the number of patients who discontinued the intervention as n=29		incorrect.	for highlighting this error. It has been corrected.

Issue 7 Incorrect percentage of patients who had progressed and died

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51, Section 4.3, last paragraph on the page The ERG report states "At the pre-specified update analysis in December 2014 this had increased slightly as **66%** of patients had progressed and **47%** had died in the two treatment groups of interest to this appraisal."	Proposed wording is as follows: At the pre-specified update analysis in December 2014 this had increased slightly and **56%** had died in the two treatment groups of interest to this appraisal."	This is a factual inaccuracy. Eisai cannot confirm the value of 66%, but we can confirm that in this analysis, 4 patients had died in the combination arm and 33 in the everolimus arm: 24+33/101 = 56.4%. This is the value reported in Table 12 of the ERG report on page 52.	The ERG thanks the company for highlighting this error which has been corrected.

Issue 8 Everolimus OS and PFS HRs from ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report wording appears to imply that the OS and PFS HRs for the lenvatinib combination therapy vs everolimus comparison are based on indirect treatment comparisons. Page 76, Section 4.4.4.1, Third paragraph on the page	Page 76, Section 4.4.4.1, Third paragraph on the page Proposed wording is as follows: "Results from HOPE 205 show that there was a statistically significant difference between lenvatinib combination therapy and everolimus…. The ITC, which informed the company base case showed a statistically	This is a factual inaccuracy as it implies that the OS and PFS results for lenvatinib combination therapy vs everolimus are based on an indirect treatment comparison. For clarity, the efficacy values reported in the ITC report for the	The ERG thanks the company for highlighting this inaccuracy. The errors have been corrected.

The ERG report states: "The ITC, which informed the company base case showed a statistically significant difference between lenvatinib combination therapy and everolimus…" Page 80, Section 4.4.4.2 The ERG report states: "The difference in OS was statistically significant between lenvatinib combination therapy and everolimus…based on the ITT analysis (ignoring crossover of RECORD-1" Page 87, Section 4.4.5, Second and fifth full bullet points These bullet points summarise the PFS and OS results of the ITC. Page 102, Section 5.4, Third paragraph The paragraph describes the everolimus HR from the ITC. Page 110, Section 5.4.5.1, Third paragraph The paragraph describes the PFS HR derived from the ITC for the comparison of lenvatinib combination versus everolimus.	significant difference between lenvatinib combination therapy and nivolumab…" Page 80, Section 4.4.4.2 Proposed wording is as follows: "The difference in OS was statistically significant between lenvatinib combination therapy and everolimus…based on the ITT analysis (ignoring crossover of RECORD-1 (**Please note that the comparison between lenvatinib combination therapy and everolimus is a direct comparison based on the HOPE 205 study**." Page 87, Section 4.4.5, Second and fifth full bullet points Please could the following sentence be added after the current wording: "Please note that the comparison between lenvatinib combination therapy and everolimus is a direct comparison based on the HOPE 205 study." Page 102, Section 5.4, Third paragraph and Page 110, Section 5.4.5.1, Third paragraph Please could the following sentence be added after the current wording: "Please note that the everolimus HR reported in the ITC is a direct comparison based on the HOPE 205 study."	lenvatinib combination therapy vs everolimus comparison are taken directly from the HOPE 205 study.	

Issue 9 Location of key information within company's submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93, Table 32 The information within the table refers to information within the ERG report and the relevant section of the report, not the location of the key economic information within the company's submission.	Please could the table be updated to reflect the location of key information within the company's submission.	The information in the table is incorrect.	The ERG thanks the company for highlighting this error. The table has been corrected.

Issue 10 Results of company's base case analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93, Table 33 and page 144, Table 61 The values for Total LYG are different from those reported in the clarification responses document.	The Total LYG figures should read as follows: LEN+EVE: [redacted]; Axitinib: [redacted]; Cabozantinib: [redacted] Nivolumab: [redacted]; Everolimus: [redacted]	The figures are not the same as those provided by the company in the clarification responses document.	The ERG thanks the company for highlighting this inaccuracy. Table 33 and Table 61 have been corrected.

Issue 11 Economic evaluation studies in non-UK settings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96, second paragraph The ERG report states that "the ERG is aware of economic	Proposed wording is as follows: "Initially, the ERG identified some economic evaluation studies in non-UK settings that had	This is a factual inaccuracy as the relevant information was provided in response to the clarification	The ERG thanks the company for highlighting this inaccuracy. The text has been replaced by

evaluation studies in non-UK settings that have been captured by the company's literature search for randomised clinical trials described in Section 4.1.1, yet have not been captured in the search for cost-effectiveness studies. It is unclear to the ERG how these studies could have been missed and whether any other studies relevant to a UK decision making context have been missed."	been captured by the company's literature search for randomised clinical trials described in Section 4.1.1, yet had not been captured in the search for cost-effectiveness studies. In response to clarification questions, the company identified that part of the SLR Appendix had inadvertently not initially been sent and then provided this information which showed that the studies identified by the ERG had indeed been captured in the search for cost effectiveness studies."	questions.	that suggested by the company.

Issue 12 Calculation of the pre-extrapolation and post –extrapolation survival gain ratios

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109, Section 5.4.5 At the top of the page, the ERG report states that: "…the company incorrectly calculated the ratio of these values and therefore the conclusions drawn from these values may not be accurate."	Please could this sentence be removed.	This is a factual inaccuracy. The data reported in Figure 76 of the CS are calculated in stata and cannot be directly derived from the table, as the ratio is based on the cumulative difference over the extrapolated period.	Based on the description of the methods provided in the CS, this statement is not factually inaccurate.

Issue 13 Clarification regarding adverse events included in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 120, Section 5.4.7, first paragraph	Page 120, Section 5.4.7, first paragraph	This is a factual inaccuracy as the adverse events used in the	The ERG thanks the company for highlighting these errors.

The ERG report states: "The following treatment-related adverse events (TRAEs) are included in the model…" Page 121, Section 5.4.7, Table 44 The notes underneath the table state: "The prevalence values reported are treatment-related adverse events, with the exception of cabozantinib for which only treatment-emergent adverse events were available" Page 121, Section 5.4.7.1, ERG critique The first paragraph of this section describes the adverse events used in the CSR vs those used in the CS.	Proposed wording is as follows: "The following treatment-emergent adverse events (TEAEs) are included in the model…" Page 121, Section 5.4.7, Table 44 Proposed wording is as follows (as per Figure 89 of the CS): "All prevalence values reported are for treatment emergent adverse events, except for axitinib and nivolumab which are treatment-related adverse events" Page 121, Section 5.4.7.1, ERG critique Please could the wording be amended to reflect that the adverse events used in the company submission are treatment-emergent adverse events and not treatment-related adverse events.	company submission are treatment-emergent adverse events and not treatment-related adverse events. For clarity, the rates of adverse events are taken directly from Table 27 and Table 14.3.1.2.5.1.2 of the CSR for the HOPE 205 study, which reports treatment-emergent AEs **and NOT** from Table 30 in the CSR which reports treatment-related adverse events.	The text on page 120 has been amended. The notes under Table 44 have been amended to the company's proposed change. The text in Section 5.4.7.1 has been amended to reflect the corrections.

Issue 14 DSA ICERs for scenario on everolimus generic price

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 147, Table 62 The values for some of the ICERs are different from those reported in the clarification responses document.	The ICERs should read as follows: LEN+EVE vs Axitinib: 32,638 LEN+EVE vs Cabozantinib: 1,386 LEN+EVE vs Everolimus: 121,894	The figures are not the same as those provided by the company in the clarification responses document.	The ERG thanks the company for highlighting this error. The ICERs for the everolimus generic price scenario have been corrected. The ERG also noted that the

			results of this analysis appear to be erroneous. A note has been added to the table highlight this.

Issue 15 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 88, Second paragraph The following sentence is used twice in error in the ERG report: "However, there are several first and second order curves with a similar DIC for OS." Page 105, Table 38, D2a: Baseline data The ERG report states: "Baseline data for PFS and OS were informed by the HOPE 205 trial and were considered to be **reflective appropriate** for the model population." Page 105, Table 38, C1: Internal consistency The ERG report states: "There was an error in the use of treatment unit costs for everolimus monotherapy, which the company corrected following clarification questions, as well as	Page 88, Second paragraph Propose to remove the duplicate sentence. Page 105, Table 38, D2a: Baseline data Proposed wording as follows: "Baseline data for PFS and OS were informed by the HOPE 205 trial and were considered to be **reflective and appropriate** for the model population." Page 105, Table 38, C1: Internal consistency Proposed wording as follows: "There was an error in the use of treatment unit costs for everolimus monotherapy, which the company corrected following clarification questions, as well as an error in the calculation of QALYs, which led to **a proportion** of patients post progression having a utility relating to pre-progression."	Typographical errors	The ERG thanks the company for highlighting these errors. The proposed changes have been made.

an error in the calculation of QALYs, which led to **patients a proportion** of patients post progression having a utility relating to pre-progression."			

Issue 16 Typographical errors in tables

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69, Table 26, AXIS study information, % of Male patients The figures for axitinib and sorafenib are interchanged. They should be 71% for axitinib and 73% for sorafenib. Page 69, Table 26, RECORD-1 study information, % Poor MSKCC patients The figure for everolimus should be 14. Page 133, Table 48 Dyspnoea is missing from table Page 134, Table 50 Everolimus column is included twice in error Page 135-136, Table 51 Hoyle and Chandiwana studies are missing from the table	Page 69, Table 26 Please could the incorrect values in the table be corrected, as indicated. Page 133, Table 48 Please could the table be updated to include dyspnoea as per Figure 83 in the CS. Page 134, Table 50 Propose to remove duplicate column. Page 135-136, Table 51 Please could the table be updated to include the Hoyle and Chandiwana studies as per Figure 91 in the CS. Page 141, Table 60 Please could the table heading be amended to refer to Figure 103 in the CS.	Typographical errors	Based on Rini 2011, the main publication of AXIS, there were 73% males in the axitinib arm and 71% in the sorafenib arm as stated in the ERG report. The ERG thanks the company for highlighting the other issues which are factually incorrect. The proposed changes have been made. Table 60 has been updated with the ERG's corrected values and, hence, the company's correction is no longer applicable.

Page 141, Table 60 Table heading refers to Figure 100 in CS, but this should be Figure 103			

Issue 17 Marking of Commercial in Confidence information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following tables do not contain any highlighting for CiC information: Page 8 Table A; Page 9 Table B; Page 93 Table 33; Page 144 Table 61 and Pages 151-156 Tables 64-75	Please could the Total costs, LYG, QALYs and the Incremental costs, LYG and QALYs be marked as CiC	To be consistent with the CS.	Confidential marking has been applied to these tables, as per the CS.